Australian Prescriber

VOLUME 30 | NUMBER 1 | AN INDEPENDENT REVIEW | FEBRUARY 2007

CONTENTS

Editorial

Nurse prescribing: adding value to the consumer experience

Margaret McMillan, Professor and Deputy Head, Faculty of Health, University of Newcastle; and Helen Bellchambers, Clinical Practice and Performance Co-ordinator, Uniting Care Ageing, Hunter, Central Coast and New England, New South Wales

Key words: nurse practitioner, quality use of medicines.

(Aust Prescr 2007;30:2–3)

In Australia there is a potential for nurses to provide a wider range of services to patients, including prescribing and management of medications. In particular, patients who are elderly, suffering chronic disease or social deprivation could benefit from increased nursing care. Often, but not always, these people are isolated because of geography and other social factors.

Nurses have always been integral to the quality use of medicines (QUM). Recent government policy statements and a report by the Productivity Commission[1] now provide both an opportunity and a challenge to nurses to extend their scope of practice. This could prevent the unhealthy outcomes that have been associated with less than optimal use of medicines. In accordance with the QUM principles, a range of health professionals working in collaboration could achieve this.[1]

Consistent with international trends, Australian nurse practitioners are now formally authorised to practise in, for example, emergency medicine, mental health, drug and alcohol management, residential aged care, sexual health and neonatal intensive care. Legislative changes to relevant Nurses Acts and Drugs and Poisons Acts across the Australian jurisdictions grant limited prescribing rights to some of these nurse practitioners. The state and territory governments are responsible for regulating the nursing profession so the progress of nurse prescribing varies between jurisdictions. Some states have already appointed nurse prescribers, while others are still piloting their implementation.

A limited number of nurses with relevant qualifications and experience will be able to prescribe drugs from a restricted formulary according to agreed protocols. Some of these nurses will be part of general practices working in a collaborative medical team, whereas others will be working in isolation.

Much of the literature published over the past three decades on the progressive implementation of nurse prescribing comes from the UK, the USA and more recently Australia. A literature review undertaken by the Victorian nurse practitioner taskforce identified the following benefits associated with extending prescribing rights to nurse practitioners:

- improved patient care
- increased convenience for patients
- improved nurse–patient relationships
- improved collaborative practices within the healthcare team
- potentially reduced costs.[2]

An evaluation of nurse prescribing in the UK found that it was generally safe and effective in practice. Nurses, doctors and patients were positive about their experience of nurse prescribing although half of the nurses surveyed said they needed more professional development. Informal peer support was regarded as important in nurse prescribing.[3]

Nurses play a key role in co-ordinating, integrating and educating patients as well as providing clinical expertise. Nurse prescribers in the UK felt that extending prescribing rights has allowed them to make better use of their skills.[3] A major and continuing concern is that having more prescribers will result in polypharmacy and consumer confusion over medications[2],

In this issue…

Patients are sometimes given a starter pack so that they can try a new medicine before paying for a prescription. While this may be convenient, Marea Patounas and Treasure McGuire report some of the problems patients experience with starter packs.

Starter packs of beta blockers are not often seen. While prescribing patterns may have changed, Maros Elsik and Henry Krum say that there is still a role for these antihypertensive drugs.

The dose of some beta blockers may need to be reduced in patients with reduced kidney function. Randall Faull and Lisa Lee explain some of the principles of prescribing in renal disease.

Patients with diabetes may develop renal disease and they are also at risk of infected foot ulcers. Kerry Bowen tells us how these foot infections should be managed.

particularly if the prescribing nurse does not have access to the complete medical records.[4] Equally, problems may arise if drugs prescribed by a nurse are not integrated into a patient's records. However, it is possible that nurse practitioners might be able to minimise the likelihood of patients experiencing adverse events associated with medicine use.

Many general practitioners seem to have reservations about the safety of nurses assuming responsibility for diagnosis and prescribing medications.[2] There may be concerns if the nurse has to prescribe, dispense and administer a drug. In addition, issues around the legal liability of nurse prescribing remain unresolved. There is also a perceived lack of evidence about the costs attributed to a broader range of health professionals being involved in the management of medications. In a UK survey, doctors could not unequivocally conclude that nurse prescribing had reduced the workload.[3]

There is some difficulty in attributing either positive or negative patient outcomes solely to the nurse practitioner.[5] However, there are major benefits such as improved access to healthcare, better nursing assessment and treatment and a high level of patient acceptance and satisfaction that support the nurse practitioner's role in care. These benefits are likely to be extended if nurse practitioners are able to prescribe.

References

1. Australia's Health Workforce. Productivity Commission Research Report. Canberra: Australian Government Productivity Commission; 2005.
2. The Victorian nurse practitioner project: final report of the taskforce. Melbourne: Policy Development and Planning Division, Victorian Government Department of Human Services; 2000.
3. University of Southampton. An evaluation of extended formulary independent nurse prescribing. United Kingdom: Department of Health; 2005. http://www.dh.gov.uk/assetRoot/04/11/40/86/04114086.pdf [cited 2007 Jan 11]
4. Non-medical prescribing. Drug Ther Bull 2006;44:33-7.
5. Breslin E, Burns M, Moores P. Challenges of outcomes research for nurse practitioners. J Am Acad Nurse Pract 2002;14:138-43.

Conflict of interest: none declared

Letters

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

Echocardiography

Editor, – It was with great interest that I read the 'Diagnostic tests: Echocardiography' article (Aust Prescr 2006;29:134–8), particularly in relation to the ability of this test to differentiate between valvular disease and benign flow murmurs.[1] However, I was surprised that there was no 'Dental note' highlighting the importance of echocardiography in the assessment of patients requiring antibiotic prophylaxis for dental treatment.

A study found that 370 patients out of 20 000 indicated in their medical history that they had a heart murmur or had had rheumatic fever and that they usually received antibiotic prophylaxis for dental treatment.[1] After evaluation of their murmur by electrocardiography and Doppler flow ultrasonography, only 50 had a defect that met current indications for antibiotic prophylaxis for infective endocarditis.[2] Furthermore, the risk of an adverse reaction to the antibiotics and the selection of antibiotic resistant bacterial strains in these patients needs to be considered.

Dental patients reporting an indefinite history of rheumatic fever or cardiac murmur should be referred to their general practitioner, or directly to a cardiologist for diagnosis by echocardiography. This should determine whether or not they require antibiotic prophylaxis for infective endocarditis, in accordance with current guidelines.

Ray Heffer
Endodontic Registrar
Oral Health Centre of Western Australia
School of Dentistry, The University of Western Australia
Perth

References

1. Ching M, Straznicky I, Goss AN. Cardiac murmurs: echocardiography in the assessment of patients requiring antibiotic prophylaxis for dental treatment. Aust Dent J 2005;50(4 Suppl 2):S69-73.
2. Singh J, Straznicky I, Avent M, Goss AN. Antibiotic prophylaxis for endocarditis: time to reconsider [review]. Aust Dent J 2005;50(4 Suppl 2):S60-8.

Xerostomia

Editor, – I found the article on xerostomia (Aust Prescr 2006;29:97–8) to be both timely and informative. As a dentist I have experience in the UK, South Africa and the USA helping patients deal with the problems they experience post-radiotherapy for head and neck cancers.

When I attempt to discuss these issues with my Australian medical colleagues, they commonly reply that no patients experience any problems. This is in contrast to my own records which agree with the figure that 90% of patients suffer problems after radiotherapy.

There are as Professor Olver suggested a number of options being investigated to treat xerostomia. Amifostine is of benefit, but there are problems with the high incidence of nausea associated with its use (50%). The use of antioxidants is currently being investigated by the National Cancer Institute in the USA. Two forms of nitroxide are currently being examined. These are not approved by the US Food and Drug Administration for clinical use, other than for topical use to prevent hair loss and for a number of ophthalmic conditions.

I have had some success in prevention of xerostomia by employing intra-oral screens and other available antioxidants which are currently approved as dietary supplements. This is of course anecdotal and not scientifically proven but better to accept that a problem exists than to be in denial.

JF Walsh
Kojonup, WA

Professor Ian Olver, author of the article, comments:

I am pleased that Dr Walsh highlights the importance of recognising the symptomatic distress caused by xerostomia. The symptoms are difficult to manage so prevention is clearly important to investigate. Amifostine as a radioprotector has not been widely used because of its other adverse effects. Nitroxide, an antioxidant and chemoprotective drug acting partly via the p53 suppressor, is a radioprotector which has been shown to reduce radiation-induced xerostomia in mice when used topically in the mouth.[1] It is an excellent candidate for further trials in patients receiving radiotherapy, where it will be important to ascertain that the tumour is not also protected from the radiation. Anecdotal accounts of the efficacy of other drugs are useful in stimulating further clinical research in this field.

Reference

1. Cotrim AP, Sowers AL, Lodde BM, Vitolo JM, Kingman A, Russo A, et al. Kinetics of tempol for prevention of xerostomia following head and neck irradiation in a mouse model. Clin Cancer Res 2005;11:7564-8.

Editor, –The recent review of xerostomia (Aust Prescr 2006;29:97–8) with a commentary on the dental implications is timely and informative. The capacity of medication-related xerostomia to destroy the dentition is commonly overlooked by prescribers.

In an unpublished audit of patients requiring full dental clearance at the Royal Adelaide Hospital in 2004, we found that 68 of 92 (74%) had medication-related xerostomia which had destroyed their dentition. By the time the patients had presented to their dentist the condition was unrestorable and once they had their teeth extracted they often had ongoing difficulty with dentures. The patients were taking between one and ten medications, with the average being four. Antidepressants, sedatives and analgesics were the main drugs implicated in their xerostomia.

I have audited 19 patients referred to me for a medicolegal opinion on the relationship of their dental state to a work-related injury. All the patients had chronic work-related musculoskeletal injuries, mainly low back pain, and were found to have xerostomia with adverse oral affects. In 10 of the 19 patients who were on a combination of the older tricyclic antidepressants such as amitriptyline or dothiepin with narcotics (usually morphine sulphate), the dentition had been destroyed in less than one year. Three of the patients admitted to supplementing their analgesia with fairly regular cannabis and probably a number elected not to reveal this information. None of the patients had been warned of the adverse oral effects of their medications or had been advised to seek regular dental care. All presented to a dentist when it was an emergency situation and largely too late to save their dentition.

When drugs that cause xerostomia are prescribed, their effect on oral health should be made clear to the patient and a dental referral should be made.

Alastair N Goss
Professor and Director
Oral and Maxillofacial Surgery Unit
The University of Adelaide
Adelaide

Should beta blockers remain first-line drugs for hypertension?

Maros Elsik, Cardiologist, Department of Epidemiology and Preventive Medicine, Monash University and The Alfred Hospital, Melbourne, and Henry Krum, Chair of Medical Therapeutics, Professor of Medicine and Director of NHMRC Centre of Clinical Research Excellence in Therapeutics, Department of Epidemiology and Preventive Medicine and Department of Medicine, Monash University, Melbourne

Summary

Hypertension is an important risk factor for stroke and other cardiovascular events. National and international guidelines recognise five classes of drugs for the first-line treatment of hypertension, but the effectiveness of beta blockers has recently been questioned, especially in the elderly. However, achieving a lower blood pressure is more important than the choice of drug used in treatment. Many patients will need more than one drug to treat their hypertension. Beta blockers remain important and effective drugs, but age and comorbidities need to be considered when selecting a first-line drug.

Key words: aged, atenolol, stroke.

