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NPS MEDICINEWISE

CONTENTS

EDITORIAL

Quality use of medicines – are we nearly there yet?

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Key words
drug utilisation, National Prescribing Service, Pharmaceutical Benefits Scheme

Aust Prescr 2012;35:174–5

In 1992 the Australian Government adopted a policy on the quality use of medicines, or QUM.[1] The policy aimed to foster judicious, appropriate, safe and efficacious use of medicines through active partnerships between consumers, health professionals, the pharmaceutical industry and government. It became an important component of our National Medicines Policy (Fig. 1).[2]

Much has been accomplished in 20 years. For example, the government funded the National Prescribing Service (NPS) in 1998 as the principal organisation working towards QUM. The NPS, now known as NPS MedicineWise, has an independent board of directors, but is also charged with generating savings for the Pharmaceutical Benefits Scheme as a condition of continued funding. Not surprisingly therefore, NPS MedicineWise has needed to address topics which were clinically important, but also had the capacity to yield savings. Antibiotics were an early (and continuing) target as overuse and misuse promote antimicrobial resistance, create adverse events and generate unnecessary costs.

NPS MedicineWise promotes QUM through a range of activities. These include the educational visiting program to doctors through general practice networks, the National Prescribing Curriculum (now being used by senior students in almost all medical schools), the provision of objective information to health professionals, plus publications and telephone 'hotlines' for consumers. The newer 'Be medicinewise' program addresses consumer education with a special focus on older people, who have the largest medication burden.

The reach of these and other programs has increased over the years. The latest evaluation report shows 57% (13 774) of the general practitioner workforce participated in NPS MedicineWise activities in 2010–11.[3] However, relatively little attention has been given to hospitals, despite the great influence of opinion leaders such as hospital specialists on the prescribing of junior doctors and general practitioners.[4]

Meanwhile state and territory governments are building their own QUM programs and their expert advisors recently came together to form the national Council of Australian Therapeutic Advisory Groups.[5] Many general practice organisations have QUM programs. The special needs of indigenous communities are also being addressed.[6]

Supporting information for QUM comes from many sources. These include Australia's own national formulary (the Australian Medicines Handbook) and evidence-based guidelines such as those produced by Therapeutic Guidelines Ltd.

The QUMmap, a valuable database of initiatives across Australia, shows the breadth of activity in QUM.[7] Clearly the concepts and many of the tools of QUM have permeated widely in our health system.

What of outcomes? We have to accept that exemplary QUM will not necessarily improve all health outcomes. For most chronic non-communicable diseases that are at the forefront of public health concerns, factors other than medicines (exercise, diet, stopping smoking) play a big role. It is difficult but not impossible to disentangle all the influences and their quantitative contributions to achieving better health. As Professor Mant wrote at the end of the first 10 years of our QUM policy, 'A key research question will be whether better use of medicines achieves better health outcomes'.[8] This question remains unanswered for most diseases.

Not yet tackled is the quality use of complementary medicines. It is difficult to define quality use for a product whose efficacy has not been demonstrated. Under current regulations, sponsors of listed complementary products which are not making high level claims (for example to treat, modify or prevent serious illness) are required to 'hold the evidence' for

From the Editor

Welcome to the largest edition of *Australian Prescriber* ever published. There will be something for everyone in the wide variety of topics. These range from common conditions as in Jo-Ann See's review of acne to the infrequently encountered idiopathic interstitial pneumonias reviewed by Lauren Troy and Tamera Corte.

Pneumococcal pneumonia is one of the conditions which may be considered for treatment with intravenous antibiotics in the patient's home. David Looke and David McDougall's article will be of interest to health professionals in hospitals and in the community.

The quality use of medicines is important for all health professionals. As it is 20 years since Australia's policy was launched, Tony Smith reflects on what has been achieved. Looking to the future, the conference on national medicines policies in our region reports that there is still work to be done.

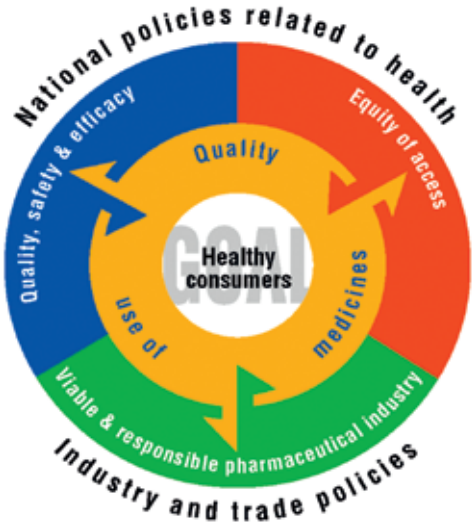
whatever they claim. This evidence is not scrutinised unless there is a postmarketing review or the product is the subject of a challenge through the Therapeutic Goods Administration. Consumers also have a right to evidence-based information about these products.

How then shall we know when we are 'nearly there' with QUM? Maybe when we have:

- consumers who are health literate and able confidently to find and use the best information about their medicines
- indices of health improving as a result of the quality use of medicines
- all future prescribers being assessed for their competence in prescribing, before graduating
- a pharmaceutical industry which is truly a partner in improving the quality use of medicines
- medicines promotion conforming to published ethical standards
- the majority of prescriptions reflecting the best evidence from guidelines
- continuing lifelong education about medicines for all health professionals
- an overarching National Medicines Policy Committee, actively monitoring and evaluating the function and progress of the whole of our national policy on medicines. ≺

Professor Smith is the former Chair of the Pharmaceutical Health and Rational Use of Medicines Committee and former Chair of the Advisory Committee on Complementary Medicines. He was also a member of the board of NPS MedicineWise.

Fig. 1 **The interlocking concentric components of the Australian National Medicines Policy**



Quality, safety and efficacy are regulated by the Therapeutic Goods Administration, equity of access is achieved through the Pharmaceutical Benefits Scheme, while the pharmaceutical industry provides the medicines we use. Quality use of medicines links all of these to the central objective of improving the health of all Australian consumers.

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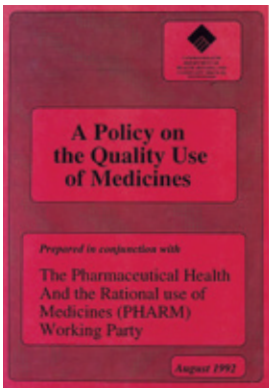

LETTERS

Letters to the Editor

Pertussis prophylaxis

Editor, – In their article on pertussis prophylaxis (Aust Prescr 2012;35:82-4) the authors recommended erythromycin 10 mg/kg (maximum 250 mg) every six hours for children aged two months or more. They make no antibiotic recommendation for children aged one month.

In 1985, good results were observed for pertussis with erythromycin estolate suspension compared to poor results with erythromycin ethyl succinate.[1] In the only randomised comparison of the two esters[2], 13 of 93 children were cured in the estolate group compared to only 4 of 97 in the ethyl succinate group (p=0.016). Ethyl succinate was given in a dose of 20 mg/kg every eight hours, which is equivalent to 15 mg/kg every six hours rather than the 10 mg/kg every six hours as recommended in the article.

Unfortunately, only erythromycin ethyl succinate suspension is available in Australia. Given the availability of azithromycin, clarithromycin and trimethoprim-sulfamethoxazole, I suggest that erythromycin ethyl succinate suspension should not be recommended for pertussis prophylaxis – and certainly not in a dose of only 10 mg/kg every six hours.

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Cheryl Jones, one of the authors of the article, comments:

Thank you to Professor Shann for his thoughtful comments about recommendations for erythromycin ethyl succinate suspension. We would like to re-emphasise the main points of our article that only under rare circumstances is antimicrobial prophylaxis indicated, as data to support efficacy and dosing are limited. Azithromycin is the preferred antibiotic for infants.

We made an error in our Table – one-month-old infants were not included. The header of the second column should read less than or equal to one month of age (≤ 1 month). The Table is based on information from the Australian Immunisation Handbook so the correct reference is reference two.[1]

The recommended dose of erythromycin 10 mg/kg (maximum 250 mg) every six hours is recommended by the Australian Immunisation Handbook[1] and other guidelines.[2,3]

We agree with the sentiment that erythromycin ethyl succinate is suboptimal for pertussis prophylaxis in infants, not only for efficacy reasons, but also for tolerability (largely gastrointestinal intolerance) and toxicity issues (pyloric stenosis in infants less than one month). Professor Shann has suggested it should not be used at all. We had recommended that its use be considered in the rare circumstances where both the use of prophylaxis is appropriate and azithromycin is not available. Arguably the assistance of public health officers in confirming the need for prophylaxis and sourcing azithromycin would be the best approach.

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Rasagiline (Azilect)

In *Australian Prescriber's* review of rasagiline (Aust Prescr 2012;35:128-35) it is noted that:

> The Therapeutic Goods Administration originally rejected the application to register rasagiline in Australia because of an apparent increase in the risk of melanoma. However it is uncertain that the drug was responsible.

I wish to point out that it is thought that melanoma and Parkinson's disease share common genetic components.[1] Furthermore there is evidence of an association between Parkinson's disease per se and melanoma.[2] Proof of the association led the Food and Drug Administration to instigate a labelling change applicable to all dopaminergic drugs in 2007. It has also been acknowledged by the TGA and the following statement is included in the

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

Australian product information for rasagiline:

> During the clinical development program, the occurrence of cases of melanoma prompted the consideration of a possible association with rasagiline. The data collected suggests that Parkinson's disease, and not any medicinal products in particular, is associated with a higher risk of skin cancer (not exclusively melanoma). Any suspicious skin lesion should be evaluated by a specialist.

In view of the evidence, Lundbeck recommends that all patients with Parkinson's disease undergo regular skin checks, including those taking rasagiline.

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Hypertension in pregnancy

Editor, – The article by Peter Donovan advises that ACE inhibitors and angiotensin receptor blockers are teratogenic in the first trimester of pregnancy (Aust Prescr 2012;35:47-50). These are commonly used antihypertensives which have specific benefits for individuals with chronic proteinuric renal disease and diabetes. Almost half of women aged 16–45 years attending a hypertension clinic in the UK were taking them.[1] The first ACE inhibitor, captopril, became available over 30 years ago.

Adverse fetal outcomes with ACE inhibitors in the first trimester had not been reported until a study in 2006 which described an increased risk of major cardiovascular and central nervous system congenital malformations.[2] This study however was widely criticised for unrealised confounding bias.[3] In particular, women with diet-controlled or undiagnosed diabetes were not excluded, and no adjustment was made for pre-pregnancy body mass. These are known risk factors for fetal malformations.

A subsequent study reported that ACE inhibitors in early pregnancy were associated with an increased risk of major congenital malformations, but this risk was attributable to maternal diabetes and not the drug.[4] Three more studies did not find an increased risk of major malformations with ACE inhibitors or angiotensin receptor blockers.[5-7]

The weight of evidence strongly suggests that ACE inhibitors and angiotensin receptor blockers are not teratogenic in early pregnancy, and that women of child-bearing age who may specifically benefit from their use may continue to do so while waiting to conceive.

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Peter Donovan, author of the article, comments:

I agree with Dr Morton that there is increasing evidence for the safety of ACE inhibitors and angiotensin receptor blockers in the first trimester of pregnancy. The retrospective cohort study[1] provides the strongest evidence of safety thus far. Although it appears that the teratogenic effects of ACE inhibitors or angiotensin receptor blockers are unlikely to be as strong as originally suggested,[2] and may be no worse than some other drugs,[1,3] I would advocate a cautious approach.

There are alternatives for treating chronic hypertension, including nifedipine and methyldopa. There is much stronger evidence for their safety, hence they should remain first line. For women with chronic proteinuric renal disease, the harm:benefit ratio may favour the use of ongoing ACE inhibitors or angiotensin receptor blockers based on the current safety data. However, there are no data suggesting that ceasing ACE inhibitors or

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angiotensin receptor blockers in women trying to conceive has detrimental effects on clinical endpoints, such as the need for renal replacement therapy, adverse pregnancy events or mortality.

As always, doctors should discuss all the relevant risks and benefits with the patient so she is able to make an informed decision about what is best for her and her future child. Pre-pregnancy counselling with a specialist such as an obstetric physician or obstetrician would be appropriate in these cases.

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Time to restock the doctor's bag

Editor, – The *National Health Act 1953* made provisions for certain drugs to be provided to prescribers, which in turn could be provided to patients free of charge in emergency circumstances. The most recent update to this list was in May 2010, when methoxyflurane was added.

The article by John Holmes (Aust Prescr 2012;35:7-9) suggests that the list is outdated. Many drugs listed are no longer first-line treatments for specific emergencies, and special populations are not considered.

An excellent example of this is the failure to include parenteral magnesium sulfate for an eclamptic seizure. Eclampsia is uncommon with an estimated incidence of 1 in 2000 maternities. When it occurs it is associated with high maternal morbidity and mortality.

Magnesium sulfate is a safe and effective therapy that reduces morbidity and mortality when given to a pregnant woman who is fitting due to eclampsia (National Health and Medical Research Council level I evidence). Multiple high-quality systematic reviews have compared magnesium sulfate with other treatments for eclampsia such as lytic cocktail (chlorpromazine, pethidine and promethazine), diazepam and phenytoin. These trials demonstrated that magnesium sulfate was more effective than historical therapies and when compared with diazepam, it reduced the risk of maternal death.

Some drug choices do not matter, but in the case of a pregnant woman with pre-eclampsia who is fitting, giving the best available drug may save her life. Magnesium sulfate is not available in the current emergency doctor's bag. We submit that it should be.

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John Holmes, author of the article, comments:

I agree that magnesium is the treatment of choice for eclampsia. However, in my view it does not meet criteria for inclusion in the doctor's bag. Magnesium is not necessarily as safe as Drs Miles and Dennis state – excessive blood levels of magnesium may be associated with respiratory depression or cardiac conduction abnormalities. This would contravene the principles that the safety of drugs available in the doctor's bag should be commensurate with the skills of general practitioners and should be administered only in settings where there are appropriate monitoring and resuscitation facilities.

Further, it could be argued that general practitioners are highly unlikely to be treating full blown eclampsia in the community. Even in home birth situations it is likely that patients with signs of pre-eclampsia would have been transferred to hospital well before progression to convulsive eclampsia was likely.

