Australian Prescriber

VOLUME 31 | NUMBER 4 | AN INDEPENDENT REVIEW | AUGUST 2008

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Editorial

Undertreatment of rural people with cardiovascular disease

Dawn E DeWitt, Professor and Head, School of Rural Health, and Dean, Rural Clinical School, University of Melbourne, Shepparton, Victoria

Key words: drug utilisation, therapeutic guidelines.

(Aust Prescr 2008;31:86–7)

A report by the Australian Institute of Health and Welfare (AIHW) shows that drugs and some interventions for cardiovascular disease are underused in rural areas.[1] It found that rural patients are getting far fewer prescriptions for beta blockers, ACE inhibitors, statins and warfarin than other Australians. For example, the report found that for males the rate of new prescriptions per 100 000 people for lipid-lowering drugs was 286 in metropolitan areas, 147 in rural areas and 10 in remote areas.[1]

Mortality rates for coronary heart disease are higher outside capital cities. The difference between rural and urban areas accounts for approximately 5000 excess deaths per year.[2] If some of the increased mortality in rural people[1,3] is the result of underprescribing for cardiovascular disease, then doctors can make a difference by addressing the issue of appropriate prescribing and 'compliance'.

Access problems probably account for much of the rural-urban gap. We know that rural patients see their general practitioners, on average, 1–2 fewer times per year than city dwellers.[1,4] Additionally, rural patients have less access to cardiologists, who are more likely to be aggressive with cardiac therapies and do not have to pay attention to the patient's many other needs. Timely access to technical intervention in acute coronary syndromes is a problem, for example if patients have to travel for hours before even being considered for thrombolytics, pacemakers or percutaneous coronary intervention.

The evidence about prevention and treatment of ischaemic heart disease has matured to the point that guidelines are relatively simple and straightforward for most patients.[1] While specialists may be more familiar with guidelines, the studies about whether or not patients with cardiovascular disease are best cared for by cardiologists, general physicians or general practitioners are conflicting. Some studies show more intervention by specialists, but no difference in mortality. Others show that patients do better if cared for by cardiologists, or doctors who graduated from medical school more recently, possibly because they have been trained to use guidelines.[5]

Even if doctors know the recommended drugs, they may be reluctant to prescribe them. For example, doctors often hesitate to prescribe beta blockers because of myths about suppression of hypoglycaemic reactions in diabetes.[6] However, patients with diabetes and cardiovascular disease benefit (reduced mortality) more than others from beta blockers so the drugs are strongly recommended.[1,6] Chronic obstructive pulmonary disease often raises concerns among doctors when beta blockers are indicated, but systematic reviews show that this concern should not prevent doctors from prescribing this life-saving therapy.[7]

Rural areas have a disproportionately high and increasing percentage of elderly patients[3] who are more likely to have cardiovascular disease, and are also likely to have other medical problems. Legitimate concerns about drug interactions and adverse effects in this vulnerable group may increase the reluctance to prescribe. However, studies looking at hypertension treatment and anticoagulation show

In this issue…

In the previous issue of *Australian Prescriber* we discussed how the initial enthusiasm for thiazolidinediones (glitazones) in diabetes was diminished by the emergence of serious adverse effects. Inside this issue we feature the incretin mimetics and enhancers and their use in the treatment of diabetes. In their reviews Johannes Prins, Anne Reutens and Jonathan Shaw all caution that the role of these new drugs requires further study.

While there are interesting new developments in the drug treatment of diabetes, it is essential that basic care is not overlooked. Kerry May explains the importance of looking after patients' feet to prevent ulcers.

Many patients with diabetes have cardiovascular disease. While there are guidelines for managing cardiac diseases, some patients do not receive optimum care. Dawn DeWitt discusses why undertreatment may be a particular problem in rural areas of Australia.

Diabetes is also associated with restless legs syndrome. Dominic Thyagarajan explains how people can be helped without the need to take neurological drugs.

that, generally, older patients should have the same goals (for example blood pressure < 130/80) as younger patients.