(Aust Prescr 2007;30:5–7)

Introduction

The antihypertensive drugs used in Australia are mainly diuretics, beta blockers, calcium channel blockers and antagonists of the renin angiotensin aldosterone system. The current National Heart Foundation guidelines for treating hypertension do not recommend a preferred first-line drug, but recognise beta blockers as an acceptable choice. However, recent publications have generated significant controversy about the role of beta blockers.

Recent evidence about beta blockers

A meta-analysis has found that, compared to placebo, beta blockers are effective drugs and are associated with a 19% lower relative risk of stroke.[1] Compared to other antihypertensive drugs, there were no differences for all cause mortality or for myocardial infarction, but beta blockers did not reduce stroke to the same extent. This was reported as a 16% higher relative risk of stroke.

The majority of trials in the meta-analysis studied atenolol. When the analysis was restricted to other beta blockers, no significant differences were found in comparison with other antihypertensive drugs. However, this restricted analysis contained only a few trials, with a low number of adverse events, so it was most likely underpowered to detect a difference. The authors of the meta-analysis concluded that all beta blockers are less effective than other antihypertensives and should not be used as first-line drugs in hypertension. However, the major differences observed between beta blockers and other antihypertensives are largely due to the influence of two trials.[2,3]

The recently published guidelines of the UK National Institute for Clinical Excellence (NICE)[4] no longer include beta blockers in their routine treatment algorithm for hypertension, citing concerns of lower effectiveness and a greater risk of diabetes especially in combination with thiazide diuretics. They also state that prospective trials with newer (more selective) beta blockers are needed.

Other evidence

With the inclusion of more trials and re-analysis of the meta-analysis[1] according to age, it was shown that for patients with a mean age under 60 years, beta blockers were no different from other drugs in reducing the composite outcome (death, stroke or myocardial infarction). In those with a mean age over 60 years, beta blockers were associated with a higher incidence of stroke – relative risk of 1.18 (95% CI 1.07–1.30) – compared to other drugs.[5] An earlier review assessing diuretics and beta blockers also found that in patients over the age of 60, beta blockers failed to favourably affect clinical end points despite an effect on blood pressure.[6]

In these reviews the excess risk of beta blockers appeared to be largely due to trials enrolling patients with an average age over 60 years. No excess risk was seen in younger patients. This suggests that beta blockers should not be first-line in the elderly.[5,6]

What matters most – lowering pressure or drug class?

Epidemiological studies consistently show that the majority of strokes are directly attributable to high blood pressure. An overview of reviews highlighted that the association of blood pressure and the risk of stroke is log linear.[7] This means that for any given absolute decrease in blood pressure from a baseline level, there is a similar relative risk reduction of stroke. The

difference in blood pressure reductions achieved by different drugs was often less than 1 mmHg, implying minimal difference between the drug classes.[7]

A collaborative trial of blood pressure-lowering treatment observed a greater risk reduction for stroke with regimens based on calcium channel blockers compared with those based on diuretics or beta blockers, but the results were of borderline statistical significance. The mean age of these patients was 65 years and there was no overall significant difference in major cardiovascular events between the drugs.[8]

Another analysis based on 61 prospective trials (12.7 million person-years at risk) concluded that throughout middle and old age, a person's usual blood pressure is strongly and directly related to vascular and overall mortality, without any evidence of a threshold down to at least 115/75 mmHg.[9] Stroke is much more common in older age than in middle age and, given the continuous relationship observed between blood pressure and the risk of death from vascular disease, the absolute benefits of a lower blood pressure are likely to be greatest for those at greatest absolute risk of vascular disease.

These large reviews suggest that reducing blood pressure is more important than the drug used. Achieving a lower blood pressure will result in a reduction in the risk of major adverse events.

Antihypertensive effect of beta blockers

There are different types of beta blockers (Table 1). They vary in their lipophilicity, receptor specificity, mode of elimination, half-life, primary indications and cost.

The exact mechanism by which beta blockers exert their antihypertensive effect is uncertain. Possible actions include a reduction of cardiac output (negative inotropic and negative chronotropic effect), an effect on vascular resistance, as well as an inhibitory effect on the release of renin (which is stimulated by the sympathetic nervous system) and central effects that may be influenced by the hydro- or lipophilicity of the beta blocker.

Many patients taking beta blockers in clinical trials required combination therapy, especially with thiazide diuretics, to achieve their target blood pressures. This has been raised as evidence that beta blockers have a weak antihypertensive effect. However, the need for combination therapy is not unique to beta blockers and many trials show better blood pressure control with combination therapy rather than single drug therapy, largely irrespective of the initial drug class used.

Table 1
Classes of beta blockers

Action	Adrenergic selectivity	Examples
Non-selective	$beta_1$ and $beta_2$	propranolol sotalol*
Selective	$beta_1$ > $beta_2$	atenolol metoprolol succinate metoprolol tartrate (sustained release) bisoprolol
Non-selective and vasodilating	$beta_1$, $beta_2$ and $alpha_1$	labetalol carvedilol
Non-selective and vasodilating (nitric oxide pathway)	$beta_1$ and $beta_2$	nebivolol†

* used primarily as a class III antiarrhythmic drug
† not currently available in Australia

Effect on arterial pressure

In clinical practice blood pressure is measured at the brachial artery. The brachial artery diastolic pressure is a good estimate of the central aortic diastolic pressure. However, the brachial artery systolic pressure does not accurately estimate central aortic systolic pressure as the peak systolic blood pressure is only one point on the systolic pulse wave.[10,11] The central aortic pressure may be more important than peripheral pressure to outcomes such as stroke, although this remains to be proven.

In patients older than 60 years the effect of drugs on peripheral artery blood pressure may not accurately predict the changes in central aortic pressure. Specifically with atenolol, the central aortic systolic pressure is not reduced as much as the peripheral systolic pressure. In practice this means that a reduction in brachial pressure is associated with a smaller reduction in central aortic pressure. In contrast, ACE inhibitors tend to cause a relatively small change in peripheral blood pressure but a proportionately higher fall in central aortic pressure.[10] A recent study comparing amlodipine and atenolol also found that atenolol had a significantly weaker effect on central aortic pressure.[12]

Interpretation of the evidence

Although regarded as high level evidence, meta-analyses are only as useful as the trials they include. Meta-analyses that include heterogeneous trials, even when this is accounted for in the statistical modelling, need to be interpreted cautiously. In many ways they should be regarded as hypothesis generating rather than hypothesis proving. In the meta-analysis[1], the authors listed limitations such as the inability to relate outcomes to the dose and dosing of the drugs. Their inability to adjust for blood pressure control also raises concern about the strength of the results.

The majority of trials of beta blockers in hypertension have used atenolol. The few 'non-atenolol' beta blocker trials mainly studied propranolol, a few studied metoprolol and fewer still studied other or newer more selective beta blockers. Furthermore, beta blocking drugs with vasodilating properties such as carvedilol[13] and nebivolol are different and may be

more beneficial than traditional beta blockers. Whether the atenolol findings can be generalised to all beta blockers is therefore uncertain, however given the variety of drugs in the class it would seem premature to dismiss them all for the treatment of hypertension.

Beta blockers are effective at significantly reducing the risk of strokes compared to placebo or no drugs. Current data show that they are less effective at reducing stroke compared to other drugs. The evidence does raise questions about the efficacy of atenolol as a first-line drug in patients over the age of 60 years with primary hypertension and no other indications for a beta blocker. However, statements that beta blockers increase the risk of stroke are misleading.

Most patients, especially the elderly, will require several drugs to reach their blood pressure target. Beta blockers can be used in combination therapy and there may be particular indications for using them (see box). These can be secondary complications of hypertension or they may be conditions that coexist with primary hypertension. The type of beta blocker to use will be determined by the condition.

Conclusion

It is unlikely there will ever be a single ideal first-line drug for hypertension and most patients will eventually need multiple drugs to control their blood pressure. Treatment needs to be individualised for all patients.

The choice of treatment should be influenced not only by underlying cardiovascular risk factors, comorbidities and potential adverse effects, but also by the age of the patient. Beta blockers remain a viable option in the treatment of hypertension and they should not necessarily be discontinued if the clinical condition is stable and controlled or if there is another indication for their use.

Conditions where beta blockers are useful or indicated

- Ischaemic heart disease – angina (stable and unstable), postmyocardial infarction
- Tachyarrhythmias – supraventricular and ventricular tachycardia, atrial fibrillation, atrial flutter
- Chronic heart failure
- Palpitations
- Anxiety
- Essential tremor
- Migraine
- Glaucoma
- Thyrotoxicosis
- Portal hypertension

References

1. Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet 2005;366:1545-53.
2. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumenthiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;366:895-906.
3. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003.
4. UK National Institute for Clinical Excellence (NICE). Hypertension. Management of hypertension in adults in primary care: partial update. http://www.nice.org.uk/download.aspx?o=CG034fullguideline [cited 2007 Jan 11]
5. Khan N, McAlister FA. Re-examining the efficacy of beta-blockers for the treatment of hypertension: a meta-analysis. CMAJ 2006;174:1737-42.
6. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 1998;279:1903-7.
7. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke 2004;35:1024.
8. Turnbull F. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003;362:1527-35.
9. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13.
10. Morgan T, Lauri J, Bertram D, Anderson A. Effect of different antihypertensive drug classes on central aortic pressure. Am J Hypertens 2004;17:118-23.
11. O'Rourke MF. From theory into practice: arterial haemodynamics in clinical hypertension. J Hypertens 2002;20:1901-15.
12. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006;113:1213-25.
13. Messerli FH, Grossman E. Beta-blockers in hypertension: is carvedilol different? Am J Cardiol 2004;93(Suppl 9):7B-12B.

Professor Krum has been on advisory boards for beta blockers with Roche, Alphapharm and AstraZeneca.

Testing for sexually transmitted infections

Catriona Ooi, Director, Sexual Health Service, Hunter New England Area Sexual Health Service, Newcastle, and Conjoint Lecturer, School of Medicine and Public Health, Faculty of Health, The University of Newcastle, New South Wales

Summary

Rates of sexually transmitted infections are increasing worldwide and notifications are also increasing in Australia. As many sexually transmitted infections are asymptomatic, timely and appropriate testing is needed to avoid the long-term sequelae of infection, to halt transmission and to improve associated morbidity. Testing for sexually transmitted infections has evolved over time. Although nucleic acid amplification tests have an increasing role and may enable non-invasive testing, microscopy and culture are still useful investigations for some infections.

Key words: chlamydia, gonorrhoea, herpes, HIV, syphilis.

(Aust Prescr 2007;30:8–13)

Introduction

Effective testing for sexually transmitted infections needs to be acceptable to the patient and tailored and targeted appropriately to sexual risk. This risk is determined by factors such as the use of condoms and the number of sexual partners. As many common sexually transmitted infections, such as chlamydia, are largely asymptomatic, doctors need to be aware of local epidemiology and at-risk groups, in order to facilitate opportunistic screening.

To determine which tests to perform, consider the patients' individual needs and concerns, sexual activity, condom use, local epidemiology and any symptoms (Table 1). Sexual activity such as vaginal, anal or oral sex will direct from where to collect specimens. Pretest counselling and education are important. Serology for HIV should be considered for all patients. Testing for hepatitis B should be considered for those who have not been vaccinated. Homosexually active men should routinely have additional tests for both syphilis and hepatitis A.

With most infections there is a 'window period' (Table 2) before laboratory tests become positive. This period must be considered when interpreting results.

Chlamydia

Chlamydia trachomatis is the most commonly notified sexually transmitted infection in Australia and rates have risen four-fold between 1996 and 2005.[1] In up to 80% of women and 50% of men the infection is asymptomatic.[2] If untreated, chlamydia may have serious sequelae such as pelvic inflammatory disease, ectopic pregnancy and infertility in women, and epididymitis, chronic prostatitis and urethral strictures in men. Screening is recommended for all sexually active individuals younger than 25 years regardless of condom use.