Frusemide in the doctor's bag

Editor, – The recent article by John Holmes about the doctor's bag (Aust Prescr 2012;35:7-9) recommended that frusemide be relegated to a second- or third-line treatment in patients with acute heart failure. This recommendation is concerning and is counter to international evidence-based guidelines. Both the European Society of Cardiology[1] and the American Heart Association/American College of Cardiology guidelines[2] recommend the use of intravenous loop diuretics in acute heart failure. In line with this, the Heart Failure Society of America also recommends intravenous loop diuretics for acute pulmonary oedema.[3]

On their introduction, loop diuretics revolutionised the management of congestive cardiac failure. Their role remains important today. The recommendation against the use of frusemide as first-line treatment in acute heart failure in appropriately selected patients is potentially dangerous. Non-invasive ventilation strategies and intravenous nitrate therapy do have a role in acute heart failure. Evidence for their efficacy is largely based on studies where they were used with intravenous loop diuretics. The role of these therapies without the concomitant use of loop diuretics has not been established.[4-6]

In summary, intravenous loop diuretics remain a first-line component in the management of acute heart failure and suggestions to the contrary are not based on sound evidence nor supported by internationally recognised guidelines on the subject.

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John Holmes, author of the article, comments:

The mode of action of frusemide in the treatment of acute left ventricular failure is probably preload reduction. Clinical improvement is seen well in advance of its diuretic effect.[1] In this respect, frusemide is acting very similarly to nitrates. However, as mentioned in the article, there are potential adverse effects of frusemide in vascularly depleted patients and elevation of plasma renin and noradrenaline levels can exacerbate afterload, increase myocardial oxygen demand and thereby aggravate coronary ischaemia.[2] These potential effects make nitrates preferable as a first-line treatment, especially as, unlike frusemide, they have a more rapid onset of action and can be administered by intravenous infusion titrated to effect.[1,2]

My article discussed the use of emergency drugs in a general practice setting. I am therefore bemused that Drs Camuglia and Walters should criticise the established management of acute pulmonary oedema in Australian emergency departments. There is a world of difference between general practice and the management capabilities and choices available in a critical care environment. In the latter, the primary use of nitrates and non-invasive ventilation strategies in acute pulmonary oedema has been well established worldwide for over a decade.[2,3] Non-invasive ventilation in particular has been shown to reduce the need for intubation in severe acute pulmonary oedema.[4,5] Frusemide still has a role in selected cases, predominantly left-sided failure and the absence of intravascular depletion. However, the level of evidence is variously reported as II to III.

Irrespective of this, my article does not advocate removal of frusemide from the doctor's bag. However, while boluses of frusemide may be useful in a life-threatening situation outside of hospital, such treatment may be neither optimal nor appropriate in an environment where other and better therapeutic interventions are available.

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ARTICLE

Drug treatment of acne

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Key words
antibiotics, retinoids, topical administration

Aust Prescr 2012;35:180–2

SUMMARY

Acne is a common skin disorder not just confined to adolescence.

For patients with mild to moderate acne who have not responded to over-the-counter products, prescribing topical antibiotics and/or retinoids may be considered.

For patients with moderate to severe acne, oral antibiotics or the contraceptive pill can be combined with topical benzoyl peroxide or a topical retinoid.

For patients who present with severe acne nodules and cysts, or who have not responded to 12 weeks of oral antibiotics, referral to a dermatologist for oral isotretinoin is recommended.

Once acne has cleared, 3–12 months or longer with a topical retinoid may help to prevent recurrence.

Introduction

Acne is a common skin disorder in teenagers, but can also occur before adolescence and in older people. Treatment needs to be individualised according to the severity and extent of the disease. Due to the chronicity of acne, therapeutic regimens may need to be altered according to a change in the disease severity or ineffectiveness of a chosen treatment. Follow-up of the patient is therefore important. Timely and effective treatment of acne minimises the risk of long-term scarring and psychological distress.

Seeing the doctor and initial acne assessment

Before anything is prescribed, the patient needs to be assessed to exclude any contributing factors such as drugs which can aggravate acne (see Box) or underlying hormonal issues such as polycystic ovarian syndrome. A few patients may even be using thick moisturisers, cosmetics or sunscreens that are aggravating the problem.

It is important to work out a realistic treatment plan with the patient and inform them about potential adverse effects, otherwise their expectations will not be met and compliance will be poor. It must be stressed that acne treatments may take several weeks to work.

Topical over-the-counter products

Over-the-counter acne products are generally in the form of cleansers or leave-on applications that work by killing acne bacteria, drying up excess oil and sloughing dead skin cells. They usually contain ingredients such as benzoyl peroxide, salicylic acid, glycolic acid, lactic acid, sulfur or resorcinol which are useful in mild acne when lesions are superficial whiteheads, blackheads, papules and pustules.

Azelaic acid (gel and lotion) is not commonly used. However, it may be useful in acne and post-inflammatory hyperpigmentation in darker skinned patients. It is used twice daily and is considered safe in pregnancy.

Topical prescription treatments

Topical prescription treatments may be adequate for mild acne and can be combined with oral medications for moderate to severe disease or if the patient is unresponsive.

Many practitioners start with a topical antibiotic, especially for mild inflammatory lesions. However, topical retinoids can be used for inflammatory lesions as well. They are particularly helpful for blackheads and whiteheads as well as long-term maintenance therapy once the acne has cleared as they prevent blocked pores forming. If patients are not seeing significant improvement after 12 weeks, follow-up is necessary to consider adding oral treatment.

Topical therapies are not spot treatments and should be applied to the whole area affected. Acne lesions occur in a field and therefore the active lesions, as well as the microscopic microcomedone, are targeted in an all over application. The treatment should be applied to a cool, dry, clean face. Moist skin increases their absorption and therefore increases the risk of skin irritation which the patient may feel as burning or stinging.

Box **Drugs that may worsen acne**

Androgenic steroids
Corticosteroids
Anticonvulsants
Barbiturates
Lithium
Bromides
Iodides

Topical antibiotics

Topical clindamycin or erythromycin is used once or twice daily. Solution or gel formulas may be more useful for the trunk as they may cause irritation on facial inflammatory lesions. Lotions may be more cosmetically appealing for the face. It is generally recommended that antibiotics be used as combination therapy with either a topical retinoid or benzoyl peroxide or both. A combination of topical clindamycin and benzoyl peroxide product is available for once-daily use. Another combination strategy is to apply a topical antibiotic in the morning and a topical retinoid at night.

Topical retinoids

Retinoids for once daily use are adapalene, isotretinoin, tazarotene and tretinoin. A combination product of adapalene and benzoyl peroxide can be used nightly. All topical retinoids may cause skin irritation which can be improved by using them with a moisturiser.

Skin irritation

Any topical acne preparation (either over-the-counter or prescribed) may cause skin irritation so patients should be advised to:

- apply to a cool, dry face
- avoid the use of facials or scrubs before application
- start with a lower concentration of benzoyl peroxide
- wash off initially after a short application time and then gradually increase the time of application
- use every second night to begin with
- test by using on a limited area initially.

Oral prescription treatments

Antibiotics, the contraceptive pill for females, anti-androgens for females (spironolactone and cyproterone acetate) and isotretinoin are oral options for acne.

Antibiotics

Oral antibiotics are useful for moderate to severe inflammatory acne characterised by papules, pustules, nodules and cysts. They are also useful if acne is occurring in multiple sites such as the face and trunk. To minimise antibiotic resistance, oral antibiotics should not be used together with a topical antibiotic, but rather with a topical benzoyl peroxide cleanser or cream. Courses limited to 3–6 months are recommended to minimise the risk of antibiotic resistance and adverse effects.

First-line

First-line oral antibiotic therapy is doxycycline 50–100 mg daily or minocycline 50–100 mg daily. These drugs should not be given to children under 10 years of age (because of the risk of permanent discolouration of the teeth) or women who are pregnant or attempting to get pregnant because of toxic effects on fetal bone formation.

Patients should be warned of gastrointestinal adverse effects as well as the risk of vaginal candidiasis in women. Photosensitivity can occur in patients taking doxycycline. Long-term treatment with minocycline can result in abnormal pigmentation and an uncommon lupus-like drug reaction. These oral antibiotics should not be combined with oral retinoids due to the risk of benign intracranial hypertension.

Second-line

A second-line oral antibiotic is erythromycin ethyl succinate 400–800 mg twice daily. Although there is well documented evidence of antibiotic resistance to erythromycin, it is still used. Patients need to be warned that gastrointestinal upset is common and there are many potential drug interactions including with anticoagulants, digoxin, phenytoin and theophylline.

The contraceptive pill

Oral contraceptives with anti-androgenic properties should be considered for acne in girls and women who find topical therapies and oral antibiotics ineffective or only partially effective. Patients often need topical therapy while they wait for the full benefit of the pill to work, which usually takes three months.

Isotretinoin

Oral isotretinoin is the treatment of choice for patients who have not adequately responded to 12 weeks of oral antibiotics or who present initially with severe acne nodules and cysts. Referral to a dermatologist is recommended. (General practitioners cannot prescribe oral isotretinoin.) Any patient who is at risk of scarring, who has a family history of acne scarring or is experiencing severe psychological distress may also need referral.

Laboratory tests are done at baseline and during the course of treatment. With the referral letter it may be helpful to organise the baseline investigations which are a fasting cholesterol and triglyceride test, liver function tests and a pregnancy test for females. Oral isotretinoin may cause an increase in blood lipids. After the patient has had 4–8 weeks therapy, the laboratory investigations are repeated and compared to baseline. If the tests are normal they may be

repeated at the end of treatment, however if there are any abnormalities they will need repeating more regularly with or without lowering of the daily dose.

Females of childbearing age must use adequate contraception before, during and for one month after treatment because birth defects can occur.

Possible adverse effects from oral isotretinoin may be minimised by starting patients on low-dose therapy (0.2–0.5 mg/kg) and then gradually increasing the daily dose and titrating with adverse effects. Strategies for managing adverse effects include:

- using a lip balm, eye drops and moisturiser for the most common adverse effects of dry lips, eyes and skin
- having an appropriate skin care routine such as thicker moisturisers for very dry skin and using a topical steroid if indicated for dermatitis, especially in winter
- covering up and using sunscreen (factor 50) to prevent photosensitivity.

Some patients have reported mood changes while taking oral isotretinoin. If this occurs, the medication should be stopped. The patient's dermatologist should be contacted, and if necessary seek psychiatric assessment. Other reasons to contact the prescribing dermatologist may be bowel symptoms, persistent headaches or the risk of pregnancy.

Recommendations

The majority of patients with acne have mild to moderate disease and can be managed by a general practitioner. Once patients have tried over-the-counter treatments, topical antibiotics and/or topical retinoids may be prescribed. Patients should be followed up in 8–12 weeks. If there is no therapeutic benefit, oral antibiotics or a hormonal therapy can be combined with a topical therapy such as benzoyl peroxide or a retinoid.

For more severe acne cases or those not responding to a 12-week course of oral antibiotics, referral for oral isotretinoin should be considered. After acne has cleared, maintenance therapy for 3–12 months or longer with a topical retinoid is a good option. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Topical retinoids should be applied to dry skin to reduce skin irritation.
2. Oral antibiotics should be combined with topical antibiotics in cases of severe acne.

Answers on page 211

FURTHER READING

Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC, et al; American Academy of Dermatology/American Academy of Dermatology Association. Guidelines of care for acne vulgaris management. J Am Acad Dermatol 2007;651-63.

Thiboutot D, Gollnick H, Bettoli V, Dréno B, Kang S, Leyden JJ, et al. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. J Am Acad Dermatol 2009;60(5 Suppl):S1-50.

Book review

Therapeutic Guidelines: Oral and Dental. Version 2.

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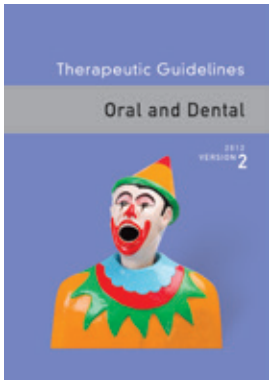

Melbourne: Therapeutic Guidelines Limited; 2012. 221 pages

Version 2 of Therapeutic Guidelines: Oral and Dental has included two new chapters, and updated all other sections. The target audience for these guidelines is not only oral health practitioners, but also general medical practitioners and other health professionals who may be called upon to provide advice on dental matters and remedies.

For dentists and oral health practitioners the guidelines provide a well cross-referenced coverage of drugs and therapeutic regimens used in general dental practice. They are presented in an easy-to-read style with sufficient detail for a practitioner to make sensible clinical decisions on a patient's needs and options with respect to common drugs used in modern dentistry. Interactions between a patient's medical condition and therapy impacting on dental care have been reviewed in the light of contemporary best evidence and practice.

The sections on dental caries and periodontal diseases would seem very useful for medical and allied health clinicians, as too the specific section on 'management of dental problems for medical practitioners'. The use of fluorides in the 'dental caries' section however is already outdated, with the acceptance by the Therapeutic Goods Administration of over-the-counter fluoride toothpaste now containing up to 1500 ppm fluoride ion. Further, the use of high fluoride toothpaste containing 5000 ppm is now an accepted part of oral hygiene for dentate residents in residential aged-care facilities.[1]

These guidelines will be a useful reference for all oral health, medical and allied health clinicians.

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ARTICLE

Management of Parkinson's disease

SUMMARY

Parkinson's disease has a wide variety of motor and non-motor symptoms.

Treatment aims to control the patient's symptoms by replenishing the dopaminergic system with levodopa or dopamine agonists. Monoamine oxidase B inhibitors are also effective first-line drugs.

Keeping symptoms under continual control early in the course of the disease may have beneficial effects as Parkinson's disease progresses.

Therapy is tailored to each patient's response to the drugs and their ability to tolerate them. Limited responses of motor and many non-motor symptoms may require the addition of other treatments.

The adverse effects of drugs used in the treatment of Parkinson's disease are usually reversible.

Symptom fluctuations in response to regular medication are an indication for specialist referral.

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Key words
dopamine agonists, levodopa, monoamine oxidase inhibitors

Aust Prescr 2012;35:183–8

Introduction

Parkinson's disease is a common neurodegenerative disorder, which particularly involves the loss of nigral dopaminergic neurons. The cardinal motor features are rigidity, bradykinesis, rest tremor and postural instability. Non-motor features are common both early and late in the disease course and include autonomic, neuropsychiatric and cognitive disturbances. Parkinson's disease has manifestations beyond the nigrostriatal system so it is not surprising that some motor features (such as postural instability) and many non-motor features have a limited response to dopaminergic drugs.