Indigenous Australians have high rates of heart disease. Living in a remote area, as well as having comorbidities, may make them less likely to receive coronary interventions.[8]

Some patients do not fill their prescriptions and the major problem here seems to be cost.[9] The AIHW report does not address this directly, but, for example, general patients prescribed an ACE inhibitor, a beta blocker and a lipid-lowering drug would pay about $90 per month. Rural patients also face higher costs accessing medical care, although their incomes tend to be lower than those of urban residents.

Assuming cost issues can be overcome, what about compliance? The report reveals that rural patients are actually slightly more compliant than their city peers, but many stop taking the drugs because of adverse effects or a lack of understanding about their treatment.[1] Better doctor-patient communication and more time spent reviewing medication compliance might help. However, I know from experience as a rural doctor that the pressure on general practitioners to see more patients may subvert preventive therapies or counselling when doctor availability and waiting lists are problems and diverting 'crises' are common.

I think we can do better in the country. We should firstly think about cardiovascular disease and know the major recommendations. Secondly, we need to schedule time to review treatment or consider ordering a medication review. Adherence to lipid-lowering therapy improves if patients get their cholesterol checked and have their medications reviewed by their own doctor.[10] Improved adherence then improves mortality.[9,11]

Other health professionals could be involved in a structured campaign that goes straight to rural people. For example, if the main problem is access, we could look at mechanisms in pharmacies that appropriately identify people who would benefit from cardiovascular drugs. Rural pharmacies and general practices could be given support to improve patient knowledge and adherence to treatment. Staff could ask a few direct questions about heart disease or risk factors. A 'yes' then prompts a pharmacy or practice nurse review of whether the patient's blood pressure is controlled and whether they are taking the recommended list of medications.

The Commonwealth government has increased the number of medical school places across Australia. The new rural clinical schools are training 25% of the nation's medical students, so that in about 10 years we may have enough doctors for regional and rural Australians. In the meantime, knowing the guidelines and being mindful of the gap in mortality, rural doctors should work with other health professionals to identify patients for whom cardiovascular medications could prove life-saving, and work together to close the gap.

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Conflict of interest: none declared

Letters

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

Sulfur allergy

Editor, – I refer to the article ' 'Sulfur allergy' label is misleading' (Aust Prescr 2008;31:8–10). In ophthalmology, it has been customary to use acetazolamide tablets for raised intraocular pressures not responding to local therapy. I note that your article does not mention acetazolamide.

I would be grateful for your advice about possible allergic reactions to acetazolamide. My concern relates to one patient who had a severe anaphylactic reaction, presumed to be due to acetazolamide.

Roger McGuinness
The Eye Institute
Bondi Junction, NSW

Dr William Smith, one of the authors of the article, comments:

The essential question is whether a patient who has a history of an allergic reaction to a sulfonamide antibiotic (sometimes inappropriately referred to as 'sulfur allergy') is at increased risk of an allergic reaction to acetazolamide compared to a patient with a history of allergy to an unrelated drug, or with no drug allergy history.

It is known that being allergic to one drug increases the risk of allergy to other drugs, regardless of the structural difference or similarity of the second drug. In fact the more drugs one is allergic to, the greater the risk that one will have a reaction to any other drug. This is a separate issue to cross-reactive allergy, which depends on the structural relatedness of the drug, such that the immune system, primed to respond to one drug, will react with a second structurally similar drug.

Firstly, acetazolamide, although a sulfonamide, is not a sulfonylarylamine sulfonamide and is therefore thought to be not sufficiently structurally similar to sulfonamide antibiotics to be cross-reactive to the immune system. Secondly, a survey of patients with a history of sulfonamide antibiotic allergy did not show an increased incidence of allergic reactions to non-antibiotic sulfonamides (including acetazolamide) above that conferred by a history of allergy to unrelated drugs.[1]

The patient who had anaphylaxis to acetazolamide constitutes anecdotal evidence. It is most likely that this allergic reaction was coincidental and not specifically related to a previous history of allergy to sulfonamide antibiotics.