Testing

In Australia, nucleic acid amplification tests – polymerase chain reaction (PCR) and ligase chain reaction (LCR) – are accurate and reliable. The chlamydia PCR is highly specific (99–100%) with a sensitivity of 85–90%.[3] These tests allow non-invasive and self-collected sampling. One study evaluating nucleic acid amplification tests of self-collected vulval-introital specimens, first void urine samples and clinician-collected cervical samples found the self-collected swabs and urine specimens to be acceptable alternatives to cervical sampling.[4]

A positive result from a chlamydia nucleic acid amplification test is likely to be a true positive. However, these tests have only been validated for use in urine, cervical and urethral samples. Although these tests can be used to analyse samples from other sites, such as rectum and vagina, the results should be interpreted with caution.

Chlamydia trachomatis cultures are the test of choice if the results are to be used in legal investigations as culture has a high specificity. Culture also allows for antibiotic sensitivity testing, but has the disadvantage of relatively low sensitivity and high cost. Culture is also labour intensive, technically difficult and has a long turnaround time.

Herpes

Genital herpes is the clinical manifestation of infection with either herpes simplex virus type 1 or herpes simplex virus type 2 at genital sites. Infection is common and often asymptomatic. In Australia it is estimated that up to 25–30% of people are seropositive for herpes simplex virus type 2 and 80% are seropositive for herpes simplex virus type 1.

Table 1

Screening guidelines for different populations *

Who	Routine tests (regardless of condom use)	Other tests to consider	When
Heterosexual men and women	Chlamydia (cervix/urine) Hepatitis B (consider vaccination†)	Depending on sexual practice: – gonorrhoea (cervix/urine/throat/anal) – chlamydia (anal) Depending on local epidemiology: – Trichomonas – syphilis – baseline serology for HIV	Consider annual screening for those who have changed partner, more frequently depending on risk
Men who have sex with men	Gonorrhoea (throat/anal) Chlamydia (urine/anal) Hepatitis A (consider vaccination†) Hepatitis B (consider vaccination†) Syphilis HIV	Anal test indications: – any anal sex with casual partners – any unprotected anal sex – any anal symptoms – HIV positive – past history of gonorrhoea – contact with any sexually transmitted infection – request	Annually if asymptomatic, more frequently depending on sexual risk
Young people (<25 years)	Chlamydia (cervix/urine) Hepatitis B (consider vaccination†)	Gonorrhoea Baseline serology for HIV	Annually for those who have changed partner, more frequently depending on risk
Sex workers	Gonorrhoea (cervix/urine) Chlamydia (cervix/urine) Syphilis Hepatitis B (consider vaccination†) HIV Gonorrhoea (throat/anus)	Depending on sexual practice: – chlamydia (anal) – hepatitis A (consider vaccination)	Every 3–6 months
People who inject drugs	Chlamydia (cervix/urine) Hepatitis B (consider vaccination†) Hepatitis C Syphilis HIV	Hepatitis A (consider vaccination)	Annually if asymptomatic, more frequently after particular risk episode

* Adapted from: Clinical guidelines for the management of sexually transmitted infections among priority populations. The Royal Australasian College of Physicians, Australian Chapter of Sexual Health Medicine, 2004

† Once patient immunised against hepatitis A/hepatitis B, further serology is unnecessary

Table 2

Tests for sexually transmitted infections

	Test	Specimen	Window period	Indication	Comments
Chlamydia	PCR/LCR	Urine, swab (urethra/cervix)	2–7 days	Screening and diagnosis	PCR at high vaginal and rectal sites not validated Retesting at one month post-treatment if indicated
	Culture	Swab – any site			Highly specific, use in legal situations
Herpes	PCR	Lesion	Lesion	Diagnosis	Negative PCR or viral culture does not exclude infection
	Viral cultures	Lesion	Lesion	Diagnosis	
	EIA/ELISA	Blood	3–12 weeks	Screening	Type-specific or herpes simplex virus type 2 serology most useful. Beware false results
	Western blot	Blood	3–12 weeks	Screening	
Gonorrhoea	PCR/LCR	Urine, swab (urethra/cervix)	24 hours	Screening and diagnosis	PCR at high vaginal, throat and rectal sites not validated
	Culture	Swab (urethra/cervix/throat/rectum)		Screening/diagnosis Confirmation of PCR	Culture allows antibiotic sensitivity and specificity testing
Syphilis	Dark ground microscopy	Lesion	3–30 days, if chancre	Diagnosis early syphilis	Only with symptoms
	PCR/LCR	Lesion, tissue, CSF, blood	3–30 days, if chancre	Diagnosis early syphilis	Not widely available
	EIA	Blood	2–12 weeks	Screening	Repeat serology for those with suspected exposure
	RPR/VDRL	Blood VDRL-CSF	3–12 weeks	Screening, diagnosis/staging, treatment response, reinfection	
	FTA-abs TPPA/TPHA	Blood	3–12 weeks	Confirmation of diagnosis	
HIV	HIV antibody: – EIA – Western blot	Blood	6–12 weeks	Screening/diagnosis	Gold standard test
	p24 antigen		earliest 2 weeks		Transient, may be absent after 2 weeks
	Qualitative PCR HIV DNA (proviral DNA)				Useful for early diagnosis
	Quantitative HIV RNA (viral load)				Beware false positives

PCR	polymerase chain reaction	RPR	rapid plasma reagin	TPPA	treponema pallidum particle agglutination
LCR	ligase chain reaction	VDRL	venereal disease research laboratory	TPHA	treponema pallidum haemagglutination test
EIA	enzyme immunoassay	CSF	cerebrospinal fluid		
ELISA	enzyme-linked immunosorbent assay	FTA-abs	fluorescent treponemal antibody absorption		

Testing

The clinical diagnosis is unreliable and must be confirmed. Whether tests are done depends on the presence of symptoms, however patients who are asymptomatic still shed the virus. Type-specific testing should be undertaken to identify herpes simplex virus type 1 or type 2, as knowing the type gives important prognostic information and may direct education and counselling. Direct detection tests (PCR, viral culture, immunofluorescence) can detect herpes simplex virus in swabs of lesions or infected secretions. However, viral cultures, immunofluorescence and, to a lesser extent, PCR swabs may all produce false negative results. A negative test therefore does not rule out genital herpes.

Although slow and labour-intensive, viral culture is type specific and has long been regarded as the gold standard due to its specificity of nearly 100%. Sensitivity varies greatly as it depends on viral shedding, transport conditions, specimen quality and the timing of specimen collection. Indeed, virus isolation may range from 52–90% for vesicles to 19–27% for crusted lesions.

Type-specific PCR is both sensitive and specific. Studies have shown that tests using PCR may increase the rate of virus detection by 24–71%.[5,6] Herpes simplex virus immunofluorescence is rarely performed despite its high specificity as it has low sensitivity (80%). The results may depend upon specimen quality and the experience of the laboratory technician.

Serological tests which are not type specific have little diagnostic value and are not recommended. Herpes simplex virus type-specific antibody tests are widely available, however they vary in sensitivity and specificity. Only those based on glycoprotein G have acceptable accuracy with good sensitivity and specificity in high prevalence populations. The positive predictive value (the proportion of positive results that are true positives) is lower in groups with a low prevalence of infection.[7] With some tests for herpes simplex virus type 2, clinicians should be aware of the possibility of cross-reactivity between herpes simplex virus type 1 and type 2 antibodies. The gold standard for serological tests is the western blot. This test is highly sensitive and specific for both herpes simplex virus types 1 and 2, but it is expensive and not widely available. The window period for serological tests ranges from 2 to 12 weeks.

Screening serology may be useful in epidemiological studies, but is of limited benefit for asymptomatic patients. A positive serology test in those with no symptoms is unlikely to change treatment decisions or behaviour, and may lead to significant psychological distress. Herpes simplex virus serological tests may be useful in pregnancy, partners of herpes simplex virus-infected individuals and patients with HIV.

Gonorrhoea

Notification rates for gonococcal infections are increasing. In Australia, men who have sex with men, those who have had sexual contact abroad and rural and remote indigenous communities have the highest rates of gonorrhoea. Most urethral infections are symptomatic, however the majority of rectal, pharyngeal and cervical infections will be silent, only becoming symptomatic when complications such as pelvic inflammatory disease occur.

Testing

Microscopy and culture are the mainstay of testing. Culture is highly specific and allows for antibiotic sensitivity testing, but the sensitivity of the test may drop with lengthy delays between the collection site and the laboratory. Nucleic acid amplification tests are more robust. These newer tests have a high sensitivity (90–95%) and specificity (98–100%) for swab samples.[3] Non-invasive testing with first void urine samples and self-collected anal swabs are an option, however in women endocervical swabs are more sensitive than urine samples (94.2% vs 55.6%). Like nucleic acid amplification tests for chlamydia, those for gonorrhoea have only been validated for use with urine, cervical and urethral samples. The positive predictive value of nucleic acid amplification tests for gonorrhoea decreases in a low prevalence population resulting in higher rates of false positive results. Where possible, positive results should be confirmed with culture for antibiotic sensitivity testing and to exclude false positives particularly in low-risk individuals.

Syphilis

The rates of syphilis in Australia are about 10/100 000, nearly double that in New South Wales, and up to 140/100 000 in the Northern Territory, with a national indigenous rate of 300/100 000.[8] Despite remaining fairly stable in the heterosexual community, syphilis rates continue to rise in homosexually active men.[8] Other groups in Australia at risk of syphilis include rural and remote indigenous communities and those from overseas. Most infections are detected in the late latent phase, when the patient is asymptomatic, having passed the early infectious stages unrecognised and undiagnosed.

Testing

National antenatal screening includes syphilis testing. Diagnostic serological tests are widely available, cheap and accurate. For most patients, diagnosis and staging of infection depends upon interpretation of a combination of treponemal and nontreponemal tests.

Serology

The nontreponemal tests are the venereal disease research laboratory test and the rapid plasma reagin test. They detect non-specific antibodies. These tests are simple and cheap with sensitivity of 78–86% in primary syphilis, virtually 100% in secondary syphilis and 95–98% in late latent infection. They may cross-react with other treponemal infections and false positive

results may occur in 1–2% of the population in association with pregnancy, HIV and other medical conditions. False negative results may occur in patients with very high titres – the prozone phenomenon. The titre is both a marker of infectivity and reinfection, and is used to monitor response to treatment.

Treponemal tests detect antibodies that are specific for treponemes. They include the treponema pallidum particle agglutination tests, treponema pallidum haemagglutination test and fluorescent treponemal antibody absorption test. These tests are mostly used to confirm the diagnosis. The treponeme-specific tests have a sensitivity of about 80% in primary syphilis and nearly 100% thereafter. The syphilis enzyme immunoassay may be used for screening sera. It has a sensitivity of 82–100% and specificity of 97–100%.[9]

The nontreponemal tests may become negative after treatment, however they may remain positive at a low titre for life. Similarly, most of those with reactive treponemal specific tests will remain positive for life regardless of treatment or disease activity, with 15–25% of those treated in primary syphilis reverting to negative serology after several years.[10]

Other tests

For symptomatic patients with lesions suggestive of primary or secondary syphilis, direct detection methods, such as dark ground microscopy, may be used, however these are not widely available. Performed correctly, dark ground microscopy has a sensitivity of up to 74–86% and is 97% specific. However, accuracy may vary depending on the age and condition of the lesion. Microscopy also requires trained laboratory staff, specialised equipment and rigorous conditions for the storage and transport of the sample. In primary syphilis (that is, before the production of syphilis antibodies) this method is highly sensitive and specific compared to serological testing.