Non-pharmacological management

Non-drug therapies have a significant role in the treatment of Parkinson's disease and include counselling and education for both patients and carers. This includes providing information about which commonly prescribed drugs to avoid, for example dopamine-blocking drugs such as metoclopramide, prochlorperazine, haloperidol and risperidone. It is important to increase general fitness and well-being and maintain core balance and strength which may improve gait and postural stability. Physiotherapy with large amplitude physical training improves motor function[1] and allied health professionals can provide specific strategies to overcome disabilities such as start hesitancy, freezing of gait, festination and falls. Lee Silverman voice training is an established technique which has been proven to improve voice quality and audibility when patients adhere to the long-term strategy.[2] Nutrition should be considered in all stages of Parkinson's disease.

Supportive care is vital in very advanced phases of Parkinson's disease as drugs become poorly tolerated, motor fluctuations increase and non-levodopa responsive symptoms dominate. Counselling is part of the management of non-motor symptoms such as anxiety and depression, cognitive dysfunction and dementia.

Pharmacological management

There are no proven neuroprotective treatments for Parkinson's disease, but drugs are effective in symptom control, particularly in the early stages of the disorder. Treatment is then increased as required.

When to start treatment

Deciding when to start drug therapy for Parkinson's disease should be individually tailored to a patient's symptoms, circumstances and comorbidities. Treatment is indicated when symptoms impact on quality of life. When treatment is needed there is no evidence to support undue delay because of concerns about levodopa toxicity or the development of treatment resistance.[3] The aim is to control symptoms and maintain an 'on' state.

Some drugs with good symptomatic benefit are speculated to have a role in neuroprotection and some specialists advocate their use from the time of diagnosis.[4] Delayed start trials have been used to try and differentiate symptomatic from disease-modifying effects. A recent delayed start study of rasagiline, a monoamine oxidase B inhibitor, in treatment-naïve patients with mild Parkinson's disease showed a small benefit in the low-dose (1 mg) treatment group. This was not seen with the 2 mg dose and a clear explanation for this has not been established.[5] Further studies are needed before such treatments are considered truly disease modifying. Until a drug is unequivocally proven to slow disease progression, the time to commence treatment will remain contentious.

What to start

Motor features of early Parkinson's disease typically respond well to dopamine replacement therapies. The choice of drug therapy (Table 1) includes levodopa in combination with a dopa-decarboxylase inhibitor, a dopamine agonist or a monoamine oxidase B inhibitor. Rasagiline would be an appropriate first-line drug to consider for those with mild symptoms.

Table 1 **Drugs to manage motor symptoms of Parkinson's disease**

Class of drug	Name	Adverse effects	Comments
Levodopa/dopa-decarboxylase inhibitors	Levodopa/carbidopa Levodopa/benserazide	Nausea, constipation, postural hypotension, hypersomnolence, sudden sleep episodes, impulse control disorders, hypersexuality, confusion, hallucinations	Most effective symptomatic treatment Generally well tolerated and lower adverse effect profile than other drugs Minimum of 3 times daily dosing Used in early and advanced Parkinson's disease
	Controlled-release formulations	As above	Reduced and variable absorption leads to variable efficacy Main role is in stabilising nocturnal symptoms
	Short-acting formulations	As above	Used as rescue therapy in advanced Parkinson's disease Avoid use in early Parkinson's disease – may increase risk of motor fluctuations
	Enteral levodopa/carbidopa gel suspension	As above plus complications relating to percutaneous enteral tube	Consider in advanced Parkinson's disease where oral therapies have failed to control severe motor fluctuations
Dopamine agonists	Non-ergot derived: Pramipexole Rotigotine patch (TGA approved, not PBS listed) Ropinirole (TGA approved, not PBS listed for Parkinson's disease)	Nausea, constipation, postural hypotension, hypersomnolence, sudden sleep episodes, impulse control disorders, hypersexuality, confusion, hallucinations, peripheral oedema	Good symptomatic therapy Less dyskinesias/motor fluctuations compared to levodopa Higher incidence of adverse effects, especially impulse control disorders, hypersexuality and neuropsychiatric effects Available as once-daily dosing in oral and topical forms (rotigotine not currently PBS listed)
	Ergot derived: Cabergoline Bromocriptine Pergolide	As above plus cardiac valvular disease and pleuropulmonary/retroperitoneal fibrosis	Have been superseded by non-ergot drugs due to risk of fibrotic complications Monitoring essential (interval echocardiograms, respiratory function and chest X-ray) for those unable to switch from ergot preparations
	Apomorphine (injection)	As above plus skin nodules, skin necrosis	Used as subcutaneous bolus doses for rescue therapy in advanced Parkinson's disease with motor fluctuations Used as continuous infusion for advanced Parkinson's disease with motor fluctuations Often requires concomitant domperidone to manage nausea Requires high level of patient/carer support and education
Catechol-O-methyltransferase inhibitor	Entacapone	Diarrhoea, nausea, abdominal pain, discolouration of urine and sweat	Reduces 'wearing off' symptoms by prolonging the effect of levodopa May induce dyskinesia
Monoamine oxidase type B inhibitors	Selegiline Rasagiline	Nausea, hallucinations	Both drugs have a putative role in neuroprotection, although no conclusive evidence to date
Anticholinergics	Benzhexol Benztropine	Confusion, hallucinations, memory disturbance, dry mouth, constipation, urinary retention, glaucoma	Consider for treatment of levodopa-resistant tremor in younger patients No benefit for other motor symptoms Poorly tolerated in older people
N-methyl-D-aspartate antagonist	Amantadine	Hallucinations, confusion, livedo reticularis	Main role is in treatment of dyskinesia Small symptomatic benefit Tolerability problems

PBS Pharmaceutical Benefits Scheme TGA Therapeutic Goods Administration

Levodopa/dopa-decarboxylase inhibitors have the highest efficacy for motor symptoms and tend to have slightly better tolerability, particularly when started in low doses. The simplest dosing regimen is to commence a set dose at a set time and thereafter monitor the efficacy in terms of the dose required for symptom relief and the duration of that response. Box 1 shows a typical levodopa dosing regimen. A three-times daily starting frequency is required due to the short half-life of levodopa.

As the disease progresses it is important to establish the dose that relieves the increasing symptoms. This usually requires increasing the frequency of dosing from three to four (and often five) times a day (Box 2) with the addition of a long-acting preparation at bedtime.

Dopamine agonists are also effective first-line drugs and may be associated with less dyskinesia than levodopa/dopa-decarboxylase inhibitors. They are available in once-daily preparations. Long-term data suggest no significant difference in outcomes between patients started on levodopa/dopa-decarboxylase inhibitors and those given dopamine agonists.[6] It is common as time progresses to use a combination of these drugs.[4]

Adverse effects

All patients should be appropriately counselled before treatment and monitored for adverse effects throughout their lifelong treatment course. Most adverse effects are reversible. Cardiac valvular fibrosis and pulmonary fibrosis from the ergot-derived dopamine agonists such as cabergoline and pergolide may be irrreversible and some cases require surgical intervention. This risk seems most apparent amongst patients who have had more than six months duration of treatment and in those on higher doses of ergot-dopamine agonists, although individual susceptibility factors are not yet known.[7] Patients taking these drugs require constant monitoring and where possible switching to a non-ergot derived dopamine agonist such as pramipexole, ropinirole or rotigotine is desirable.

Non-motor adverse effects of dopaminergic therapy include nausea, postural hypotension, cognitive symptoms, hallucinations, psychosis, hypersomnolence, sudden sleep episodes and impulse control disorders (gambling, compulsive behaviours and hypersexuality). Such adverse effects can occur with all dopaminergic therapies, although are more common with dopamine agonists, which can also cause peripheral oedema. The risk of impulse control disorders is significantly higher with dopamine agonists. Pretreatment counselling and sustained clinical vigilance for these disorders is essential. A reduced dose of pramipexole is needed in patients with impaired renal function and doses should be increased cautiously in older people.

Dopaminergic drugs sometimes increase the non-motor symptoms of Parkinson's disease. Many of the drugs cause gastrointestinal adverse effects. If drug treatment is required for nausea or vomiting, metoclopramide and prochlorperazine should be avoided due to their dopamine blocking effects. Domperidone is the preferred treatment for these symptoms.

Inadequate response

If the patient's symptoms are not controlled it is important to exclude other diseases. As Parkinson's disease progresses slowly, any sudden deterioration is an indicator of a co-existent medical condition, such as a urinary tract infection, or problems with compliance. Adherence can be a particular problem given the frequent dosing schedule of levodopa preparations, but may be helped by providing the medicines in a multidose pack.

Box 1 Typical regimen for starting levodopa *

Step 1: Start at 50 mg 3 times a day for 2 weeks

Step 2: Increase to 100 mg 3 times a day. Continue until there is a clinical need for a change in dose. This will vary between individuals depending on the severity of their Parkinson's disease (e.g. could range from weeks to years).

Step 3: Increase to 150 mg 3 times a day if not coming 'on'

or

change to 100 mg 4 times a day if coming 'on' but not making it from dose to dose

or

change to 100 mg 3 times a day with entacapone if not coming 'on' or not making it from dose to dose

or

add pramipexole extended-release once daily if not coming 'on' or not making it from dose to dose

* Strength refers to levodopa dose alone, regardless of whether in combination with a dopa-decarboxylase inhibitor/catechol-O-methyltransferase inhibitor

Box 2 Typical levodopa dosing times

3 times a day – 6 am/12 pm/6 pm

4 times a day – 6 am/10 am/2 pm/6 pm

5 times a day – 6 am/9 am/12 pm/3 pm/6 pm

A prolonged-release formulation can be used at bedtime

Sustained failure to achieve adequate symptom control with a particular levodopa or dopamine agonist regimen should prompt an increase in the dose of that drug or consideration of combination therapy.

A fluctuating or erratic treatment response in early Parkinson's disease may reflect variable absorption of oral therapy. Separating levodopa therapy from meals can improve absorption. Consideration of drugs which provide more continuous dopaminergic stimulation such as once-daily pramipexole or the rotigotine patch may be helpful.

Nocturnal symptoms are often improved with the addition of long-acting dopamine agonists (particularly if the patient has restless legs) or controlled release levodopa/dopa-decarboxylase inhibitors. Non-motor symptoms such as nocturia may also need to be addressed (Table 2).

Some patients with tremor refractory to levodopa therapy may respond to dopamine agonists. Anticholinergic drugs can cautiously be tried in younger patients and are occasionally useful in reducing saliva production. However, they can have significant cognitive adverse effects such as hallucinations, particularly in older people.

Treatment of motor fluctuations and dyskinesia

Motor and non-motor fluctuations occur as Parkinson's disease progresses. This can make drug therapy challenging.[10] Fluctuations include the return of symptoms at the end of the dose interval ('wearing off'), failed symptom relief and sudden and unpredictable 'offs' of both motor and non-motor type. Increased dosing is also associated with so-called drug-induced dyskinesias resembling choreiform movements which occasionally can be localised, but generalise as the disorder progresses. These can occur in peak dose and diphasic* patterns.

'Wearing off' between doses can be managed by increasing the dose, reducing the dose interval (if using levodopa/dopa-decarboxylase inhibitors) or adding other drugs. Entacapone is a further inhibitor of levodopa breakdown and in combination with levodopa/dopa-decarboxylase inhibitors reduces 'wearing off' and increases the potency of an individual dose of levodopa. Often a dose reduction of approximately 25% is needed when entacapone is added. Dopamine agonists are also useful in smoothing out the end-of-dose 'wearing off' effect by reducing the severity of the 'off' period. Monoamine oxidase B inhibitors can also be considered in this situation. Dose failures may respond to oral rescue therapy with short-acting levodopa/dopa-decarboxylase inhibitors.

Involuntary motor movements or dyskinesias are often not troubling to patients, so they do not always require a change of treatment if good 'on' time is maintained. Disabling dyskinesias may require dose reduction at the risk of loss of efficacy. Amantadine has a mild to modest benefit in controlling motor symptoms and can reduce dyskinesia, however it has potential adverse effects including confusion, peripheral oedema and livedo reticularis.

Treatment options for motor complications refractory to oral therapies

Specialist referral and co-management of patients as time progresses is needed to manage the more challenging aspects of motor fluctuations. Non-oral therapies including apomorphine, intestinal levodopa infusion and deep brain stimulation can be considered when standard drug therapy fails to effectively manage motor fluctuations. All these treatments require ongoing involvement of a multidisciplinary team experienced in managing advanced Parkinson's disease.

Apomorphine

Apomorphine is an injectable dopamine agonist which can be given as intermittent bolus doses or by continuous subcutaneous infusion. Intermittent boluses are effective rescue therapy for disabling motor 'off' symptoms, while continuous infusion can reduce daily 'off' time and reduce the required doses of oral drugs.[11] Apomorphine has the same potential adverse effects as oral dopamine agonists and may cause injection site reactions and skin nodules. Patients may need domperidone to prevent vomiting.

Intestinal levodopa infusion

Continuous administration of levodopa/dopa-decarboxylase inhibitors in gel form via a percutaneous enteral tube is available for advanced Parkinson's disease with severe motor fluctuations refractory to oral therapy. Typically, patients carry an infusion pump around the waist or across the shoulder allowing continuous infusion during waking hours, with the option to extend to a 24-hour infusion to cover nocturnal symptoms if required. It overcomes complications relating to variable absorption of levodopa secondary to delayed gastric emptying and protein consumption. Usually, oral therapy can be withdrawn. Several studies, including some small randomised controlled trials have shown improvement in motor function, motor fluctuations and quality of life. Complications include all those seen in standard

* Diphasic dyskinesia occurs as the levodopa concentration rises and then falls

Table 2 **Management of non-motor features of Parkinson's disease**

Non-motor manifestation		Management options
Cardiovascular	Postural and postprandial hypotension	Increased fluid and salt intake, frequent small meals, compression stockings (above knee) Avoid antihypertensives Domperidone +/– fludrocortisone Pyridostigmine Midodrine (Special Access Scheme only)
Gastrointestinal	Constipation	Good hydration, high fibre diet, laxatives Avoid anticholinergics
	Gastroparesis (nausea, bloating, abdominal pain, early satiety)	Postural advice, frequent small meals Domperidone
	Dysphagia and dysphonia	Speech therapy assessment, Lee Silverman voice training Dopaminergic therapy – may be partially levodopa responsive
	Drooling	Dopaminergic therapy Anticholinergics (beware adverse effects) Salivary gland botulinum toxin injections
Genitourinary	Urinary irritability (frequency, urgency, urge incontinence, nocturia)	Avoid diuretics including coffee Perform post-void bladder scan to rule out retention before starting therapy Oxybutynin, amitriptyline, tolterodine, prazosin, duloxetine
	Erectile dysfunction	Dopamine agonists Sildenafil or similar oral therapy – check for postural hypotension before prescribing Specialist referral for counselling/consideration of intracavernosal and surgical treatments
Neuropsychiatric and cognitive	Anxiety	'Off' state anxiety may respond to an increase in dopaminergic therapy Antidepressants (tricyclics or selective serotonin reuptake inhibitors) Counselling, support, psychotherapy
	Depression	Counselling, support, psychotherapy Dopamine agonists may have antidepressant properties[8] Antidepressants (tricyclics or selective serotonin reuptake inhibitors)
	Psychosis	Non-troubling hallucinations do not require drug treatment For distressing hallucinations/paranoia: • exclude treatable causes of delirium • modify Parkinson's disease drug therapies (reduce or cease anticholinergics, monoamine oxidase B inhibitors, amantadine, dopamine agonists, catechol-O-methyltransferase inhibitors) • reduce levodopa if no response • quetiapine appears to have a relatively low incidence of extrapyramidal effects (clozapine has less extrapyramidal effects but its use is limited by adverse effects and need for monitoring)
	Cognitive impairment	Manage as for distressing psychosis Cholinesterase inhibitors improve cognition and activities of daily living in Parkinson's disease dementia,[9] but are currently only approved in Australia for Alzheimer's dementia
Sleep	Excessive daytime sleepiness	Rule out other causes of ineffective sleep (e.g. sleep apnoea, depression, nocturia, inadequately controlled Parkinson's disease motor symptoms) Reduce dopaminergic therapy if possible Sleep attacks may necessitate reduction of dopaminergic therapy at expense of motor control
	Restless legs syndrome	Dopaminergic therapy
	REM sleep behaviour disorder	Clonazepam
Pain	Pain/sensory symptoms	Establish whether present during a motor 'on' or 'off' state and adjust dopaminergic therapy appropriately If unrelated to dopaminergic therapy, consider simple analgesics, drugs for neuropathic pain, antidepressants, chronic pain management strategies

oral levodopa therapy. Additional complications related to the technical aspects of the infusion system, including tube removal/dislocation, local infection, peritonitis and intestinal obstruction, are reported in 20–70% of patients.[12]

Functional neurosurgery

There are two main neurosurgical options for Parkinson's disease. The first is lesional surgery, which permanently ablates a target region to achieve either tremor control or lessen dyskinesia. The second is deep brain stimulation surgery. This is reversible and provides continuous electrical stimulation to a target from an implanted pulse generator (battery) which is adjustable via an externally applied programmer. Several randomised controlled trials have shown deep brain stimulation improves motor symptom control, reduces motor fluctuations and improves quality of life in people with advanced Parkinson's disease.[13-15] Sustained motor benefit over 10 years has been demonstrated.[16] Often dopaminergic drug therapy can be significantly reduced following deep brain stimulation which is of particular benefit when the drugs are difficult to tolerate.

Both forms of functional neurosurgery carry immediate perioperative risk and deep brain stimulation carries additional risks associated with the implanted hardware and stimulation field effect. Deep brain stimulation is not a cure, and inevitably symptoms of Parkinson's disease progress, but possibly at a slower rate.[17] Australian referral guidelines for deep brain stimulation are available.[18]

Management of non-motor symptoms

Patients with Parkinson's disease may have autonomic dysfunction, neuropsychiatric symptoms and cognitive impairment. Non-motor symptoms contribute significantly to the morbidity of Parkinson's disease. Interestingly, some of these are present as part of the 'off' phenomena and remain responsive to levodopa, but many are not and warrant management in their own right. Adverse effects of dopaminergic therapies often overlap with non-motor symptoms so the combined opinion of movement disorder specialists, neuropsychiatrists and other specialists is often important. Common non-motor problems and possible treatment options are outlined in Table 2.

Conclusion

Parkinson's disease is a progressive neurological disorder with motor and non-motor features. It has significant cost and burden of care to the community over a prolonged course. Treatment is aimed at maintaining continuous relief of motor and non-motor symptoms. Drugs may be necessary, but are not sufficient to maintain quality of life in the long term. As the disease progresses, specialist referral and allied health involvement is important. The patient will need collaborative assistance from general practitioners, movement disorder specialists, neuropsychiatrists and allied health professionals. ≺

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. Levodopa therapy should be delayed as long as possible as it is only effective for a limited time.

4. Dopaminergic therapy may exacerbate the non-motor symptoms of Parkinson's disease.

Answers on page 211

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Top 10 drugs

These tables show the top 10 subsidised drugs for the year July 2011 – June 2012.

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

	Constituent drug	PBS/RPBS ‡
1.	atorvastatin	82.99
2.	rosuvastatin	38.14
3.	irbesartan	31.58
4.	perindopril	31.16
5.	paracetamol	29.64
6.	candesartan	27.43
7.	ramipril	24.95
8.	amlodipine	23.33
9.	simvastatin	22.03
10.	esomeprazole	21.91

DDDs in this table include use in combination products

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

	Drug	PBS/RPBS ‡
1.	atorvastatin	10 855 535
2.	rosuvastatin	7 035 996
3.	esomeprazole	6 069 831
4.	paracetamol	5 362 780
5.	perindopril	3 926 940
6.	simvastatin	3 800 924
7.	pantoprazole	3 789 090
8.	metformin hydrochloride	3 427 052
9.	salmeterol and fluticasone	3 130 577
10.	irbesartan	3 079 136

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

	Drug	Cost to government (A$)	DDD/1000 pop/day * PBS/RPBS ‡	Prescriptions PBS/RPBS ‡
1.	atorvastatin	606 051 755	82.99	10 855 535
2.	rosuvastatin	369 088 997	38.14	7 035 996
3.	ranibizumab	367 753 306	§	172 785
4.	adalimumab	205 117 624	0.39	115 277
5.	esomeprazole	178 922 823	21.91	6 069 831
6.	salmeterol and fluticasone	177 315 166	¶	3 130 577
7.	olanzapine	159 400 059	3.05	965 797
8.	clopidogrel	139 521 901	11.00	2 635 142
9.	etanercept	131 116 800	0.26	74 605
10.	rituximab	129 299 223	§	59 284

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people in every thousand Australians are taking the standard dose of a drug every day. (For WHO definition of DDD see www.whocc.no/ddd/definition_and_general_considera/)

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

‡ PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

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

¶ This combination does not have a DDD allocated

Source: Drug Utilisation Sub-Committee (DUSC) Database, as at 3 October 2012. © Commonwealth of Australia.

Data are based on date of supply with processing date up to the month of September 2012. Data exclude 'Under co-payment' and 'Closing the gap' prescriptions processed by the Department of Human Services.

ARTICLE

Asia Pacific Conference on National Medicines Policies

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SUMMARY

Medicines have an important role in providing health for all people. National medicines policies can help to achieve this goal.

Delegates from the Asia Pacific region have met to discuss how to actively implement national medicines policies. Although the countries are diverse, they have common challenges such as access to medicines, antibiotic resistance and the rational use of medicines.

Health insurance schemes can improve access to medicines. The pharmaceutical industry also needs to be involved in achieving universal access and rational use.

Consumer groups have an important role in ensuring policies are implemented. They can also be involved in promoting health literacy.

There is a need to build the capacity of drug regulatory agencies in the region. Regional cooperation will be needed to tackle problems of medicines quality, safety and rational use.

Introduction

Universal health coverage is the most powerful component of public health.[1] An important element of this commitment is universal access to essential medicines.[2] Robust and effective national medicines policies are an important tool in achieving the objectives of universal access. Good policies appropriately implemented can help achieve health objectives within budgetary constraints.[3] While many countries in the Asia Pacific region say they have a policy, implementation has been inconsistent and in some cases early momentum has been lost. The consequence is that access to essential medicines remains compromised.[4]

Australia is unusual among developed nations in having an integrated national medicines policy. This is not the situation in many of the countries in the region. There are problems with access and affordability, and high out-of-pocket expenses can impoverish people on low incomes.

The Sydney conference

A conference was held in Sydney on 26–29 May 2012 (see www.apcnmp2012.com.au) to emphasise the importance of actively implementing a national medicines policy to promote universal access to, and rational use of, essential medicines of assured safety, efficacy and quality. The 230 conference participants, a mix of policy makers, health professionals, regulators, academics, consumers and representatives of pharmaceutical industry, came from 45 countries. The diversity of the countries is reflected in their populations – small Pacific islands with populations of less than 25 000 inhabitants (Nauru, Tuvalu, Palau) compared to China and India with a combined population over 2.5 billion. Around half of the participating countries were low to low-middle income countries, but there were also high income countries like Australia, Brunei Darussalam, Japan, the Republic of Korea and Singapore.

The conference was a follow-up to the successful International Conference on National Medicinal Drug Policies held in Sydney in 1995.[5] Discussions at the 1995 conference endorsed the role and importance of having a national medicines policy and focused on four selected themes:

- the quality of medicines
- equity of access to medicines
- rational use of medicines
- the role of the pharmaceutical industry

These themes are reflected in the four pillars of the Australian National Medicines Policy:[6]

- safe and efficacious medicines of appropriate quality (functions managed by the Therapeutic Goods Administration (TGA))
- affordable access (through the PBS)
- the quality (or rational) use of medicines (a key role of NPS MedicineWise)
- a viable and responsible pharmaceutical industry (supported through a range of taxation, trade and financial incentives, government policy and codes of practice).

For a policy to be effective, activities need to be integrated within a functioning health system. At the time of the 1995 conference, elements of the Australian National Medicines Policy were in place, however an integrated policy was not launched until December 1999.

17 years on … what's different?

The 2012 conference focused on the importance of an effective, enacted national medicines policy in ensuring access to good quality medicines and their rational use. The range of countries, their sizes and economic diversity mean that the challenges of policy implementation differ. Some countries have substantial local manufacturing and export medicines, others are completely reliant on imports. While some countries have embraced information technology using data for real-time analysis of medicines use, others have few data for monitoring performance and informing policy development. The policy themes of 1995 remain largely unchanged in 2012, however there are new challenges in each of the policy areas.

Safe, effective, good quality medicines

While international attention focuses on fraudulent or counterfeit medicines,[7,8] a big concern is poor quality (substandard) medicines. A study of 1437 samples of five classes of antimalarial drugs purchased in South East Asia between 1999 and 2010 found that 35% failed chemical analysis, 46% of 919 failed packaging analysis, and 36% of 1260 were classified as falsified (counterfeit).[9] In 2008, a heparin produced with contaminated raw material procured from Asia caused deaths in the USA.[10] Unregulated companies and poor adherence to good manufacturing practice and international regulatory standards threaten medicine users worldwide, particularly in countries which are reliant on imports but lack their own regulatory framework or laboratory testing capacity.

Solutions

Possible responses to these challenges include regional sharing of information about manufacturing quality, strengthening the capacity of drug regulatory authorities for quality assurance activities, enforcement of regulations, and legal prosecutions. Medicines inspectors need to be empowered to act – to seize goods and shut down operations when necessary – and to be trained in the evidential standards needed for successful prosecutions. The plethora of medicine products, inadequate numbers of qualified staff and corruption threaten these regulatory efforts. Agencies like the TGA have an important role in undertaking product testing and supporting capacity building in the region through leadership and sharing information.

Safety

Medicines safety is more than adverse drug reaction reporting. While the World Health Organization (WHO) provides guidelines for establishing pharmacovigilance centres,[11] these centres are not feasible in many smaller countries. In addition, these centres do not deal with other safety problems related to poor quality medicines (substandard or counterfeit products), or physical problems (for example products degraded by poor storage conditions or a lack of refrigeration).

There is an important role for medication error reporting systems to cover problems related to dispensing, prescribing and administering of medicines. Equally important is the ability to investigate and respond to these problems. This is a particular challenge when implementing national medicines policies with limited resources. These countries will need access to external experts and laboratories to support investigations until they build their own local capacity.

Affordable access to medicines

An emerging challenge is the transition from the treatment of acute disease and infections to the management and prevention of chronic disease.[12] 'Vertical disease' programs, supported by international donors, have had enormous success in delivering both health care and medicines for tuberculosis, malaria and HIV. However, sustained efforts will be required to ensure adequate funding for medicines to treat chronic non-communicable diseases such as diabetes and cardiovascular disease. Without attention to this emerging need, there will be more examples of 'I wish I had AIDS', in response to the relatively poor access to affordable treatment for patients with diabetes compared to HIV in Cambodia.[13]

Solutions

Health insurance schemes have the potential to improve affordable access to medicines in the region. An important consideration is what is included in a minimum benefits insurance package, balancing healthcare needs with financial constraints. Poor medicines coverage policies that do not meet prioritised healthcare needs may threaten the viability of these insurance schemes. The conference posed the difficult ethical question that if it is not possible to provide universal coverage, how can we best allocate the resources available?

Generic medicines have a key role in cost containment and for increasing affordable access to medicines. However, concerns about the quality of generic medicines in some countries create mistrust and poor acceptance by consumers and prescribers. While drug regulatory authorities have an important role in assessing bioequivalence and ensuring manufacturers comply with good manufacturing practice, education strategies are also needed to promote confidence and more widespread acceptance and use of generic medicines.