The nucleic acid amplification tests such as syphilis PCR have sensitivity of 91% and specificity approaching 100%. They have the ability to detect as few as 10 treponemes per lesion. The tests are useful for the diagnosis of congenital syphilis, however they require serological confirmation once the child reaches a certain age.[9] A reactive treponemal test at 18 months is diagnostic of congenital syphilis. These tests are not widely available in Australia and are not routinely used for screening.

HIV

In Australia, the highest risk of HIV exposure occurs in homosexually active men and those from, or those who have had sexual contact in, high prevalence countries. Given the serious sequelae of untreated infection, testing should be offered to everyone presenting for sexually transmitted infection screening, those specifically asking for HIV testing and pregnant women. Pre- and post-test counselling are essential and should cover associated legal aspects and test limitations including window periods.

Testing

HIV antibody testing is used for screening. Typically, sera are first tested with an enzyme immunoassay or enzyme-linked immunosorbent assay. If either test is positive, a confirmatory western blot, the gold standard, is performed. The window period for HIV antibody tests to become positive is three months, but symptomatic patients may have positive antibody tests three weeks after the onset of clinical signs and symptoms.

HIV may be detected earlier with HIV antigen tests. These tests are costly and specialised, usually requiring a reference laboratory. Direct viral detection should be undertaken only if clinically indicated. Viral protein tests such as the p24 antigen may become positive within a few days of symptoms, however this will be absent after two weeks. Detection of viral nucleic acid can be qualitative, PCR for HIV DNA (proviral DNA testing), or quantitative, HIV RNA (viral load). These tests may become positive within days and will remain positive as the antibody develops. For immediate diagnosis, qualitative proviral DNA is recommended. Quantitative HIV RNA testing is not generally recommended as it has a 3% false positive rate in the acute setting.[11]

Human papillomavirus

Anogenital human papillomaviruses are sexually transmitted and extremely common, with up to 75% of sexually active individuals having evidence of current or past infection.[12] Patients presenting with genital warts may have concurrent sexually transmitted infections, and appropriate screening is recommended.

While most infections are subclinical and transient, others may cause a spectrum of disease from genital warts to cervical cancer. Although cervical cancer is a rare outcome of human papillomavirus infection, over 99.7% of cervical cancers are positive for human papillomavirus DNA. Cervical screening programs and guidelines capture many cases of cervical change related to high-risk human papillomavirus types, however the diagnosis of genital warts remains largely clinical.[13]

Conclusion

Accurate and appropriate screening for sexually transmitted infections is essential to prevent significant individual morbidity and mortality and is highly important for public health. As well as the diagnosis and management of each individual, opportunistic testing for other infections, safe sex advice, education and contact tracing of partners is often required.

References

1. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia. 2006 annual surveillance report. Sydney: National centre in HIV epidemiology and clinical research; 2006.
2. Gaydos CA, Howell MR, Pare B, Clark KL, Ellis DA, Hendrix RM, et al. Chlamydia trachomatis infections in female military recruits. N Engl J Med 1998;339:739-44.

3. Cook RL, Hutchison SL, Ostergaard L, Braithwaite RS, Ness RB. Systematic review: noninvasive testing for Chlamydia trachomatis and Neisseria gonorrhoeae. Ann Intern Med 2005;142:914-25.
4. Carder C, Robinson AJ, Broughton C, Stephenson JM, Ridgway GL. Evaluation of self-taken samples for the presence of genital Chlamydia trachomatis infection in women using the ligase chain reaction assay. Int J STD AIDS 1999;10:776-9.
5. Scoular A, Gillespie G, Carman WF. Polymerase chain reaction for diagnosis of genital herpes in a genitourinary medicine clinic. Sex Transm Infect 2002;78:21-5.
6. Ramaswamy M, McDonald C, Smith M, Thomas D, Maxwell S, Tenant-Flowers M, et al. Diagnosis of genital herpes by real time PCR in routine clinical practice. Sex Transm Infect 2004;80:406-10.
7. Strick L, Wald A. Type specific testing for herpes simplex virus. Expert Rev Mol Diagn 2004;4:443-53.
8. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia. 2005 annual surveillance report. Sydney: National centre in HIV epidemiology and clinical research; 2005.
9. Peeling RW, Ye H. Diagnostic tools for preventing and managing maternal and congenital syphilis: an overview. Bull World Health Organ 2004;82:439-46.
10. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. MMWR 2002;51:RR-6.
11. HIV/Viral hepatitis: a guide for primary care. Sydney: Australasian Society for HIV Medicine; 2002. p. 30-6.
12. Koutsky L. Epidemiology of genital human papillomavirus infection. Am J Med 1997;102(Suppl 5):3-8.
13. Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities. Canberra: National Health and Medical Research Council; 2005.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 27)

1. A negative viral culture for herpes simplex does not exclude infection.
2. Up to 80% of women infected with chlamydia are asymptomatic.

Dental notes

Prepared by Dr M McCullough of the Australian Dental Association

Testing for sexually transmitted infections

Dentists may not realise that there is an increase in the proportion of cases of genital herpes that are caused by herpes simplex virus type 1. In developed countries there is an increase in the proportion of adults who have not been exposed to herpes simplex virus type 1 during childhood but who contract it genitally in adulthood. The recurrence rate of genital herpes due to type 1 is apparently less frequent than with type 2. Conversely, there are several reports of primary herpetic gingivostomatitis and up to 4% of recurrent herpes labialis being caused by herpes simplex virus type 2. Dentists treating these patients should be aware of this developing trend and the availability of laboratory tests to aid them in their diagnosis.

Tests for sexually transmitted diseases have shortcomings such as the window period required before the test becomes positive. This is particularly important for dentists or their staff who sustain a needle-stick injury.

Further reading

Lafferty WE. The changing epidemiology of HSV-1 and HSV-2 and implications for serological testing. Herpes 2002;9:51-5.

Olin L, Wald A. Case report: symptomatic oral herpes simplex virus type 2 and asymptomatic genital shedding. Herpes 2006;13:25-6.

Lowhagen GB, Tunback P, Bergstrom T. Proportion of herpes simplex virus (HSV) type 1 and type 2 among genital and extragenital HSV isolates. Acta Derm Venereol 2002;82:118-20.

Starter packs: a good start to therapy?

Marea P Patounas, Team Leader, Medicines Contact Centre, and Treasure M McGuire, Assistant Director of Pharmacy, Mater Misericordiae Health Services, Brisbane

Summary

Samples of drugs are often given to doctors by pharmaceutical representatives as part of a marketing strategy. Despite the well described advantages of drug samples, little has been published on the potential adverse outcomes. A series of consumer calls to the Adverse Medicine Events Line has highlighted concerns regarding the quality use of medicines associated with drug samples. The most commonly reported problems were drug samples being supplied to patients with inadequate information regarding dosage, administration, storage and possible adverse effects. In addition, some patients were given excessive quantities of a drug. To reduce such adverse outcomes, the drug industry, health professionals and consumers should be aware of the potential problems associated with starter packs.

Key words: Adverse Medicine Events Line, consumer information, drug industry.

(Aust Prescr 2007;30:14–16)

Introduction

Starter packs are samples of drugs given to doctors by pharmaceutical representatives, often as part of a marketing strategy. Medicines Australia's Code of Conduct states that starter packs are '… a quantity of a product supplied without cost to medical practitioners, dentists and hospital pharmacists'.[1]

The pros and cons of starter packs

There are both advantages and disadvantages in the provision of starter packs. From a manufacturer's perspective, starter packs provide an avenue to introduce new or unique products to the marketplace. Evidence suggests that drug samples influence prescribing behaviour and increase prescribing of a particular product.[2,3,4,5] Advantages for doctors include being able to assess the efficacy or tolerability of new treatments and to provide immediate treatment such as antibiotics after hours. This is especially beneficial in remote or rural populations. Likewise, patients can try a new drug before having to pay for a prescription and may be able to access drugs that are not yet available on the Pharmaceutical Benefits Scheme (PBS).

These advantages must be weighed against significant, but less well described, disadvantages. These include unregulated supply and the potential for:

- use of expensive medicines when effective and less expensive alternatives are available[4,6]
- increased demand for drugs not listed on the PBS
- issue of expired or poorly stored stock[7]
- inability to track or recall the product[7]
- medicine issued without a label or accompanying consumer medicines information.[8]

Samples are big business. Marketing expenditure on drug samples by American pharmaceutical companies has increased annually since 1996, with a total estimated allocation of US$10.5 billion in 2001.[9] Yet a recent literature review identified only 23 papers that had studied the impact of sampling in any capacity. The primary focus of these studies was the influence of drug samples on prescribing behaviour. Very little has been published on the potential adverse outcomes associated with samples.[10]

Consumer calls to the Adverse Medicine Events Line

The Adverse Medicine Events Line is a national consumer hotline for reporting 'when things go wrong with medicines'. This two-year project, funded by the Australian Council for Safety and Quality in Health Care and operated by Mater Pharmacy Services, identified a series of calls from consumers where provision of starter packs by doctors resulted in either poor quality use of medicines or an adverse outcome. The motivation for these consumer calls was primarily inadequate drug information. None of the samples had been labelled, none was accompanied by consumer medicines information or simple written instructions regarding dosage, administration, indication, storage, possible interactions or adverse effects. The nature of these events and the related quality use of medicine problems are described in Table 1.

> Lack of information accompanying starter packs can cause medicine misadventure

Table 1

Patient reports of problems involving drug samples given without labelling or written information

Case	Problems
1. A 78-year-old male was given a rofecoxib sample (25 mg/day). A celecoxib prescription (200 mg/day) was given at the next visit. On the third visit, the patient took an empty starter pack of rofecoxib and asked for a refill.	Lack of documentation led to the doctor being unaware of the patient using both COX-2 inhibitors for one month. Patient was not aware that both medicines were for osteoarthritis.
2. A 75-year-old female was given a rofecoxib sample for osteoarthritis. She had no recollection of dosage or administration with regard to food.	Anxious patient had failed to initiate the starter pack. A previous reaction to an unrelated drug had heightened her anxiety.
3. A 66-year-old male was given pravastatin samples. No information was provided on dosage or administration with regard to food.	Patient did not commence medicine because of lack of counselling. He could not recall being given any information.
4. A 50-year-old female was given quetiapine samples. She rang to clarify the indication for the new medicine. She thought it was for pain relief since her consultation was for pain and her previous medicine was celecoxib.	Patient was unaware that she had been given an antipsychotic medicine and intended to commence quetiapine 'as required'.
5. A 47-year-old female rang because she had forgotten the dose of her new medicine. She had been given one month's supply of meloxicam samples at two doses (7.5 mg and 15 mg) for osteoarthritis.	One week treatment delay due to patient's concern with regard to lack of directions from the doctor and lack of medicines information or label.
6. A 53-year-old female was given a sample of 10 indapamide tablets.	Patient was unsure if she could drink alcohol with the new medicine.
7. A 32-year-old female was given multiple samples of fluoxetine (60 mg/day), clonazepam (4 mg/day) and quetiapine (200 mg/day).	Patient took the drugs for three weeks concurrently, before questioning how best to take them and what the potential adverse effects were.
8. A 50-year-old female was given one month's supply of fluoxetine samples for premenstrual tension.	Patient experienced insomnia, nausea, diarrhoea and palpitations and was unaware that these were probably drug-induced.
9. A 63-year-old male was given samples of imiquimod cream for solar keratosis.	Patient experienced severe erythematous lesions 48 hours later. He was concerned that the lack of consumer medicines information delayed him linking the symptoms with the new medicine.
10. A 48-year-old female was given a few glyceryl trinitrate tablets in a clear plastic specimen container after hospital discharge for a suspected heart attack. She was told to swallow half a tablet with water for chest pain.	Possible loss of drug efficacy due to incorrect information about its administration and storage.
11. A 28-year-old male was given four fluvoxamine starter packs to 'take the edge off'.	Patient did not take the drug due to inadequate medicines information. Large quantities of starter packs provided.
12. A 39-year-old male was given 80 risperidone tablets (2 mg) as samples.	Dose of half tablet daily equated to 160 days supply.
13. An 89-year-old female was given esomeprazole 40 mg samples to take twice daily. Written medicines information she obtained from another source gave different instructions (40 mg daily, reducing to 20 mg daily after one month). She was confused about correct dosing.	Patient did not want to start medicine until correct dose was clarified.