Rational use of medicines

It has been suggested that policies relating to the rational use of medicines (called quality use of medicines in Australia) can only be pursued after addressing the problems of medicines regulation, quality, access, pricing, financing, cost containment and generics.[14] In many Asian countries, medicines sales are used as a means for revenue generation to support the delivery of health services, making promotion of rational use extremely difficult. Perhaps it is not surprising that the rational use of medicines is often forgotten or considered too hard, but it needs to be aligned with the rest of a national medicines policy if the policy is to be effective. Key challenges in the region are the absence of data to clearly define the problems and a limited workforce able to design, implement and evaluate interventions to improve medicines use.[15]

Solutions

The WHO has advocated 12 key interventions to promote more rational use of medicines.[16] While most countries have some policies that support the implementation of these interventions, these need to be addressed comprehensively and systematically. The conference heard that those countries with more comprehensive policies to support the quality use of medicines do seem to achieve increased rational use.[17]

Pharmaceutical industry

Both multinational and local manufacturers need to be active participants in discussions about increasing access to medicines and ensuring quality products are available through a secure supply chain. They also need to improve policies and practices for medicines promotion, and explore new business models that recognise the need to balance profits with affordable and universal access to medicines. Important economic challenges remain for industry with differential pricing of medicines in low to middle income countries and more widespread use of pharmacoeconomic analyses to inform purchasing decisions by health insurance managers and governments. Already there is evidence, particularly from the multinational companies, of a willingness to be involved in providing affordable, universal access to medicines. The Access to Medicine Index* provides a method to monitor and evaluate the performance of the pharmaceutical industry in areas such as research and development, equitable pricing, patents and licensing, along with product donations and philanthropic activities.

* www.accesstomedicineindex.org/methodology-index-2012

What's new?

Several new challenges have emerged since 1995.

Health literacy

National medicines policies have to address the issue of providing quality medicines information to consumers and health professionals, particularly given the importance of adhering to the treatment of chronic illness. While the need for consumers to be informed and health literate seems obvious, strategies for achieving this are not. The conference heard about activities that focus on improving health literacy and consumer knowledge about medicines. People can learn basic concepts of over-the-counter medicines in group sessions from responsible media or peer-educators. By understanding medicine labels and product contents, consumers can make more informed medicines purchases. Some interventions have aimed at women as consumers of healthcare and the source of medicines knowledge within families. A challenge for all of these programs is showing that improved knowledge translates into behavioural change and sustained improvements in medicines use.

Advocacy and civil society

The development of the Australian National Medicines Policy was the result of strong consumer (civil society) advocacy and lobbying in the 1990s.[6] While there are examples of consumer activism in other countries (such as India, Thailand and China), a lack of financial support for consumer groups and poor access to policy makers make progress difficult. Some recent advocacy has relied on networking across borders to share evidence and develop strategies for engagement in policy development and reform.

It is critical that civil society organisations are involved in policy discussions about universal access. A key challenge remains engaging civil society to pressure governments to deliver policies which enhance affordable access and guarantee that safe and high quality medicines are available.

Antimicrobial resistance and antibiotic use

Antimicrobial resistance is a global problem.[18,19] Contributing factors include high rates of antibiotic prescribing by doctors and non-medical prescribers, inappropriate choices of antibiotics, availability of antibiotics without a prescription, community expectations of a 'quick fix', and widespread and routine use in veterinary and agricultural practice. It is difficult to assess the extent of the problem as there are few reliable data available and it is a challenge to convince policy makers, health professionals and consumers that this is a real or soluble problem.

Regional collaboration and partnerships are essential and this is the strategy behind Action on Antibiotic Resistance.[20] This network has programs in South East Asia which link researchers, advocacy groups, and those engaged in prevention, control and management of antimicrobial resistance at community and hospital levels. Projects include Antibiotic Smart Use (Thailand), Smart Use of Antibiotics (Indonesia) and the Antimicrobial Stewardship Programme (Singapore).

What's needed?

Further implementation of national medicines policies in the Asia Pacific region requires renewed political will and commitment to medicines policies. There are also important needs for improving healthcare delivery systems including capacity building within countries, information sharing and the collection and analysis of data to monitor performance and progress.

Building capacity

Capacity building is required in several areas – regulatory activities, evaluation of medicines for inclusion on essential medicine lists and reimbursement programs, monitoring medicines use and the design, delivery and evaluation of programs for rational use and medicines safety. There are opportunities for regional sharing of information on quality assurance, medicine prices and health financing initiatives.

Processes can be adapted from vertical disease programs to improve medicines procurement, supply and distribution.

Regional analyses by the WHO have identified needs for training in clinical pharmacy, clinical pharmacology and pharmaceutical sector management, and also problems of health system fragmentation associated with donor and vertical disease management programs. Much better coordination is required.

Developing data

Data collection and analysis are needed to support the monitoring of drug regulatory authorities and their activities including inspections and product testing, performance of medicine supply and distribution systems, medicines affordability, availability and use. A first step is examining routinely collected data to assess its usefulness for monitoring and reporting. Where routine data collection does not exist, it will be necessary to identify (and commit to build) minimum data sets to inform and monitor the delivery of a national medicines policy. There is also a role for the development of validated indicators that can be used for within-country monitoring and between-country comparisons.

What's next?

A significant theme of the conference discussions was the value and importance of regional collaboration and networks, to share experiences, information and expertise. To build on this momentum, a small number of regional projects will be undertaken to foster relationship building and information exchange. Some early successes with these projects will encourage support for further collaboration and promote further country-specific activities.

The successful implementation of national medicines policies is critical to improving the health outcomes of people in our region. This conference addressed many of the practical aspects and solutions that will help facilitate this. There was widespread support from participants for another conference in three to five years to continue the dialogue, and to report on policy developments and on progress towards universal access to medicines. <

Details of the program, presentations at the conference and the full conference report will be available at www.apcnmp2012.com.au

Conflict of interest:
Professor McLachlan has received funding for a PhD scholarship from GlaxoSmithKline investigating ethnic differences in drug response, funding for a research assistant for development of a herb-drug interaction database from IMGateway, and an investigator-initiated research grant from Pfizer. Other research funding is provided by NHMRC Project Grants.

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ARTICLE

Parenteral antibiotics at home

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SUMMARY

Giving parenteral antibiotics to patients at home compared to in hospital presents unique challenges.

The number of visits a health professional can make to a patient's home per day and the stability of an antimicrobial drug in solution may restrict the choice of therapy.

Novel administration methods and devices allowing bolus dosing or continuous infusions can be used to enable convenient and practical home treatment of many serious infections that have no oral therapy available.

Identifying suitable patients and antimicrobials as well as appropriate monitoring is key for treatment to be successful.

Introduction

Outpatient intravenous antimicrobial therapy has been practised in the USA since the 1970s and in Australia since the mid-1990s. A number of infections, such as acute cellulitis, lower respiratory tract infections and exacerbations of bronchiectasis, osteomyelitis and infective endocarditis, can now be treated safely at home.

Many infections can be treated orally. However, because of increasing antibiotic resistance, many infections that were once treated with oral antibiotics have to be treated parenterally.

Models of care

A number of programs for home-based therapy have been developed. They can be roughly divided into three categories:

- healthcare professionals visit a patient's home regularly to administer therapy
- patient administers their own therapy at home after successful training
- patient attends regular appointments at the hospital for treatment.

The first category, in which nurses and other health professionals visit patients to administer treatment, dominates in Australia and was first adopted in Victoria in 1994.[1] Other programs do exist and the patient self-administration model is an attractive option in Australia given large geographical areas and long distances between regional areas and metropolitan hospitals.

Patient selection

The selection of patients for admission to home programs is the key to ensuring that complications that require urgent intervention in the acute hospital environment are minimised. The following points need to be addressed before admission into a program:

1. It needs to be confirmed that parenteral antibiotics are truly required and that effective oral therapy cannot be given. Many conditions such as pneumonia and osteomyelitis can be effectively managed with oral antibiotics.
2. The patient needs to be well enough to be at home. Comorbidities such as unstable diabetes, relative hypoxaemia, severe pain, cognitive dysfunction and visual or auditory handicap are contraindications.
3. The patient has to be willing to accept the program. Obligations of the patient and program of care should be discussed with the patient and carer.
4. The home environment must be suitable. There needs to be a clean, light area where intravenous line access can be performed. There also needs to be a refrigerator, telephone and a carer who is able to contact the program in an emergency.
5. Distance of the patient's home from the treating centre needs to be taken into account in terms of frequency of visits.
6. A clear understanding of medical responsibility is essential. Many programs have their own medical staff and patient care responsibility is transferred to a doctor working in the program. Other programs are led by non-medical healthcare professionals and medical responsibility remains with the referring doctor.
7. Home care should never be accepted when it is second best to inpatient management. Transfer to a home program when a patient threatens self-discharge is strongly discouraged. Reasons for the patient's desire to self-discharge against advice should be carefully sought and advice to remain in hospital should be communicated in a culturally appropriate and non-judgemental fashion.
8. The presence of substance abuse such as alcoholism or illicit drugs is a contraindication.

9. Appropriate intravenous access is essential. In some circumstances, daily cannulation for once-daily intravenous therapy when the duration of therapy is likely to be only a few days may be the simplest option. Peripheral intravenous cannulae left in situ in the patient's home are generally not a good option as they are less able to be well secured, have higher risks for infection or thrombophlebitis, and should be changed regularly. Patients requiring longer courses of therapy generally require a device that can remain in situ for a longer period of time. Peripherally inserted central cannulae have revolutionised intravenous antibiotic administration at home, and have in general low rates of complications. Increasingly, insertion of lines is performed in radiology departments where ultrasound guidance allows insertion into large veins in the upper arm, under full aseptic conditions. Other patients who may require frequent treatment courses for chronic conditions, such as cystic fibrosis, will have long-term tunnelled catheters such as Portacaths or Hickman lines.

Indications for home intravenous therapy

Only a small number of bacterial infections need to be treated with intravenous antibiotics in the home. Many mild to moderate infections can be effectively treated with oral antibiotics. For example, mild to moderate pneumonia can generally be treated orally, and even more severe cases can be changed from intravenous medications to oral once the patient is stable.[2] Similarly, urosepsis such as pyelonephritis can often be treated with oral drugs initially if the patient is stable and not vomiting, or changed to oral therapy once stable and the microbiology results are available.[2]

Streptococcal cellulitis often does not respond to oral therapy, and in the absence of severe sepsis or comorbidity it is a suitable condition for initial intravenous antibiotics at home (Table 1). For example, once-daily intravenous cefazolin plus oral probenecid is effective for moderate to severe cellulitis.[3]

Patients who have been treated and stabilised in hospital and require prolonged courses of intravenous antibiotics are commonly treated at home. Examples of indications include infective endocarditis, osteomyelitis, infected prosthetic material, brain, lung and liver abscess, exacerbations of bronchiectasis or cystic fibrosis, and specific diseases such as melioidosis. Examples of intravenous antibiotic regimens given at home are listed in Table 1.

Antibiotic resistance

Unfortunately because of the increasing incidence of antibiotic resistance in hospitals and the community, many infections that once had oral antibiotic options now only have parenteral drugs available. The rise of community-acquired methicillin-resistant *Staphylococcus aureus*, multidrug resistant *Escherichia coli* urosepsis and multidrug resistant tuberculosis means that long courses of intravenous antibiotics are needed. This situation is becoming more frequent as the development of new antimicrobial drugs has all but come to a halt.

Antibiotic selection

When choosing an antibiotic, evidence-based guidelines should be followed.[2] Only when the preferred therapy cannot be given in the home should an alternative broad spectrum drug be used.

The resources of the home program may affect the choice of antibiotic. In practice, most services will only be able to visit a patient once a day, few can visit more often. The two key factors in assessing whether an antibiotic is appropriate for use in a home program are drug stability and administration intervals. Other factors, including toxicity and whether adequate monitoring is possible, are also important.

Stability

Antibiotics must be sufficiently stable for the duration of the infusion or for extended periods if manufactured in advance. Stability is usually defined as greater than 90% of the original concentration remaining at the end of the infusion. Ampicillin and

Table 1 **Examples of infections and treatments used in hospital in the home**

Condition	Treatment
Viridans streptococcal endocarditis	Benzylpenicillin 10.8 g daily by continuous IV
MSSA blood stream infection	Flucloxacillin 8 g daily via continuous IV
MSSA infective endocarditis	Flucloxacillin 12 g daily via continuous IV
ESBL *Escherichia coli* UTI	Ertapenem 1 g daily as an IV bolus
Streptococcal cellulitis	Cefazolin 2 g IV daily with oral probenecid 1 g daily
MRSA septic arthritis	Vancomycin 1.5 g twice daily or 2–3 g daily via continuous IV (adjust for renal function and titrate to plasma concentrations)
Diabetic-foot osteomyelitis	Ticarcillin/clavulanic acid 12.4 g daily via continuous IV
Bronchiectasis exacerbation	Ceftazidime 6 g daily via continuous IV
Pneumococcal pneumonia	Benzylpenicillin 7.2 g daily by continuous IV OR ceftriaxone 1 g daily IV

MSSA methicillin-sensitive *Staphylococcus aureus*
MRSA methicillin-resistant *Staphylococcus aureus*
ESBL extended spectrum beta-lactamase producing
UTI urinary tract infection
IV intravenous administration

amoxicillin are commonly used in hospitals but are unsuitable for home programs given their low stability in aqueous solution.[4]

The stability of many antibiotics is temperature dependent and whilst they may be stable in a refrigerator for extended periods they can rapidly degrade at room and body temperature. This is an important consideration when giving continuous infusions. During an infusion, temperatures can reach more than 31° C.[5,6] Benzylpenicillin, for example, is a useful antibiotic to treat many streptococcal and enterococcal infections. However unless the antibiotic is compounded using a buffer, it rapidly degrades with 1–5% remaining after 24 hours at body temperature.[6,7]

Meropenem, a carbapenem drug that is often required to treat multidrug resistant pathogens, is poorly stable in solution and is unsuitable for continuous infusions.[8] A strategy where it is compounded and kept in the patient's refrigerator, then given eight-hourly rather than as a continuous infusion, helps overcome this problem. Continuous infusion with the bag of meropenem inside an ice pack has also been attempted. A large body of information exists on drug stability and specialty pharmacy services may be able to assist.

Administration intervals

If the patient can only be visited once a day, prescribing of antibiotics is limited to either once-daily bolus dosing or 24-hour infusions. The optimal method of administering an antibiotic will depend upon the pharmacological properties of the drug which can be separated into three categories – concentration-dependent killing, total exposure and time-dependent killing (Table 2).[9]

Bolus administration is appropriate for antibiotics that exhibit concentration-dependent killing. Aminoglycosides require high peak concentrations to maximise their effectiveness, but have a prolonged post-antibiotic effect. This allows time for the drug to be washed out, thereby minimising toxicity.

Continuous infusions are appropriate if the antibiotic effectiveness is determined by the time (T) that the antibiotic remains above the minimum inhibitory concentration (MIC) and the drug is sufficiently stable. For example, beta-lactams (penicillins, cephalosporins and carbapenems) display this property so can be administered via continuous infusion. Unfortunately not all the beta-lactams are stable for 24 hours in solution.

Twice-daily infusions of vancomycin or similar can be managed using programmable continuous ambulatory delivery pumps where the day's supply of vancomycin is delivered as two infusions 12 hours apart. Given the practicalities of many home services however, continuous infusions are often used and evidence is emerging that this method is satisfactory although comparative trials are lacking.

Monitoring

Monitoring patients enrolled in home programs is crucial to maximise efficacy and minimise toxicity. Therapeutic drug monitoring should be undertaken at least weekly for vancomycin and usually more often for aminoglycosides. There are very few indications such as multidrug resistant tuberculosis that warrant long-term aminoglycoside treatment and alternative antibiotics should always be used if appropriate.[2] Aminoglycoside toxicity is related to duration of therapy and patients being treated for longer than five days are at significantly increased risk of both renal and vestibular ototoxicity. Close monitoring including weekly audiometry is recommended. Therapeutic drug monitoring is available throughout Australia for other antibiotics including beta-lactams and teicoplanin, and may be useful in certain patients upon specialist advice.

Table 2 **Drug administration intervals and pharmacological properties**

Pharmacological property	Goal	Examples	Administration method
Concentration-dependent killing	Maximise the concentration above the minimum inhibitory concentration (Cmax:MIC)	Aminoglycosides	Intermittent
Total exposure	Maximise the total exposure of the body to the antibiotic (AUC:MIC)	Vancomycin Fluoroquinolones	Intermittent/ continuous infusions
Time-dependent killing	Maximise the time the concentration is above the minimum inhibitory concentration (T>MIC)	Beta-lactams Lincosamides	Continuous infusions

Cmax maximum plasma drug concentration during a dosing interval
MIC minimum inhibitory concentration
AUC area under the plasma drug concentration-time curve
T time

ARTICLE

Potential harms

There are several risks for patients being treated in the home with intravenous antibiotics. Non-compliance with the non-antibiotic aspects of treatment such as bed rest, limb elevation and dressing changes can be a problem. Adverse events related to the venous access device are also of concern. A safety audit at our institution in 2009 revealed that approximately 5% of patients experienced a complication with their peripherally inserted central catheter lines (for example clots, infections) – this equates to less than 1 per 1000 catheter days. Adverse drug reactions including anaphylaxis are also potential risks. Generalised skin eruptions from long courses of penicillins, cephalosporins and carbapenems may arise some weeks after starting therapy and may be heralded by a rising eosinophil count.

Conclusion

The treatment of infections with intravenous antibiotics in the home is an established treatment modality. Careful patient selection, safe intravenous access and appropriate training and monitoring means that many patients can be treated at home. Unfortunately, the rise of multidrug resistant infections means more patients will need prolonged courses of intravenous antibiotics. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

5. Meropenem can be given as a 24-hour continuous infusion.
6. Ampicillin is not suitable for hospital in the home because of stability problems.

Answers on page 211

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Book review

Gone viral: the germs that share our lives

Frank Bowden
Sydney: NewSouth Books; 2011.
224 pages

You would be forgiven for thinking that a book about 'bugs' is boring. From his basic training in infectious diseases at St Vincent's Hospital in Melbourne, through life in the Northern Territory coordinating sexually-transmitted disease programs, to working as a staff specialist in Canberra, Frank Bowden's colourful memoir is anything but boring.

If you've ever wondered what happened to SARS (Severe Acute Respiratory Syndrome) or asked yourself why smallpox is the only disease to be eradicated by vaccination, this is the book for you. Swine flu, meningitis, MRSA (methicillin-resistant *Staphylococcus aureus*), necrotising fasciitis and donovanosis are but a few diseases you will encounter. Anecdotal stories bring this fascinating, terrifying and sometimes just plain gross topic to life.

It is hard not to laugh out loud in parts, particularly when Professor Bowden describes the time he saw his first case of 'saxophone penis'. However, it is not all fun and games. The chapter 'Life during wartime' is more sombre as he recounts life on the wards in the 1980s during the HIV epidemic. Or the time he was called to the morgue to a schoolboy who went to bed feeling unwell only to be found dead in the morning from overwhelming meningococcal sepsis.

The statistics on syphilis, gonorrhoea and chlamydia in Aboriginal women will shock you. Frank Bowden shares his sometimes controversial views on infection control and the 'triumphs and failings' of the health system in these communities.

Despite it being a page turner, I did feel some points were laboured – the author dedicates a whole chapter to his personal experience of a needlestick incident during the initial years of HIV. I also skimmed the chapter on hand hygiene in hospitals despite its interesting historical references to puerperal sepsis.

This easy-to-read, witty account of life in a world of germs, complete with a glossary and index, has wide appeal. If you are a clinician, public health enthusiast or just wanting to know the facts behind the headlines, this book is as entertaining as it is informative and is perfect for a Sunday afternoon read.

Fiona G Mackinnon PhD (Microbiology)
Deputy editor
Australian Prescriber

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Volume 3, Number 6, December 2012

In this issue

Ondansetron and QTc interval prolongation – dosing change

To reduce the risk of QTc interval prolongation, health professionals are advised that the 32 mg once-daily intravenous dose of ondansetron is no longer recommended and should not be used.

Ondansetron is a potent, highly selective $5HT_3$ receptor antagonist. It is indicated for use in the prevention of chemotherapy-induced nausea and vomiting and post-operative nausea and vomiting.

Study results

A recently completed study has shown that ondansetron at a single intravenous dose of 32 mg can cause QTc interval prolongation, which in turn could lead to torsade de pointes.[1] At the highest tested dose of 32 mg intravenously over 15 minutes, the maximum mean QTc interval prolongation was about 20 milliseconds and the upper bound remained greater than 10 milliseconds during the two hours after the infusion. This suggests that this dose could result in a clinically significant degree of QTc interval prolongation in some patients.

Information for health professionals

Health professionals are advised of the following information:

- Intravenous doses greater than 8 mg (up to a maximum of 16 mg) should be infused over at least 15 minutes
- No single intravenous dose of ondansetron should be greater than 16 mg
- There are no changes to the recommended dosing with oral or rectal ondansetron formulations. Dosing with all formulations should be as described in the approved Product Information (PI).[2]
- Patients should be assessed for QTc interval prolongation or cardiac arrhythmia before being prescribed ondansetron
- Avoid ondansetron in patients with congenital long QT syndrome
- Caution should be exercised when prescribing for patients who have or may develop QTc interval prolongation, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or who take other medicines that can lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and hypomagnesaemia should be corrected before using ondansetron.

The sponsor has updated the PI and written a Dear Healthcare Professional letter advising of the revised dosing recommendations.

Health professionals are encouraged to report any suspected adverse events to the TGA.

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2. Zofran Product Information. GlaxoSmithKline Australia Pty Ltd. 2011 Nov.

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

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

Domperidone (Motilium) – serious ventricular arrhythmias and sudden cardiac death

Health professionals are advised that domperidone should be initiated at the lowest possible dose in adults. Recent epidemiological studies have shown that the use of domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death, particularly in patients taking daily doses greater than 30 mg, and in patients older than 60 years of age.

Patients should be advised to stop taking domperidone and seek immediate medical attention if they experience signs or symptoms of an abnormal heart rate or rhythm while taking domperidone. These include dizziness, palpitations, syncope or seizures.

Domperidone is a gastrointestinal motility modifier indicated for the short-term treatment of symptoms associated with idiopathic or diabetic gastroparesis in adults, and is also indicated for intractable nausea and vomiting from any cause.

Evidence of risk

The epidemiological studies showed that the risk of sudden cardiac death and/or serious ventricular arrhythmias was higher in patients using daily doses greater than 30 mg[1] and in patients older than 60 years of age[2].

Information for health professionals

Health professionals are advised:

- Domperidone should be initiated at the lowest effective dose
- The risk of serious ventricular arrhythmias or sudden cardiac death may be higher in patients taking daily doses greater than 30 mg, and in patients older than 60 years of age
- Domperidone is contraindicated with ketaconazole, erythromycin or other potent CYP3A4 inhibitors which prolong QTc interval such as fluconazole, voriconazole, clarithromycin and amiodarone
- Domperidone should be used with caution and at the lowest effective dose in at-risk patients such as those:
  - with existing prolongation of cardiac conduction intervals (particularly the QT interval)
  - using potent CYP3A4 inhibitors which may increase plasma levels of domperidone such as itraconazole, amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, diltiazem, verapamil and aprepitant
  - with significant electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia)
  - with underlying cardiac diseases such as congestive heart failure.

The dose of domperidone may be adjusted upward with caution to achieve the desired effect as needed. The expected benefit of an increased dose should outweigh the potential risks. The maximum dose of domperidone is 80 mg.

Domperidone should not be used in children.

Patients should be advised to stop taking domperidone and seek immediate medical attention if they experience signs or symptoms of an abnormal heart rate or rhythm while taking domperidone. These include dizziness, palpitations, syncope or seizures.

The PI for domperidone has been updated to include the new drug dosage and usage recommendations, as well as information about the risk of serious ventricular arrhythmias and sudden cardiac death.

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2. Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. Pharmacoepidemiol Drug Saf 2010;19:881-8.

MEDICINES SAFETY UPDATE

Cardiovascular safety risk with fingolimod (Gilenya) – updates to the Product Information

The TGA is advising health professionals of important cardiovascular safety related changes to the fingolimod (Gilenya) Product Information including new contraindications.

Fingolimod is a sphingosin 1-phosphate receptor modulator used in the treatment of relapsing remitting multiple sclerosis and secondary progressive multiple sclerosis to delay the progression of physical disability and reduce the frequency of relapse.

Following a review of the cardiovascular safety of fingolimod, the PI has been updated with new contraindications and a new precaution regarding first-dose monitoring and QTc interval prolongation.

Following the death of a patient in the US within 24 hours of their first dose of fingolimod, the US Food and Drug Administration (FDA) undertook a re-evaluation of safety data related to the cardiovascular effects of fingolimod. The FDA could not definitively conclude that the administration of fingolimod was related to the patient's death but made a number of recommendations to improve the safe use of the drug.

Fingolimod is now contraindicated:

- in patients with specific cardiac conditions; and
- with concomitant treatment with Class Ia or Class III anti-arrhythmic drugs during fingolimod initiation.

The Precautions section has been updated to include first-dose monitoring, with emphasis on cardiac monitoring, namely pulse, blood pressure and electrocardiogram. Should a patient require pharmacological intervention during the first-dose observation, overnight monitoring in a medical facility should be instituted and the first-dose monitoring strategy should be repeated after the second dose of fingolimod.

More information

Health professionals are advised to consider this new cardiovascular safety information when prescribing fingolimod. For full prescribing details, health professionals should refer to the Gilenya PI, available from the TGA website.

Disposal of unwanted medicines

Health professionals may like to inform their patients that they can safely dispose of expired, unwanted, or unused medicines, at no cost, by taking them to their community pharmacist.

Medicines may become unwanted after they expire, if they remain unused, or after the TGA publishes a safety alert recommending their disposal. Disposal of any expired and unwanted medicines can also take place with the consent of the consumer if a need is identified after a Home Medicines Review, or by a health professional.

The Australian Government-funded Return Unwanted Medicines (RUM) Project facilitates the collection and disposal of expired, unwanted or unused medicines from the community. The RUM Project operates nationally with the cooperation of the pharmaceutical industry bodies in Australia.

The RUM Project uses the national community pharmacy network to collect unwanted medicines, which are then disposed of through high temperature incineration. This means of disposal reduces the risk of accidental use of medicines and prevents environmental damage from unsafe disposal, such as flushing medicines down the toilet, tipping them down the sink or putting them out with the garbage.

More information on the RUM Project for consumers and pharmacists is available at www.returnmed.com.au.

MEDICINES SAFETY UPDATE

Changes to over-the-counter cough and cold medicines for children

Health professionals are advised that the TGA has recently completed a review of the safety and efficacy of over-the-counter cough and cold medicines for use in children.

The TGA concluded that there are no immediate safety risks with these medicines. However, the review found there is evidence that they may cause harm to children, while the benefits of using them in children have not been proven.

As a result, these medicines:

- should not be given to children under 6 years of age
- should only be given to children aged 6 to 11 years on the advice of a doctor, pharmacist or nurse practitioner
- should be labelled with warnings and instructions to the above effect
- should only be available in child-resistant packaging.

Health professionals are advised that no changes have been made to the scheduling of these medicines and a prescription is not required. A recommendation for treatment with these medicines for a child under 6 years of age constitutes off-label use.

Existing stock with older labelling can still be sold for adults and children aged 12 years and over (or 6 to 11 years on the advice of a health professional) until stocks are exhausted.

For further details of the review, see the TGA website: www.tga.gov.au/industry/otc-notices-cough-cold-review-outcomes.htm.

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

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

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

Reports may be submitted:

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

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

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DISCLAIMER

ARTICLE

Management of the idiopathic interstitial pneumonias

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SUMMARY

The idiopathic interstitial pneumonias are characterised by varying degrees of lung inflammation and fibrosis. They include primary fibrotic disorders, such as idiopathic pulmonary fibrosis, and primary inflammatory disorders, which may or may not be associated with lung fibrosis.

Distinguishing between idiopathic pulmonary fibrosis and the inflammatory idiopathic interstitial pneumonias is crucial. Early investigation and specialist referral is recommended.

There is no therapy proven to influence the progression or survival of idiopathic pulmonary fibrosis. Patients need supportive and palliative care, and if appropriate, early referral for lung transplantation.

The inflammatory idiopathic interstitial pneumonias are managed with anti-inflammatory drugs with the aim of short-term response followed by longer-term stability. Early treatment is important, as once the disease is severe, it has a similar outcome to idiopathic pulmonary fibrosis.

Introduction

Interstitial lung disease refers to a diverse group of parenchymal lung diseases (Fig. 1). They all result in damage to the lung interstitium, with varying patterns of inflammation and fibrosis. Interstitial lung disease may be idiopathic (the so-called idiopathic interstitial pneumonias), or associated with exposure to drugs or environmental triggers, or underlying connective tissue disease.