This series of cases shows that lack of information accompanying starter packs can cause medicine misadventure, specifically:

- increased patient anxiety
- treatment delay
- unintended doubling-up of similar medicines
- inadvertent use of two strengths of the same medicine
- inappropriate use due to patient confusion.

In addition, this case series highlighted the fact that some patients were being given excessive quantities of a drug. With starter packs, there is also an increased potential for medication error when the same health professional prescribes, dispenses and possibly administers the drug without any checks on the process.

Regulation of starter packs

The provision of starter packs by primary health carers requires that medicines be appropriately labelled and accompanied by consumer medicines information or equivalent. Failure to label starter packs contravenes some state and territory legislation. A legislative review[11] led to agreement that labelling of prescription starter packs will be regulated.[1] The feasibility of this remains to be determined.

Conclusion

To minimise medicinal misadventure, the drug industry, health professionals and consumers need to be aware of the potential consequences for the quality use of medicines when starter packs are provided.

References

1. Medicines Australia Code of Conduct. 14th ed. Canberra: Medicines Australia; 2003. http://www.medicinesaustralia.com.au/pages/images/Product%20Starter%20Packs.pdf [cited 2007 Jan 15]
2. Adair RF, Holmgren LR. Do drug samples influence resident prescribing behavior? A randomized trial. Am J Med 2005;118:881-4.
3. Gonul FF, Carter F, Petrova E, Srinivasan K. Promotion of prescription drugs and its impact on physicians' choice behavior. J Marketing 2001;65:79-90.
4. Morelli D, Koenigsberg MR. Sample medication dispensing in a residency practice. J Fam Pract 1992;34:42-8.
5. Roughead EE, Harvey KJ, Gilbert AL. Commercial detailing techniques used by pharmaceutical representatives to influence prescribing. Aust N Z J Med 1998;28:306-10.
6. Chew LD, O'Young TS, Hazlet TK, Bradley KA, Maynard C, Lessler DS. A physician survey of the effect of drug sample availability on physicians' behavior. J Gen Intern Med 2000;15:478-83.
7. Backer EL, Lebsack JA, Van Tonder RJ, Crabtree BF. The value of pharmaceutical representative visits and medication samples in community-based family practices. J Fam Pract 2000;49:811-6.
8. Hall KB, Tett SE, Nissen LM. Perceptions of the influence of prescription medicine samples on prescribing by family physicians. Med Care 2006;44:383-7.
9. Blankenhorn K, Lipson D. Business watch – 2001 in review. Med Mark Media 2002;37:46-62.
10. Groves KE, Sketris I, Tett SE. Prescription drug samples – does this marketing strategy counteract policies for quality use of medicines? J Clin Pharm Ther 2003;28:259-71.
11. Galbally R. National competition review of drugs, poisons and controlled substances legislation. Final report Part A. Canberra: Therapeutic Goods Administration; 2001. http://www.tga.gov.au/docs/html/rdpdfr.htm [cited 2007 Jan 15]

Conflict of interest: none declared

Electronically tested

Australian Prescriber was one of the first medical journals in the world to make its full text freely available on the internet. Many thousands of people visit the website (www.australianprescriber.com).

A survey of visitors to the website has confirmed that the information is useful to health professionals and the public. More than 96% said the information in *Australian Prescriber* was appropriate for their needs. The 'New drugs' section was particularly well regarded with 92% of respondents finding the commentaries useful.

Among the health professionals, 78% said that their attitudes had been influenced by *Australian Prescriber* and a similar number said it had helped them make therapeutic choices.

People welcomed the free access to the website and said it was easy to find what they were looking for. Some people prefer the search function, while others use the electronic index.

The editorial independence of *Australian Prescriber* is important. More than 95% of participants identified the website as a useful resource for independent information on drugs and therapeutics.

Many health professionals still prefer to read their drug information on paper. To assess their opinions, the hard copy of the journal is currently being evaluated in another survey. The results of these surveys will be used to continue the development of *Australian Prescriber.*

Prescribing in renal disease

Randall Faull, Senior Consultant Nephrologist, Royal Adelaide Hospital, and Associate Professor of Medicine, University of Adelaide, and Lisa Lee, Renal Pharmacist, Royal Adelaide Hospital

Summary

The appropriate prescribing of many drugs depends on knowledge of the patient's total renal function, which is proportional to their body mass. The Cockcroft-Gault method of calculating creatinine clearance takes into account the patient's weight. The recently introduced estimated glomerular filtration rate, which is now routinely reported with biochemistry test results, is useful for screening for renal disease, but is unsuitable for calculating doses as it does not take into account the patient's size. Both are unreliable at extremes of weight. The list of medications that need dosage adjustment according to renal function is long, but includes commonly prescribed drugs such as antivirals, hypoglycaemic drugs (metformin, sulfonylureas, insulin), spironolactone and allopurinol.

Key words: creatinine clearance, drug therapy, glomerular filtration rate, kidney disease.

(Aust Prescr 2007;30:17–20)

Introduction

The clearance of many drugs and their metabolites depends on adequate renal function. Renal clearance is especially important for some drugs where the gap between efficacy and toxicity is narrow. Doses of these drugs need careful adjustment if they are prescribed for patients with impaired renal function. Some drugs also have the potential to cause renal toxicity. This is particularly likely to occur in patients who already have some degree of renal impairment, although other factors can increase the risk.

Estimating renal function

An accurate estimation of renal function, or glomerular filtration rate (GFR), requires sophisticated techniques that are unsuitable for routine or repeated use. In practice, the serum creatinine concentration is used for day-to-day assessment of renal function. It has limitations, but it remains a robust and practical parameter for most clinical situations.

Serum creatinine

The serum creatinine concentration has important limitations when used for estimating renal function.

1. There is an inverse relationship between serum creatinine and renal function. A doubling of serum creatinine represents a halving of GFR. A person's serum creatinine can rise from 60 to 120 micromol/L and so still be in the normal range (typically 50 to 120 micromol/L), yet the renal function has deteriorated dramatically.
2. Renal function declines steadily with age in adults, but this is not reflected in the serum creatinine, which remains steady or may only increase slightly with age (in the absence of overt renal disease, where it may rise more obviously). An 80-year-old will have approximately half of the renal function of a 20-year-old, despite both having the same serum creatinine concentration.
3. Renal function has an approximately linear relationship with lean body mass. In the presence of the same serum creatinine, a 120 kg person will have twice the renal function of a 60 kg person because they have bigger kidneys.
4. Women have a lower muscle mass than men of equivalent weight and age. A woman's serum creatinine represents approximately 0.85 of the renal function of a man with the same serum creatinine.

These limitations are particularly relevant and must be addressed when attempting to measure renal function for the purpose of calculating drug doses.

Creatinine clearance

The serum creatinine concentration represents a balance between its production in the body (from muscle) and its excretion by the kidneys. From this can be derived an estimation of the creatinine clearance by the kidneys, in millilitres per minute (mL/min) or millilitres per second (mL/sec). This is the notional volume of serum that is cleared of creatinine in those times. The creatinine clearance is the 'poor man's' equivalent of the formal measurements of GFR, but for most clinical purposes is an adequate measurement of renal function.

Direct determination of creatinine clearance requires simultaneous measurement of the concentration of creatinine in the serum and in a timed urine specimen (usually 24 hours).

Timed urine collections are labour-intensive and notoriously unreliable. As a result many equations for estimating creatinine clearance have been derived that only need measurement of serum creatinine. The most widely recognised of these is the Cockcroft-Gault formula, which relies on patient age, weight, gender and serum creatinine.

$$\text{creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{lean body weight (kg)} \ (\times 0.85 \text{ for females})}{\text{serum creatinine (micromol/L)} \times 0.815}$$

The accuracy of this formula for estimating creatinine clearance is equivalent to that from a timed urine collection, so there is no good reason for using a 24-hour collection. Manufacturers' renal dosing recommendations for medications are based on Cockcroft-Gault estimates of renal function, so this formula is also recommended when estimating creatinine clearance for the purpose of calculating drug doses that vary according to renal function.

Clinicians should be aware of some important limitations of the Cockcroft-Gault estimation of renal function. It is:

- not validated in some populations
- unreliable in extremes of body size (that is, in severe malnutrition or obesity)
- imprecise and unreliable for rapidly changing renal function (for example intensive care, acute renal failure).

What is estimated GFR?

Australian pathology laboratories have started routinely including an estimated GFR (eGFR) in all biochemistry reports that include serum creatinine. The reporting of serum creatinine has also been standardised to be in micromol/L (so the actual number is 1000 times that when reported as mmol/L).

The formula used to calculate eGFR was derived as part of a large study of the effect of dietary protein restriction on the progression of renal failure. (This was the Modification of Diet in Renal Disease study, hence the MDRD formula.[1]) The advantage of this formula is that it does not require knowledge of the patient's height or weight as the eGFR is calculated using serum creatinine, age and gender.

It is crucial that clinicians realise that the eGFR is not estimating the patient's **actual** GFR, but is estimating an **adjusted** GFR – which assumes that the patient is of average body size. This explains how the number can be calculated without any knowledge of the patient's actual size. Average body size equates to a body surface area of 1.73 m^2, and so the eGFR is reported as mL/min/1.73 m^2. In practice, this means that while one person who is twice the size of another, of the same age, gender and serum creatinine, will have twice the actual GFR, the eGFR for both will be the same.

The eGFR is primarily intended to be a screening tool for renal disease in the community, in association with other signs of renal disease such as urinary abnormalities and hypertension. It has similar limitations as the Cockcroft-Gault equation[2], including that it is not validated in Aboriginal and Torres Strait Islander people.

eGFR is not preferred for calculating drug doses

Drug dosing should be based on the patient's actual GFR and not an adjusted GFR. While recognising that the Cockcroft-Gault equation has limitations, it does at least take into account body size when estimating GFR, whereas the eGFR does not. Using the eGFR to calculate dosages would lead to overdosing of small patients and underdosing of large patients. Overdosing increases the risk of toxicity of drugs with a narrow therapeutic range, while underdosing reduces efficacy. The MDRD formula used to calculate eGFR can be manipulated to adjust for a patient's body surface area (if the patient's height and weight are known). A recently published observational analysis suggests wide variation between the formulas.[3] However, as yet it is unknown whether the MDRD formula is superior to Cockcroft-Gault for calculating drug doses.

Prescribing for dialysis patients

For the purpose of drug prescribing, patients on dialysis (haemodialysis or peritoneal dialysis) should be considered to have a creatinine clearance/GFR of less than 10 mL/min. Certain drugs are actively removed from the circulation during dialysis, and this needs to be considered when deciding on the timing of administration as well as the dosage. Factors that may reduce the extent to which a drug is dialysed include large molecular size of the drug, high protein binding, large volume of distribution and high lipid solubility. In addition to these parameters, the type of dialyser membrane may also affect drug clearance, as will blood and dialysate flow rates. If a drug is known to be dialysed, patients having haemodialysis may be instructed to take the drug after the dialysis session.

Dose alteration in renal impairment

Once renal impairment has been detected and creatinine clearance estimated, the need for dose alteration of renally cleared drugs must be determined. Generally dose adjustment is needed when the creatinine clearance is below 60 mL/min. People who have been taking a drug for many years may need a dose adjustment as they age. Adjustments can be achieved by a reduction in dose, or an extension of the dosing interval, or both. Knowledge of appropriate dosage adjustment is important to ensure the drug is effective and that accumulation and further kidney damage is avoided. There are various references to consult in Australia including the approved product information and the Australian Medicines Handbook. International references include the Renal Drug Handbook and Drug prescribing in renal failure.[4] Table 1 lists some of the commonly prescribed drugs that require dose alteration in renal impairment.

Table 1

Commonly prescribed drugs that require dose adjustment in renal impairment

Class	Examples
Antibiotics/antifungals	aminoglycosides (e.g. gentamicin), vancomycin, ceftazidime, cefepime, cephazolin, ciprofloxacin, fluconazole, piperacillin, carbapenems (e.g. meropenem), sulfamethoxazole
Antivirals	famciclovir, aciclovir, valaciclovir, valganciclovir, ganciclovir
Anticoagulants	low molecular weight heparins (e.g. enoxaparin)
Cardiac drugs	digoxin, sotalol, atenolol
Diuretics	If creatinine clearance is less than 30 mL/min: – avoid potassium-sparing diuretics due to risk of hyperkalaemia – thiazide diuretics have limited efficacy
Opioids	morphine, codeine, pethidine (due to risk of accumulation of active or toxic metabolites)
Psychotropics/anticonvulsants	amisulpride, gabapentin, lithium, levetiracetam, topiramate, vigabatrin
Hypoglycaemic drugs	metformin, glibenclamide, glimepiride, insulin
Drugs for gout	allopurinol, colchicine
Others	lamivudine, methotrexate, penicillamine

Antiviral drugs

Renal clearance is the major route of elimination for many antivirals, including those used for treating herpes simplex, herpes zoster and cytomegalovirus infections (such as aciclovir, famciclovir, valganciclovir and ganciclovir). In patients with renal impairment, renal clearance of these drugs is reduced and the elimination half-life is significantly prolonged. As a result, normal doses will accumulate and may lead to neurological signs such as dizziness, confusion, hallucinations, somnolence and convulsions, as well as more rarely, tremor, ataxia, dysarthria, seizures and encephalopathy. These adverse effects are dose-related and reversible on stopping the drug. They are especially problematic in elderly patients or patients taking other neurotoxic medications. If essential, it may be possible to reintroduce the drug at a lower dose.

Hypoglycaemic drugs

Renal function needs to be considered when prescribing three of the major groups of hypoglycaemic drugs – biguanides (metformin), sulfonylureas and insulin.

Metformin

Metformin has been associated with rare but potentially fatal lactic acidosis. This is thought to result from accumulation of metformin when renal impairment reduces renal clearance. The risk of lactic acidosis is potentially enhanced in conditions where tissue hypoperfusion and hypoxaemia are a problem (for example in cardiac or respiratory failure, or following a myocardial infarction), with increasing age and with higher doses of metformin (generally above 2 g/day). The common adverse effect of nausea is also dose-related and more likely to occur in the presence of renal impairment.

No definitive guidelines exist on reducing the dose of metformin in renal impairment, and lactic acidosis has been reported with doses as low as 500 mg/day.[5] Ideally, metformin should be avoided in patients with a creatinine clearance of less than 30 mL/min and should be used with caution, at a reduced maximum daily dose of 1 g, in patients with a creatinine clearance of 30–60 mL/min. For those patients with a creatinine clearance of 60–90 mL/min, the recommended maximum daily dose is 2 g. Metformin should also be withheld temporarily in patients undergoing surgery, suffering from dehydration, trauma or serious infections, or undergoing procedures likely to affect renal function (for example, contrast studies).

Sulfonylureas

Long-acting sulfonylureas such as glibenclamide and glimepiride are associated with a higher risk of hypoglycaemia in comparison to short-acting sulfonylureas. In patients with renal impairment and/or advanced age, the risk of hypoglycaemia is increased. These drugs are inherently long-acting as well as having metabolites that are excreted renally. Shorter-acting sulfonylureas such as gliclazide or glipizide are a safer choice in patients with renal impairment. They should be started at a low dose and increased gradually.

Insulin

Renal elimination accounts for up to half of the clearance of insulin, so as renal failure progresses, less insulin is excreted, so smaller doses are required. Patients with diabetes and renal impairment can also have unrecognised gastroparesis which may disconnect absorption of ingested food from the time of the insulin injection. This can lead to erratic glucose regulation that may be complicated by frequent episodes of hypoglycaemia.

Spironolactone

Since the publication of the Randomized Aldactone Evaluation Study[6] in 1999, the use of spironolactone, in conjunction with an angiotensin-converting enzyme (ACE) inhibitor, has increased. In this trial, the addition of spironolactone significantly improved morbidity and mortality in patients with advanced heart failure. However, almost immediately following this publication came reports of an increase in hospital admissions (and subsequent deaths) related to hyperkalaemia.[7]

Hyperkalaemia is a particular problem for patients with renal impairment and its risk is heightened by advanced age, doses of spironolactone exceeding 25 mg/day, dehydration, diabetes mellitus, and simultaneous treatment with non-steroidal anti-inflammatory drugs, ACE inhibitors or angiotensin receptor antagonists. Prescribers are urged to frequently monitor serum potassium, creatinine and urea when starting spironolactone for heart failure, and to consider avoiding its use in patients with a creatinine clearance of less than 30 mL/min.

Allopurinol

Allopurinol is used in the management of gout to lower serum and urinary uric acid concentrations. As allopurinol, and its active principal metabolite oxypurinol, are mainly excreted in the urine, they accumulate in patients with poor renal function so the dose should be reduced. The manufacturers recommend starting treatment with a maximum dose of 100 mg/day and increasing it only if the serum or urinary urate is not satisfactorily controlled.

Hypersensitivity reactions to allopurinol are characterised by fever, chills, leucopenia, eosinophilia, arthralgia, rash, pruritis, nausea and vomiting. The frequency of this reaction is thought to be increased in patients with renal impairment, and in those who are concomitantly taking allopurinol and a thiazide diuretic. Caution is advised when using this combination in renal impairment.

Conclusion

Adjusting the dose of renally cleared drugs is important when prescribing for patients with renal impairment. There are many drugs that require dose adjustment according to renal function. Estimation of creatinine clearance and hence renal function can be determined using the Cockcroft-Gault equation. The role of the MDRD equation (expressed as eGFR on biochemistry reporting) is currently as a screening tool for kidney disease.

References

1. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.
2. Mathew TH. The Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. Med J Aust 2005;183:138-41.
3. Wargo KA, Eiland EH 3rd, Hamm W, English TM, Phillippe HM. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. Ann Pharmacother 2006;40:1248-53.
4. Aronoff GR, Berns JS, Brier ME, Golper TA, Morrison G, Singer I, et al. Drug prescribing in renal failure: dosing guidelines for adults. 4th ed. Philadelphia: American College of Physicians–American Society of Internal Medicine; 1999.
5. Nisbet JC, Sturtevant JM, Prins JB. Metformin and serious adverse effects. Med J Aust 2004;180:53-4.
6. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17.
7. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543-51.

Further reading

Nankivell BJ. Creatinine clearance and the assessment of renal function. Aust Prescr 2001;24:15-7.

Johnson CA, Simmons WD. 2006 Dialysis of drugs. Wisconsin: Nephrology Pharmacy Associates; 2006. http://www.nephrologypharmacy.com/pub_dialysis.html [cited 2007 Jan]

Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function – measured and estimated glomerular filtration rate. N Engl J Med 2006;354:2473-83.

The Renal Drug Handbook. 2nd ed. Ashley C, Currie A, editors. Oxford: Radcliffe Medical Press; 2004.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 27)

3. Estimates of glomerular filtration rate are unreliable if the creatinine clearance is rapidly changing.
4. Renal impairment increases the risk of lactic acidosis in patients taking metformin.

Managing foot infections in patients with diabetes

Kerry Bowen, Diabetes Education Centre, Royal Newcastle Hospital, Newcastle, New South Wales

Summary

Foot infections are a significant cause of morbidity for patients with diabetes and if left untreated can lead to amputation. Patients need to be instructed to wash, dry and examine their feet daily and are encouraged to seek medical attention promptly if they see signs of foot infection or new ulcer formation. Empirical use of antibiotics will often be necessary while awaiting the results of bacteriological and imaging investigations. When in doubt about the severity of infection urgent referral to a surgeon or specialist foot service for a second opinion is advised. Hospitalisation for observation, parenteral antibiotic therapy and possible surgical intervention may also be necessary. Diabetic arthropathy needs to be considered when signs mimicking infection are present in the absence of ulceration. Osteomyelitis or plantar space infection should be excluded as complicating factors if there is not rapid clinical improvement after starting antibiotic therapy.

Key words: antibiotics, ulceration.

(Aust Prescr 2007;30:21–4)

Introduction

Many people with long-standing diabetes mellitus are predisposed to foot injury, ulceration and infection because they have poor glycaemic control, peripheral vascular disease and/or peripheral neuropathy. For these patients even a trivial foot injury may rapidly lead to ulceration and infection. Everyone with diabetes should be advised to wash, dry and examine their feet daily and avoid excessive heat and cold, as well as trauma. Patients should seek medical attention promptly if they see signs of foot infection or new ulcer formation such as broken skin, changes in skin colour, bruising or swelling. If left untreated, diabetic ulcers can lead to amputation.

How ulceration occurs

When peripheral neuropathy predominates, the intrinsic muscles of the foot may waste, with clawing of the phalanges a result. This can lead to malposition of the fat pads that protect the plantar surfaces of the metatarsophalangeal joints causing adverse shearing and direct pressure on the tissue between the plantar surface and the now unprotected bony joints. These forces generate a reactive tissue oedema which breaks through to the skin surface to form an ulcer. When neuropathy is present, these ulcers may be painless. They may sometimes be quite large by the time they are detected if the patient is not carrying out daily foot inspection. Many of these shear-induced lesions will become infected, some even before surface ulceration presents itself. The presence of callus is often a marker for future ulceration. Callus should be pared back regularly by a suitably-trained podiatrist, nurse or medical practitioner.[1]

When ischaemia predominates, ulceration may often be initiated by ill-fitting footwear. Interdigital vessel occlusion may lead to ulceration and gangrene of a single digit. Obstruction more proximally may lead to wider gangrenous changes in the forefoot. On occasion this may be complicated by secondary bacterial infection.

Microbiology

In diabetes, infections that threaten the foot are usually caused by bacteria. Infected ulcers commonly have staphylococcal, streptococcal or facultative anaerobes such as *Bacteroides* species or faecal coliforms present.[1,2] Single or multiple pathogens may be identified. Enteric pathogens can coexist with *Streptococcus* or *Staphylococcus* species in some instances. In humid climates fungal infections involving the web spaces of the foot may predispose an at-risk individual to secondary bacterial invasion.

Assessment

There are numerous algorithms and clinical pathways available to guide management of diabetic foot ulcers.[2] A practical approach is to assess the ulcerated area for signs of active infection such as raised surface temperature, redness of the surrounding skin, necrosis, localised oedema and odour. Mapping of temperature changes over the foot can be carried out using an infra-red thermometer.