Over the past decade, there has been reclassification of the idiopathic interstitial pneumonias to include:

- idiopathic pulmonary fibrosis (previously called cryptogenic fibrosing alveolitis)
- non-specific interstitial pneumonia
- cryptogenic organising pneumonia (previously called bronchiolitis obliterans with organising pneumonia or BOOP)
- acute interstitial pneumonia
- respiratory bronchiolitis-interstitial lung disease
- desquamative interstitial pneumonia
- lymphocytic interstitial pneumonia.[1]

Idiopathic pulmonary fibrosis is the most common of the idiopathic interstitial pneumonias. It is a primary fibrotic condition. There is progressive pulmonary fibrosis and the median survival is 3–5 years.[2-5] Although there are several placebo-controlled clinical trials in progress, current treatment options are limited. The emphasis is on supportive care.

In contrast to idiopathic pulmonary fibrosis, the other idiopathic interstitial pneumonias are thought to be primary inflammatory conditions (Table 1). They have a much better prognosis.[2] However, if left untreated, fibrosis becomes more established, and the outlook is similar to that of idiopathic pulmonary fibrosis. In these diseases, treatment with anti-inflammatory drugs is the key, aiming to maximise and preserve functional status.[6]

Investigation

A patient with complaints of shortness of breath, exercise intolerance and persistent dry cough may be suspected of having interstitial lung disease. Fine inspiratory crepitations, fingernail clubbing and signs of respiratory compromise increase suspicion. Distinguishing an idiopathic interstitial pneumonia from other interstitial lung diseases requires careful history taking with regard to exposures, family history

Table 1 **Classification of the idiopathic interstitial pneumonias** [6]

Pathological process	Idiopathic interstitial pneumonia subtype
Primary fibrosis	Idiopathic pulmonary fibrosis
Inflammation leading to fibrosis	Fibrotic non-specific interstitial pulmonary fibrosis
Primary inflammation	Cellular non-specific interstitial pneumonia
	Cryptogenic organising pneumonia
	Acute interstitial pneumonia
	Lymphocytic interstitial pneumonia
	Respiratory bronchiolitis-interstitial lung disease

and systemic features. Serological tests may also help to confirm or exclude connective tissue disease. Other investigations help to establish both the diagnosis and the severity of the interstitial lung disease (see Box).

A multidisciplinary approach, combining clinical, radiological and, if available, histological evidence is considered the gold standard for diagnosing idiopathic interstitial pneumonias.[7] Even using this approach, the ultimate diagnosis may remain elusive, particularly in more advanced disease.

With such differing prognoses and treatment approaches, distinguishing idiopathic pulmonary fibrosis from other idiopathic interstitial pneumonias is important early in the illness. Idiopathic pulmonary fibrosis may be diagnosed if there is a typical clinical picture supported by characteristic changes on high resolution computed tomography (for example bilateral sub-pleural honeycomb changes, most marked at the bases). In such cases, histological confirmation is unnecessary, but if there are atypical clinical or radiological features, surgical lung biopsy may be required. Endobronchial or transbronchial biopsies are not considered adequate to make a diagnosis of idiopathic interstitial pneumonia. The 'usual interstitial pneumonia' histological pattern seen at biopsy is consistent with the diagnosis of idiopathic pulmonary fibrosis.[8]

Referral

All patients with idiopathic interstitial pneumonia require early review at a specialist referral centre, with expert radiology and pathology services. This ensures that those with a potentially treatable disease have timely access to appropriate therapies.

General management of idiopathic interstitial pneumonia

Any patients who smoke must be encouraged to stop. Supportive therapy, including access to palliative care and supplemental oxygen therapy, is important to optimise quality of life. Recent studies in interstitial lung disease have shown short-term improvements in dyspnoea, exercise capacity and quality of life

Box **Baseline investigations in idiopathic interstitial pneumonia**

Always

Chest X-ray

High resolution computed tomography

Pulmonary function testing

Arterial blood gas analysis

Serology for autoimmune disease

Sometimes

Echocardiogram

Right heart catheterisation

Six minute walk test

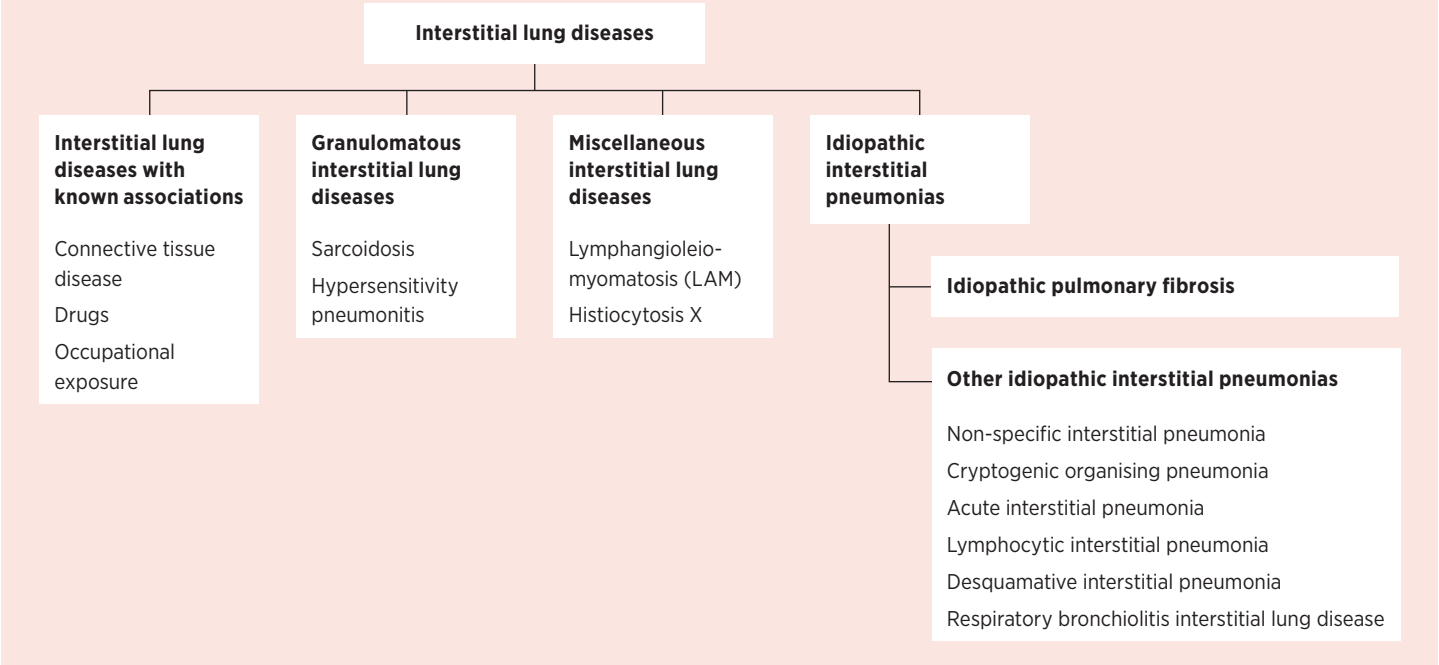
Cardiopulmonary exercise test

Bronchoscopy/bronchoalveolar lavage

Surgical lung biopsy

Overnight sleep study

Fig. 1 **Classification of the interstitial lung diseases** [1]



following pulmonary rehabilitation,[9-11] although this benefit appears to dissipate at six months.

Oxygen therapy

Current recommendations for supplemental oxygen are extrapolated from studies of chronic obstructive pulmonary disease.[8,12] Australian guidelines recommend oxygen therapy for patients with resting hypoxaemia (PaO_2 <55 mmHg, or <60 mmHg in the presence of pulmonary hypertension).[13] Nocturnal and exercise-induced hypoxaemia are markers of a poor prognosis in patients with idiopathic interstitial pneumonia,[14-16] but the benefit of using supplemental oxygen overnight, or during exercise, is not clear and the subject of ongoing research.

Comorbidities and complications

All patients with idiopathic interstitial pneumonias should be offered influenza and pneumococcal vaccines routinely. Prompt treatment with appropriate antibiotics for intercurrent infections is important. Patients have an increased prevalence of gastro-oesophageal reflux disease, obstructive sleep apnoea and pulmonary hypertension.[8,17-20] Treatment of these conditions may be beneficial, but this is currently being assessed in clinical trials. Hospitalised patients with idiopathic interstitial pneumonia have an increased risk of venous thromboembolic disease so prophylactic anticoagulation is needed.

Palliative care

General practitioners will often be involved in the palliative care of patients with advanced disease. Aside from oxygen, these patients may benefit from opioids to alleviate dyspnoea and cough. Support from community palliative care services and professionals with mental health training will also be important for many patients and their families.

Lung transplantation

In a subgroup of patients with idiopathic interstitial pneumonia, referral for lung transplantation is an appropriate and important strategy. Patients with idiopathic pulmonary fibrosis have the highest overall mortality amongst those awaiting lung transplantation.[17,21] Referral is considered when the diffusing capacity of the lung for carbon monoxide (DLCO) falls below 40%, or there is significant progression over six months (as determined by a 10% or greater drop in forced vital capacity (FVC) and/or 15% or greater fall in DLCO).[8]

Specific therapy for idiopathic pulmonary fibrosis

In a disease with such limited prognosis, the goals of therapy are to slow the decline in pulmonary function and to maximise quality of life. Multiple therapies have been tested in randomised placebo-controlled trials, with disappointing results (Table 2). Without any proven effective treatment, expert consensus and international guidelines recommend referral to specialist centres for participation in clinical trials of antifibrotic drugs.[8]

Antioxidant therapy (N-acetylcysteine)

Acetylcysteine is the precursor of the antioxidant glutathione. It replenishes glutathione stores in the lung correcting the oxidant-antioxidant imbalance, which is thought to be important in the pathogenesis of idiopathic pulmonary fibrosis.

In one study, the addition of high-dose N-acetylcysteine (600 mg orally three times daily) to low-dose prednisolone and azathioprine was associated with a significant reduction in the fall in lung function (FVC and DLCO) at 12 months.[34] A subsequent placebo-controlled trial aimed to compare this 'triple therapy' with N-acetylcysteine alone. However, the triple therapy arm was recently stopped because of increased mortality (11% versus 1% in the placebo arm). The N-acetylcysteine and placebo arms continue, with results expected in the coming year.[35]

Table 2 **Drug trials in idiopathic pulmonary fibrosis**

Drug	Action/class	Number of patients	Result
Pirfenidone[22,23]	Antifibrotic agent	107	Reduced decline in lung function in 2 of 3 Phase III studies
		779	Further study in progress (ASCEND)
BIBF1120[24]	Antifibrotic agent	432	Reduction in decline in lung function, fewer acute exacerbations per year in Phase II study
			Phase III study in progress
Colchicine[25]	Antifibrotic agent	487	No benefit over placebo
Interferon-γ-1b[26]	Antifibrotic agent	330	No benefit over placebo
Etanercept[27]	TNF-α receptor antagonist	88	No benefit over placebo
Bosentan[28,29]	Endothelin receptor antagonist	158, 616	No benefit over placebo
			May benefit patients with pulmonary hypertension
			Similar results with ambrisentan[30]
Sildenafil[31-33]	Phospho-diesterase 5 inhibitor	180, 14, 15	No improvement in 6 minute walking distance
			May benefit patients with idiopathic pulmonary fibrosis and pulmonary hypertension

Anti-inflammatory therapy

Historically, treatment of idiopathic pulmonary fibrosis was based on the suppression of inflammation. However, it now seems likely that patients who appeared to respond to anti-inflammatory therapy in early studies did not have true idiopathic pulmonary fibrosis. It is now clear that high-dose corticosteroids do not improve quality of life or survival, but have considerable adverse effects. Expert consensus therefore does not support the use of corticosteroid monotherapy in idiopathic pulmonary fibrosis.[8] There is no evidence for the use of other immunosuppressants including cyclophosphamide.[36,37]

Acute exacerbations

Aside from treating intercurrent infections, and other reversible components, management of acute exacerbations of idiopathic pulmonary fibrosis can be difficult. Most patients will require hospitalisation and specialist care. While many clinicians will give corticosteroids, there are no controlled trials to support this practice.[8]

Treatment of other idiopathic interstitial pneumonias

Inflammation, with or without progression to fibrosis, plays an important role in the pathogenesis of other idiopathic interstitial pneumonias. In contrast to idiopathic pulmonary fibrosis, the goal of therapy is to first achieve and subsequently maintain the patient's best clinical and functional status.

Initial treatment with high-dose corticosteroids is often warranted, with review of steroid-responsiveness at 4–6 weeks. The steroids are usually tapered to the lowest possible maintenance dose, while monitoring clinical and functional parameters.

If the response to high-dose corticosteroid therapy is suboptimal, addition of other immunosuppressive drugs may be necessary. Immunosuppressive drugs may also be needed as steroid-sparing drugs when corticosteroids cannot be reduced to acceptable doses (generally considered to be a daily dose of prednisone 10 mg or less). The drugs commonly used in maintenance therapy include azathioprine, mycophenolate mofetil and oral or intravenous cyclophosphamide. They are usually used in combination with low-dose prednisone.[6,7]

Specific treatment strategies

In patients with primary inflammatory processes and fibrosis, as in fibrotic non-specific interstitial pneumonia, close observation is vital. Immunosuppressive therapy should be started in progressive or moderately severe disease so as not to miss an important window of treatment responsiveness. Once fibrotic non-specific interstitial pneumonia becomes advanced the patients have similar outcomes to those with idiopathic pulmonary fibrosis.

Desquamative interstitial pneumonia and respiratory bronchiolitis interstitial lung disease are both related to tobacco consumption. Smoking cessation must be stressed and is sometimes the only intervention necessary. Corticosteroids and other anti-inflammatory drugs may be considered for cases of refractory desquamative interstitial pneumonia.

Any patients who smoke must be encouraged to stop

Cryptogenic organising pneumonia is usually steroid-responsive, although there is a high incidence of relapse. Some patients may go on to a progressive fibrosing organising pneumonia which may be refractory to steroids, but may respond to more aggressive anti-inflammatory therapies.

Lymphocytic interstitial pneumonia may be associated with autoimmune or lymphoproliferative disease, as well as HIV infection. Corticosteroids can be of benefit, and treating the underlying disorder may also help. Acute interstitial pneumonia and acute exacerbations of the other idiopathic interstitial pneumonias are usually treated in hospital, with attention to reversible factors and implementation of high-dose immunosuppression. Pulsed intravenous methylprednisolone followed by second-line immunotherapy is a reasonable strategy although there is little controlled evidence to support this approach.