The presence of peripheral vascular disease can usually be determined quickly using observation and palpation. The capillary refill time is not considered to be sensitive or reliable enough to allow differentiation between vascular, ischaemic

or neuroischaemic ulcers. Measurement of the ankle-brachial index or assessment of the arterial pressure waveforms of the posterior tibial and dorsalis pedis arteries using hand-held Doppler may provide further useful information.[3]

If infection is evident or suspected, deep wound swabs or needle aspiration of the exudate should be taken for bacteriological analysis before starting antibiotic treatment. If an ulcer can be probed down to bone then osteomyelitis is likely to be present. Surgical biopsy of the affected area may be useful for collection of subsequent specimens for microbiological examination if deterioration occurs after empirical antibiotic therapy is commenced.

It is usual to take a wound swab even if a patient is not exhibiting any clinical signs of infection in an ulcer which is clean, does not probe to bone, is not producing large amounts of exudate, and has granulation tissue. The swab should be taken as localised and as deep as possible. If a pathogen or commensal is present on a wound swab with no clinical signs of infection then a topical bacteriocidal dressing, such as one containing nanocrystalline silver, may help clear the wound of both types of bacteria. A positive culture result may also help direct antibiotic treatment if overt infection subsequently develops.

The estimated depth and diameter of the wound should be recorded at each visit – a tracing around the edge of the wound onto a sterile transparent double-layered plasticised dressing performed using a no-touch technique provides a useful record.

Additional tests that need to be performed on diabetic patients with foot infections include full blood count, erythrocyte sedimentation rate, electrolytes, HbA1c, plus renal and liver function tests. Weekly measurement of the C-reactive protein titre during treatment of a foot infection may help determine progress.

Imaging

When clinical signs of inflammation are evident, lateral, antero-posterior and oblique X-ray views of both feet should be performed with the X-ray request specifying the anatomical location of the ulcer and mentioning the possibility of underlying osteomyelitis, diabetic arthropathy and gas formation. Bone infection usually has to be present for several weeks before it is detectable on plain X-ray films, so serial X-rays at one to four weekly intervals may be necessary if clinical infection fails to resolve and the initial X-ray was clear.

If infection of bone or soft tissues is suspected it is prudent to consult with a nuclear medicine physician before a radioisotope scan is ordered as it may be of limited usefulness. Magnetic resonance imaging (MRI) of the affected area may be useful for differentiating infectious from non-infectious inflammatory conditions.[2] However, if MRI facilities are not available a surgeon should be able to make a decision on whether to explore and debride an ulcer based on clinical examination.

Consult with a nuclear medicine physician before a radioisotope scan is ordered as it may be of limited usefulness

Differential diagnoses

Diabetic osteoarthropathy (Charcot's arthropathy) can often mimic a cellulitic process of the mid-foot or forefoot. Although a non-infective process in its pure form, it may sometimes present with sudden onset of oedema, redness, increased heat and sometimes pain. Elevation of the foot overnight can often help in making the diagnosis if X-ray signs are absent, as any oedema will often subside in the absence of infection. However, radionucleotide scanning must be performed if diabetic arthropathy is suspected, as increased isotope uptake in affected joints may be an early finding with this condition. Again, it is best to consult the nuclear medicine physician beforehand to ensure that the appropriate isotopes are used. MRI can also be used if available, as it may detect the bone oedema that can accompany diabetic arthropathy. Early diagnosis is important as appropriate treatment will prevent progressive foot deformity and subsequent disability.

Gout needs to be considered as a differential diagnosis when ulceration is not present and the diabetic patient presents with a swollen, hot, red and painful toe. The possibility of a fracture must not be forgotten. In all such cases, X-ray is mandatory as a baseline and follow-up examination because in patients with diabetes, osteomyelitis may occasionally present as the so-called 'sausage toe' – a hot and swollen toe – with or without accompanying ulceration of the phalanx.

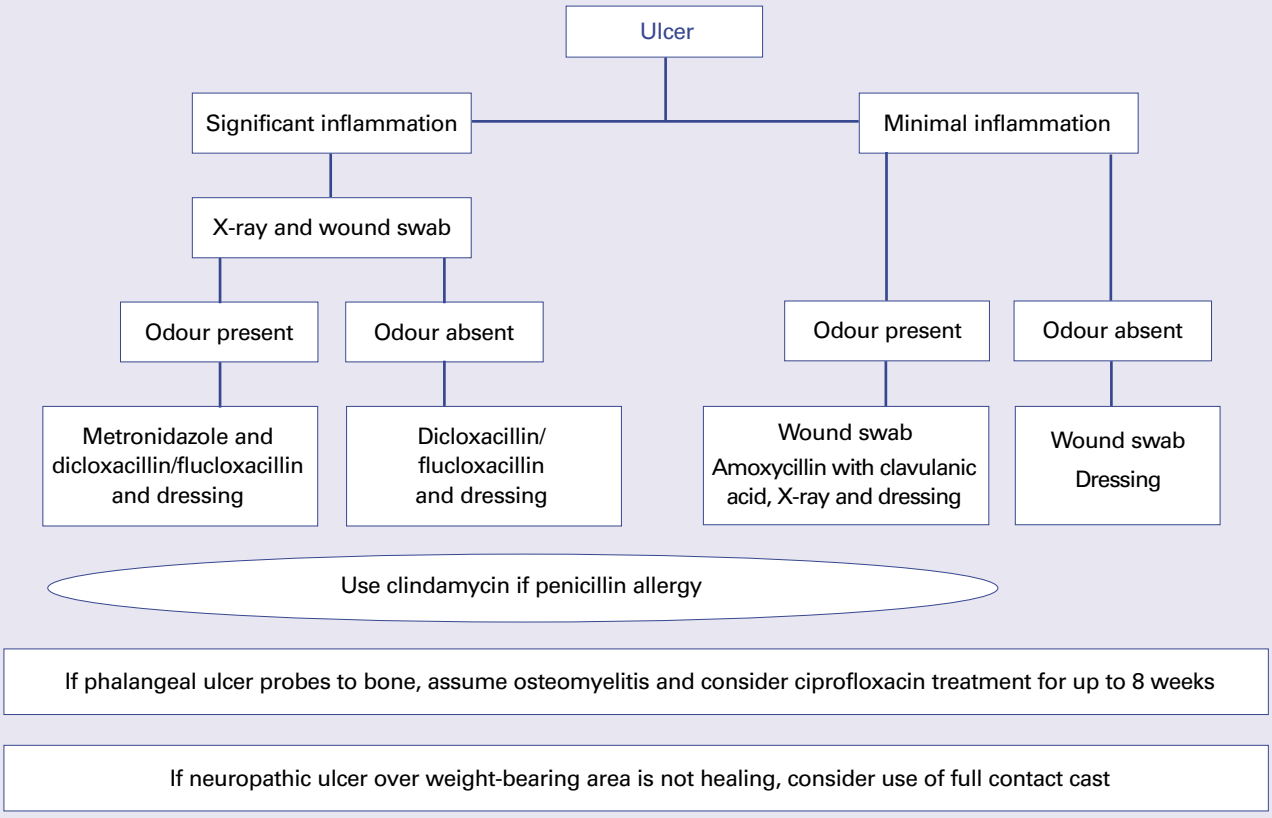
Ischaemic foot ulcers may be painful and sometimes the surrounding tissues may appear erythematous. A thorough clinical examination with a positive Buerger's test suggests that ischaemia, not infection, is likely to predominate. When in doubt, antibiotics should be used empirically and the patient brought back within two or three days for review of progress.

Antimicrobial therapy (see Fig. 1)

The initial choice of outpatient-administered antibiotic therapy will be empirical.[1] Where minimal inflammation is evident and the ulcer is both shallow and odourless a suitable wound dressing should suffice. If the ulcer is also malodorous an oral antibiotic can be trialled. Amoxycillin with clavulanic acid is a reasonable first choice. Dicloxacillin or flucloxacillin should be used when the clinical findings of localised erythema, swelling and heat without significant accompanying odour suggest that staphylococcal or streptococcal infection is likely. Clindamycin can be used in place of a penicillin if the patient has a history of penicillin hypersensitivity. Metronidazole combined with either dicloxacillin or flucloxacillin provides a reasonable oral antibiotic combination to use in systemically well patients, where an

Fig. 1

Initial treatment guide for localised diabetic foot ulcers



inflamed wound or ulcer appears localised with no necrosis but is malodorous, implying that the infection may be caused by a faecal organism or *Bacteroides* species. Occasionally, superficial pseudomonas infection is present, sometimes evident as a greenish hue over the surface of the ulcer. Application of a dilute acetic acid solution will often destroy this.

Antibiotic treatment should be given for at least 7–14 days in infections that appear to be localised to a digit. In more severe cases other indicators, such as a drop in C-reactive protein from significantly elevated to near normal, or arrest of bone destruction as shown on sequential X-rays, may assist in determining the duration of antibiotic therapy.

If a phalangeal ulcer probes to bone, or if the diagnosis of osteomyelitis of the phalanx is made using radioisotope or X-ray evidence then resolution may sometimes be obtained with oral ciprofloxacin 500 mg twice a day for 6–8 weeks. Removal of any loose sequestrum readily accessible to sterile forceps may hasten wound closure.

Vancomycin and rifampicin are commonly used if there is bacteriological evidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in the wound and active involvement of the deep tissues is suspected.[2] For MRSA infections it is helpful to seek the advice of a microbiologist or infectious diseases physician before commencing treatment.

Interdigital fungal foot infections may generate a portal of entry for bacteria and so foot hygiene is important. Methylated spirits can be used to keep the interdigital spaces dry and free of fungal colonisation.

Dressings: broad principles

If the ulcer is dry use a moisturising dressing such as a gel and avoid thin film dressings. If the wound is moist use an absorptive dressing such as foam or alginate. If the ulcer is superficially infected use a dressing that incorporates a bacteriocidal agent such as nanocrystalline silver.

Other advice and follow-up

Regular outpatient review will be required several times in the first week or two of antibiotic treatment if there is any doubt in the clinician's mind about the severity of the infection or if there is concern that the patient may not be able to adhere to the recommended treatment regimen. Patients must not put their weight on ulcers in weight-bearing areas. The application of a total contact cast from forefoot to below the knee, which is reapplied every 1–2 weeks, is the best way to achieve total 'off-loading' when all else has failed. Avoid a cast if the patient has significant peripheral vascular disease.[1,3]

If pre-existing peripheral vascular disease is likely to hinder the healing process a vascular surgeon should assess the patient's suitability for a bypass or stenting procedure.

Conclusion

All foot infections in the diabetic patient need to be taken seriously. Small surface lesions may conceal significant deeper pathology requiring surgical intervention or aggressive antibiotic therapy. When in doubt about the severity of an infection, or if diabetic (Charcot's) arthropathy is suspected, seek an immediate second opinion from an orthopaedic surgeon or diabetes foot service. If this is not available then the patient should be admitted to hospital for observation and further investigations.

References

1. Jeffcoate WJ, Harding KG. Diabetic foot ulcers. Lancet 2003;361:1545-51. http://image.thelancet.com/extras/02art6190web.pdf [cited 2007 Jan 15]
2. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2004;39:885-910. http://www.journals.uchicago.edu/CID/journal/issues/v39n7/34365/34365.html [cited 2007 Jan 15]
3. Edmonds ME, Foster AV. Diabetic foot ulcers. BMJ 2006;332:407-10.

Further reading

Campbell LV, Graham AR, Kidd RM, Molloy HF, O'Rourke SR, Colagiuri S. The lower limb in people with diabetes. Position statement of the Australian Diabetes Society. Med J Aust 2000;173:369-72. http://www.mja.com.au/public/issues/173_07_021000/campbell/campbell.html [cited 2007 Jan 15]

National Institute for Health and Clinical Excellence. Type 2 diabetes – footcare: Algorithm. http://www.nice.org.uk/page.aspx?o=208094 [cited 2007 Jan 15]

http://www.diabetic-foot.com.au [cited 2007 Jan 15]

http://www.woundupdate.com [cited 2007 Jan 17]

http://www.emedicine.com/orthoped/topic387.htm [cited 2007 Jan 15]

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 27)

5. Infected diabetic ulcers may be painless.
6. Antibiotic treatment of a diabetic ulcer should not be started until the infecting organism is known.

Your questions to the PBAC

Taxanes

The listing of trastuzumab on the Pharmaceutical Benefits Scheme (PBS) in October 2006 was heralded with much fanfare. Along with this listing, changes to the prescribing requirements for taxanes also occurred. Both docetaxel and paclitaxel are now available on authority prescription for the treatment of HER2 positive early breast cancer in combination with trastuzumab. However, one group of patients will miss out on subsidised treatment. They are women with HER2 positive metastatic breast cancer who have not previously been treated with chemotherapy.

Patients with HER2 positive metastatic breast cancer can access trastuzumab under the Herceptin Access Program run through Medicare Australia. The prescribing restrictions for this program specify that the trastuzumab is to be used as a single drug or in combination with a taxane. Herein lies the problem. The current listing for taxanes on the PBS is 'advanced breast cancer after failure of prior therapy, which includes an anthracycline'. Patients with HER2 positive metastatic breast cancer who are chemotherapy naive cannot have the optimal therapy of trastuzumab in combination with a taxane, as the latter is not funded by the PBS.

Why were the taxanes made available for HER2 positive early breast cancer and not simply for all patients with HER2 positive breast cancer?

Jim Siderov
Senior Pharmacist
Cancer Services
Austin Health
Melbourne

PBAC response:

The Pharmaceutical Benefits Advisory Committee (PBAC) made its recommendation to subsidise taxanes for the treatment of HER2 positive early breast cancer in combination with trastuzumab because of evidence that this treatment combination met the requirements for PBS listing. The PBAC also recommended that the taxanes, in combination with an anthracycline and cyclophosphamide, be made available for adjuvant treatment for all patients with node positive breast

cancer. Again this recommendation was made on the basis of evidence which showed that this treatment was of acceptable efficacy, safety and cost-effectiveness.

To date, the PBAC has not been presented with evidence to show that the combination of a taxane and trastuzumab in chemotherapy naive patients with metastatic breast cancer meets the requirements for PBS listing. While it may seem reasonable to extend the listing for the taxanes for HER2 positive early breast cancer to include all HER2 positive breast cancer, the efficacy and cost-effectiveness is not necessarily the same in metastatic breast cancer as when the treatment is used in early breast cancer.

The continuing success of the PBS depends upon a rigorous evidence-based assessment of drugs for subsidy. These requirements apply in all cases and ensure consistency and fairness in the listing process.

Medicinal mishap

Cross-reactivity of penicillins and cephalosporins

Prepared by Winnie WY Tong, Basic Physician Trainee, Elizabeth A Anderson, Principal Drug Information Specialist, Department of Pharmacy, and Constance H Katelaris, Senior Consultant, Department of Clinical Immunology and Allergy, Westmead Hospital, Sydney

Case

A 73-year-old man collapsed at home. Ambulance officers noted impalpable blood pressure, shortness of breath and complaints of right-sided chest and epigastric pains.

The man had seen his family doctor earlier that day complaining of sore throat, cough and haemoptysis. He was prescribed cephalexin and had taken the first dose 10 minutes before collapsing. The man had a documented history of amoxycillin allergy with pruritis.

Oxygen and intravenous fluids were given and in the emergency department his blood pressure was 140/70. On examination he had a generalised erythematous rash that was pruritic. Wheeze and tongue swelling were absent and intra-abdominal pathology was excluded. A diagnosis of anaphylaxis to cephalexin was made. Hydrocortisone and antihistamines were given and he was admitted to hospital.

As he was taking propranolol it was ceased, as beta blockers can potentiate further anaphylactic reactions. He remained stable on oral antihistamines and was discharged after three days.

Comment

Penicillins and cephalosporins exhibit partial and incomplete cross-reactivity of up to 7% that may be related to the 'generation' of cephalosporin.[1] In clinical practice it is not uncommon for cephalosporins to be given to penicillin-allergic patients, particularly if the history of penicillin reaction was not life-threatening. However, reports of adverse outcomes, including fatalities, appear to be increasing. Over the last six months, the authors know of four cases from western Sydney including two deaths.

Reactions to beta-lactam antibiotics can be classified into immediate and non-immediate. Immediate reactions are IgE mediated and classically manifest as anaphylaxis, urticaria, angioedema, bronchospasm and allergic rhinoconjunctivitis. Non-immediate reactions such as maculopapular or morbilliform rashes are probably T-cell mediated. The most common clinical manifestation of both penicillin and cephalosporin allergy is skin reactions, occurring with a frequency of 1–3% of courses given.[1] In addition to anaphylaxis, less common but serious adverse reactions to cephalosporins include serum sickness-like reactions, acute interstitial nephritis and cytopenias.

While penicillin-induced anaphylaxis is rare (0.01–0.05% of courses), it may be fatal in 10% of cases.[2] It is difficult to obtain reliable data about the frequency of cephalosporin anaphylaxis, but published figures are 0.0001–0.1%.[1]

Whether a penicillin-allergic patient can safely take cephalosporins remains a difficult question to answer – many people labelled penicillin-allergic can actually take penicillin. Patients with a history of penicillin allergy are four times more likely to have a reaction to cephalosporins than patients without a penicillin allergy, especially if the patient is penicillin skin prick test positive.[2] It is not known if a history of anaphylaxis predicts a more serious allergic reaction. A history of mild reactions to penicillin, such as rashes, does not imply that a reaction to cephalosporins will not be life-threatening.

Side chain specific antibodies may be responsible for cephalosporin allergies rather than antibodies to the core beta-lactam ring.[1,3] This would explain the cross-reactivity between certain penicillins and cephalosporins which share similar side chains, for example, amoxycillin and cephalexin, aztreonam and ceftazidime, benzylpenicillin and cephalothin.

While the risk of a serious reaction to cephalosporins in patients with known penicillin allergy remains low, serious adverse reactions do occur, including fatalities. Before prescribing

cephalosporins it is prudent to take a careful history as to the nature of the penicillin allergy and the specific drug involved. It would be sensible to avoid prescribing drugs with the same or similar side chains, especially if an alternative non-beta-lactam antibiotic is available. If a cephalosporin is prescribed, the first dose should be taken in a monitored setting.

References

1. Kelkar PS, Li JT. Cephalosporin allergy. N Engl J Med 2001;345:804-9.
2. Lin RY. A perspective on penicillin allergy. Arch Intern Med 1992;152:930-7.
3. Baumgart KW, Baldo BA. Cephalosporin allergy [letter]. N Engl J Med 2002;346:380-1.

New drugs: transparency

Access to information about drugs is essential for the quality use of medicines. Since 2003 *Australian Prescriber* has therefore recorded details about the willingness of pharmaceutical companies to disclose the information that supported the Australian approval of their new products.[1] These details are published as the T(ransparency)-score at the end of each new drug comment in *Australian Prescriber*.

Table 1 shows the responses to requests for evaluation data between August 2005 and December 2006. The Editorial Executive Committee of *Australian Prescriber* is pleased to report that there has been an improvement since the previous report was published.[1] Most manufacturers now provide some information to assist in the preparation of the new drug comments. The Editorial Executive Committee hopes this trend to increased transparency continues.

Reference

1. Two-way transparency. Aust Prescr 2005;28:103.

Table1

Pharmaceutical company responses to requests for clinical evaluation data

Company	Drug
Manufacturer provided all requested information	
AstraZeneca	rosuvastatin
Ferring	quinagolide
Pfizer	eplerenone
Pfizer	sunitinib malate
Roche	bevacizumab
Roche	erlotinib
Roche	epoetin beta
Wyeth	tigecycline
Manufacturer provided some data	
Alcon	anecortave acetate
Arrow Pharmaceuticals	butoconazole nitrate
Arrow Pharmaceuticals	solifenacin succinate
Bayer	sorafenib tosylate
Bristol-Myers Squibb	entecavir
CSL	rabies vaccine
EpiPharm	tazarotene
Epitan	eflornithine hydrochloride
GlaxoSmithKline	rotavirus vaccine
Merck Sharp & Dohme	rotavirus vaccine
Merck Sharp & Dohme	human papillomavirus vaccine
Novartis	deferasirox
Orphan	lanthanum carbonate hydrate
Schering-Plough	posaconazole
Servier	strontium ranelate
Manufacturer had no objection to providing data but did not actually provide it	
Novartis	lumiracoxib
Manufacturer declined to supply data	
Amgen	palifermin
Genzyme	sevelamer hydrochloride
Novo Nordisk	insulin detemir
Schering	disodium gadoxetate
Manufacturer did not respond to request	
Alphapharm	cetuximab
Altana Pharma	ciclesonide
Janssen-Cilag	bortezomib
Novartis	darifenacin hydrobromide
Schering	alemtuzumab
Solvay	moxonidine

Fine-tuning the T-score in 2007

Manufacturers who provide all the information *Australian Prescriber* requests when assessing a new drug receive the highest score [T][T][T]. Some companies only provide the approved product information. Although this is helpful, the product information is a public document so does not represent greater transparency. In these cases the T-score from now on will be [T]. Manufacturers who say they have no objection to providing information, but then do not deliver it, will be considered to have declined to supply data [T]. The revised T-scores are as follows:

[T][T][T] manufacturer provided clinical evaluation

[T][T] manufacturer provided additional useful information

[T] manufacturer provided only the product information

[T] manufacturer declined to supply data

[X] manufacturer did not respond to request for data

Answers to self-test questions

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

www.australianprescriber.com

Australian Prescriber is available on the internet in full text, free of charge. Go to **New issue email alert** to be sent an email each time a new issue goes online.

Australian Prescriber mailing list

Australian Prescriber is distributed every two months, free of charge, to medical practitioners, dentists and pharmacists in Australia, on request. It is also distributed free of charge, in bulk, to medical, dental and pharmacy students through their training institutions in Australia. To be placed on the mailing list contact the *Australian Prescriber* Mailing Service.

Tick ☑ whichever of the following apply:

I have access to the *Australian Prescriber* website on the internet ☐ Yes ☐ No

☐ Place me on the mailing list

☐ Delete me from the mailing list

☐ Change my address

☐ Send me all the available back issues

Name: .....

Ref no.: .....
(on the address sheet above name)

Address: .....

.....

.....

Profession: .....
(general practitioner, resident, psychiatrist, surgeon, dentist, pharmacist etc.)

Postal: *Australian Prescriber* Mailing Service
GPO Box 1909
CANBERRA ACT 2601
AUSTRALIA

Telephone: (02) 6241 6044 Fax: (02) 6241 5768

Editorial office

For general correspondence such as Letters to the Editor, contact the Editor.

Telephone: (02) 6202 3100

Fax: (02) 6282 6855

Postal: The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
AUSTRALIA

Email: info@australianprescriber.com

Website: www.australianprescriber.com

Australian Prescriber

Address correspondence to:
The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
Telephone (02) 6202 3100

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

Typesetting
Barnes Desktopping and Design

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

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

NPS
National Prescribing Service Limited

Print Post Approved PP349181/00151 • ISSN 0312-8008