Conclusion

It is important to distinguish between idiopathic pulmonary fibrosis and other idiopathic interstitial pneumonias with a primary inflammatory pathogenesis, as there are major prognostic and therapeutic implications. There are no effective treatments for idiopathic pulmonary fibrosis although there are some potentially promising new antifibrotic drugs in clinical trials. The focus of treatment is on supportive care, including palliation, and management of comorbidities.

In contrast to idiopathic pulmonary fibrosis, the other idiopathic interstitial pneumonias are primary inflammatory conditions and have a better prognosis. Treatment is with anti-inflammatory drugs, aiming to maximise and preserve the patient's clinical and functional status. ◀

Dr Troy and Dr Corte are involved with the Royal Prince Alfred Hospital Interstitial Lung Disease Clinic which has received an unrestricted educational grant from Actelion.

Q:

SELF-TEST QUESTIONS

True or false?

7. Patients with idiopathic interstitial pneumonia should not be given pneumococcal vaccine.

8. High-dose corticosteroids improve the survival of patients with idiopathic pulmonary fibrosis.

Answers on page 211

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FEATURE

Medicines Australia Code of Conduct: breaches

Key words
Medicines Australia, breaches

Aust Prescr 2012;35:207

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

There were only 12 complaints made to Medicines Australia in 2011–12. Half of these complaints were made by health professionals.

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

Companies reported on tens of thousands of educational events they had organised or sponsored. Only two of these presentations resulted in complaints and neither event was found to have breached the Code of Conduct.

The largest fine this year resulted from a website which encouraged healthcare professionals and the public to petition the Government to reverse its decision to defer the listing of dabigatran, for stroke prevention in atrial fibrillation, on the Pharmaceutical Benefits Scheme. The New South Wales Therapeutic Advisory Group (NSW TAG) complained that some of the content of the website was intended to promote the product. While the Code of Conduct Committee agreed that the first version of the website was promotional, it considered that an amended version did not breach the Code. The NSW TAG appealed against that decision. While the Code of Conduct Appeals Committee decided that the second version had also breached the Code, it did not impose any additional financial sanction.

A new version of the Code of Conduct, edition 17, is scheduled to commence on 1 January 2013.

Table **Breaches of the Code of Conduct July 2011 – June 2012**

Company	Brand (generic) name	Material or activity	Sanction
Alcon Laboratories	Travatan (travoprost)	Misleading claim in detailing aid	$25 000 fine Claim not to be used again
Boehringer Ingelheim	Pradaxa (dabigatran)	Website indirectly promoting the product to the general public	$125 000 fine Website to be removed
CSL	Flomaxtra (tamsulosin)	Misleading claims in promotional material Promotion to the general public	$75 000 fine Patient educational material not to contain promotional material
Merck Sharp and Dohme	Sevikar (amlodipine with olmesartan)	Misleading claims in detailing aid	$25 000 fine Claims not to be used again
Novartis Pharmaceuticals	Onbrez Breezhaler (indacaterol)	Misleading claims in detailing aid	$100 000 fine Claims not to be used again
Sanofi-Aventis	Actonel EC (risedronate)	Promotional message in media release	$40 000 fine Material not to be used again

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2. Medicines Australia. Code of Conduct Annual Report 2012. http://medicinesaustralia.com.au/files/2010/01/20121018-PUB-CoC-AnnualReport-2011_2012.pdf [cited 2012 Nov 8]

NEW DRUGS

New drugs

Axitinib

Approved indication: renal cell carcinoma
Inlyta (Pfizer)
1 mg and 5 mg tablets
Australian Medicines Handbook section 14.2.3

Axitinib is another addition to the group of tyrosine kinase inhibitors – sorafenib, sunitinib and pazopanib* – for renal cell carcinoma. Its anti-angiogenic effects stem from its inhibition of the vascular endothelial growth factor receptors 1, 2 and 3.

Early trials of axitinib in patients with refractory metastatic disease were promising.[1,2] In a more recent open-label randomised phase III trial of 723 patients, axitinib (5 mg twice daily) was compared with sorafenib (400 mg twice daily). At enrolment, patients had progressive disease despite previous treatment with sunitinib, bevacizumab plus interferon alfa, temsirolimus or cytokines. Dose increases were allowed with axitinib (maximum 10 mg twice daily) but not with sorafenib. The patients who received axitinib survived for significantly longer without disease progression than those who received sorafenib (median of 6.7 months vs 4.7 months).[3] However, overall median survival was similar between treatments (20.1 months vs 19.2 months).

The safety of axitinib seems to be comparable to sorafenib. Adverse reactions were very common, with over half of the patients in the trial having their axitinib dose reduced or interrupted because of an event. Diarrhoea (55% of patients), hypertension (40%), fatigue (39%), decreased appetite (34%), nausea (32%), dysphonia (31%) and hand-foot syndrome (27%) were the most common. In the phase III trial, 16% of patients had a bleeding event and just over a third had anaemia. Conversely, 10% of patients had increased haemoglobin so monitoring this parameter is important. Thrombocytopenia (15%), lymphopenia (33%), creatinine elevation (55%), hypocalcaemia (39%) and lipase elevation (27%) were also common. Axitinib can affect thyroid (19.2% of patients had hypothyroidism) and liver function so these should be measured at baseline and regularly during treatment.

High blood pressure is a problem with axitinib and should be controlled with antihypertensives. In persistent cases, the axitinib dose may need to be reduced, or interrupted then restarted at a lower dose when blood pressure has normalised. Proteinuria occurs with axitinib (10.9% of patients) and should be monitored before and during treatment.

In the axitinib arm of the phase III trial, one patient died of a cerebrovascular accident and another of pulmonary embolism. Axitinib should be used with care in patients with a history of such events, particularly as they were excluded from the trial. There was also a death from gastric haemorrhage and axitinib should not be used in patients who have recently had gastric bleeding. Gastrointestinal perforation and fistulas have been reported with axitinib and patients should be monitored for symptoms during treatment.

One patient in the trial developed reversible posterior leukoencephalopathy syndrome. It can present with headache, seizure, lethargy, confusion, blindness and other neurological symptoms, with or without hypertension. Treatment should be stopped if this is suspected.

Following an oral dose of axitinib, peak plasma concentrations are reached within four hours and steady state is achieved after 2–3 days. Axitinib is metabolised in the liver and the dose should be reduced in patients with moderate hepatic impairment. Axitinib is excreted in the faeces and urine and caution is urged in patients with end-stage renal disease.

Axitinib is metabolised mainly by cytochrome P450 (CYP) 3A4, but also by CYP1A2, CYP2C19 and UGT1A1 so there is a potential for drug interactions. Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole, clarithromycin, grapefruit juice) or inducers (such as rifampicin, carbamazepine, St John's wort) may affect axitinib concentrations. If these drugs cannot be avoided, adjustment of the axitinib dose is recommended.

The prognosis for patients with advanced renal cell carcinoma is poor. Axitinib provides another option for those who have relapsed despite previous treatment. Although it may temporarily reduce disease progression, it does not seem to prolong overall survival any more than sorafenib. It is not known how axitinib will compare to other treatments for this disease.

T manufacturer provided the product information

* sorafenib – Aust Prescr 2006;29:167-71
sunitinib – Aust Prescr 2006;29:167-71
pazopanib – Aust Prescr 2010;33:193-8

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

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First published online 28 September 2012

Cyclizine lactate

Approved indication: prevention of postoperative nausea and vomiting

Valoid (Link Medical Products)

ampoules containing 50 mg/1 mL for injection

Australian Medicines Handbook section 1.2.1

About a third of patients will develop postoperative nausea and vomiting if they are not given prophylaxis. It is more common in women, especially after abdominal surgery.

Cyclizine, an antihistamine, is already being used (tablets and injectable solution) as an antiemetic after surgery in Australia. However, the solution for injection has only recently been approved by the Therapeutic Goods Administration.

A Cochrane review of antiemetics analysed 10 studies of parenteral cyclizine.[1] The trials were mainly in women having surgery (caesarean, laparoscopy), except for one study in boys. An analysis of these studies found that cyclizine decreased the risk of nausea by 65% and vomiting by 55%, compared to placebo. Overall, cyclizine's antiemetic effect was comparable to ondansetron. However in the study of boys having surgery for hypospadias, cyclizine was no better than placebo.[2]

In a trial not included in the review, cyclizine was compared to droperidol in patients administering their own analgesia after surgery. Thirty women were randomised to receive cyclizine or droperidol during surgery and then after, intravenously, with patient-controlled morphine. Nausea scores were comparable between treatments, with three patients in each group needing extra antiemetics.[3]

Cyclizine has also been used in combination with other antiemetics. Before anaesthesia, 960 women undergoing day surgery were given intravenous cyclizine 50 mg, intravenous granisetron 1 mg, or both. Postoperative nausea and vomiting were less common with combination treatment than with cyclizine or granisetron alone (17% vs 23% and 24%).[4]

Cyclizine's antiemetic effect lasts for approximately four hours. The elimination half-life is around 14 hours following a single 25 mg intravenous dose. Cyclizine can be given up to three times a day but treatment should not continue beyond 48 hours.

Drowsiness is common with cyclizine and it may have additive effects with alcohol and other drugs that cause nervous system depression such as hypnotics, sedatives and anaesthetics. Other adverse effects include dizziness, dry mouth, constipation, blurred vision, headache, somnolence, dyskinesia, tremor, convulsions, transient speech disorders and injection-site reactions. Disorientation, restlessness, agitation, insomnia and hallucinations have also been reported. Temporary paralysis has occasionally occurred in patients with underlying neuromuscular disorders.

Because of its anticholinergic effects, cyclizine may precipitate urinary retention and incipient glaucoma. Monitoring is recommended in patients with glaucoma, obstructive disease of the intestine, liver disease, epilepsy and prostatic hypertrophy. As cyclizine may cause thickening of bronchial secretions, it should be used with caution in patients with asthma or chronic obstructive pulmonary disease. This drug may increase the adverse effects of other anticholinergic drugs.

Cyclizine is contraindicated in patients with severe heart failure. It is a category B3 drug and its use in pregnancy and lactation is not recommended.

This drug is effective for preventing postoperative nausea and vomiting, and is comparable to other antiemetics such as ondansetron, granisetron and droperidol. Cyclizine is not recommended for children and there have been no studies in older people.

[X] manufacturer did not respond to request for data

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First published online 11 September 2012

NEW DRUGS

Velaglucerase alfa

Approved indication: Gaucher's disease type 1

VPRIV (Shire)

glass vials containing 400 units as lyophilised powder for reconstitution

Australian Medicines Handbook section: Appendix A

Gaucher's disease is one of the lysosomal storage diseases. A genetic disorder results in a lack of glucocerebrosidase. This enzyme deficiency leads to accumulation of glucocerebroside in macrophages, with enlargement of the liver and spleen. There can be bone involvement, anaemia and thrombocytopenia.

Enzyme replacement therapy has been available since the 1990s, first with alglucerase and later with the genetically engineered imiglucerase (Aust Prescr 1999;22:95-8). While imiglucerase was produced from Chinese hamster ovary cells, velaglucerase alfa is produced from human fibroblast cell lines. It has the same amino acid sequence as natural glucocerebrosidase.

As Gaucher's disease is relatively rare (only about 400 patients in Australia), the clinical trials of velaglucerase have been small. In a trial of adults with no recent use of imiglucerase, 12 symptomatic patients were given intravenous infusions of velaglucerase every other week for up to nine months. There were improvements in their haemoglobin and platelet counts. Liver and spleen volumes reduced. These improvements were sustained in nine patients who entered an extension study for an additional 39 months.[1]

Two doses of velaglucerase were compared in a 12-month study in children and adults. In the 12 patients who were treated at a dose of 60 units/kg the mean haemoglobin increased from 108.3 g/L to 125.5 g/L. It increased from 107.2 g/L to 131.6 g/L in the 13 patients given 45 units/kg. Platelet counts increased by 50.88 x 10^9/L with 60 units/kg and by 40.92 x 10^9/L with 45 units/kg. While both doses decreased spleen volume, there was no significant decrease in liver volume.

The 60 units/kg dose has been recommended. This is given as a one hour infusion every other week. A dose reduction may be possible depending on the response.[1]

A phase III study randomised 34 patients to be treated with velaglucerase 60 units/kg or imiglucerase for nine months. The patients' haemoglobin concentration was the primary outcome. Their mean haemoglobin increased by 16.2 g/L with velaglucerase and by 14.9 g/L with imiglucerase. There was also an increase in mean platelet counts and decreases in liver and spleen volumes. These results showed that the efficacy of velaglucerase is not inferior to that of imiglucerase.

Another trial studied 40 patients who had already been treated with imiglucerase for at least 30 months. When they were switched to velaglucerase there were no significant changes in haemoglobin or platelet counts over the next 12 months.

A shortage of imiglucerase in 2009 led to patients' treatments being reduced. Some of the effects of reduced treatment were reversed in a group of 32 patients who were switched to velaglucerase. However, imaging in ten of these patients detected an increase in liver volume in five patients after six months of velaglucerase.[2]

The safety data for velaglucerase came from 94 adults and children. Reactions to the infusion were the most common problem. These included headache, fever, nausea, dizziness and altered blood pressure. Adverse events which were more frequent than with imiglucerase included headache, fever, diarrhoea, hypertension and arthralgia. Patients may also complain of bone pain or back pain. No data are available concerning the use of velaglucerase in pregnancy or lactation.

Some patients develop antibodies to imiglucerase. Although hypersensitivity reactions have occurred with velaglucerase, so far only one patient has developed antibodies to velaglucerase. Caution is needed if the patient is hypersensitive to other enzyme replacement products.

Enzyme replacement therapy is expensive. Although the number of patients needing therapy is small, there is now another option for treatment.

T T manufacturer provided additional useful information

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First published online 28 September 2012

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

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

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

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

Erratum

Antivenom update

(Aust Prescr 2012;35:152-5)

An observant reader noticed that the photo of a tiger snake in the October issue was actually a photo of a broad-headed snake (*Hoplocephalus bungaroides*). This was an error, and here is a picture of a tiger snake (*Notechis scutatus*).

Image courtesy of Scott Eipper

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3	False	4	True
5	False	6	True
7	False	8	False

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