Current expert opinion, based on the evidence, would be that a history of sulfonamide antibiotic allergy should not be considered an absolute contraindication to the use of acetazolamide. (I acknowledge that this is contrary to the current product information; it would be wise for medicolegal reasons to employ caution in such patients.) Doctors should always be prepared to deal with allergic reactions to the medications they prescribe, although these reactions are rare. Intravenous drugs carry a risk of causing more severe anaphylaxis although not at any greater incidence compared with oral administration. The risk of such reactions will be increased above background levels in patients with a history of allergy to other drugs, particularly multiple other drugs, whether sulfonamide or not.

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Editor, – I agree that the term 'sulfur allergy' (Aust Prescr 2008;31:8–10) is misleading in relation to allergic reactions to sulfonamide drugs and the confusion is contributed by the American custom of substituting 'f' for 'ph'.

John Walker
Ear, Nose and Throat Specialist
Edgecliff, NSW

Editor, – I was interested in the article on sulfur allergy (Aust Prescr 2008;31:8–10), not only for its content but by the metamorphosis of 'sulphur' to 'sulfur'. I acknowledge that language is in a constant state of flux but is this spelling an editorial decision or are we now all to use the American pharmacopeia for drug nomenclature?

Ross MacPherson
Clinical Associate Professor
Department of Anaesthesia and Pain Management
Royal North Shore Hospital
Sydney

Editorial note:

The Therapeutic Goods Administration publishes the Australian Approved Terminology for Medicines (at www.tga.gov.au/docs/html/aan.htm). For more than a decade 'sulfur' has been the Australian approved name.

Eye drops

Editor, –The excellent article by Michael Steiner (Aust Prescr 2008;31:16–17) prompts me to submit an alternative method demonstrated by an ophthalmologist many years ago. It is particularly useful when drops are to be administered to children and elderly people.

It involves approaching the eye from across the nose into the corner near the nose so that the dropper is unseen and the tendency to blink is reduced. Even with the eye closed the drops eventually enter the area around the eye as shown by a study with pilocarpine at the time.

- Tilt the head back or lie down to face the ceiling.
- Approach the eye from across the nose and hold the dropper above the inner corner without touching it.
- Squeeze out a drop and feel the liquid run into the eye.
- Gentle pressure on the bridge of the nose for 1 to 2 minutes will slow draining and increase effect. Rubbing the eye decreases it.
- The eye may be closed while instilling the drops, especially for children, as drops flow into the eye on opening.
- Leave 5 minutes between different drops.

Peter Bayly
Consultant pharmacist
Burnside, SA

Dr Steiner, author of the article, comments:

There are of course many ways that eye drops can be instilled and that described by Peter Bayly is especially useful in fractious, frightened children. The only minor problem with it is the small risk of washing skin flora into the conjunctival sac. However, it is useful when more traditional techniques are not possible.

Subsidised medicines for Aboriginal and Torres Strait Islander people

Since August 2006, the Pharmaceutical Benefits Scheme (PBS) has been including new listings specifically for the treatment of common conditions in Aboriginal and Torres Strait Islander people. Some listings are medicines new to the PBS, while others vary the restrictions for prescribing existing PBS items. For the most up-to-date information on relevant PBS-subsidised items, and their conditions for prescribing, see the current list in the fact sheet at www.pbs.gov.au.

New listings include antimicrobial drugs for fungal and yeast infections, otitis media and whipworm. Vitamin supplements have also been added.

The items in Table 1 are available as 'Authority PBS prescriptions'. For more information about PBS access by Aboriginal and Torres Strait Islander people, send an email to pbs-indigenous@health.gov.au

For changes to this list and other listings, readers can subscribe to news alerts from the PBS at www.pbs.gov.au/html/healthpro/subscription/manage

Table 1

PBS listings as at 1 July 2008

Treatment of a fungal or a yeast infection
1. Bifonazole cream (1%) *
2. Clotrimazole lotion (1%) *
3. Ketoconazole cream (2%) and shampoo (1%, 2%) *
4. Miconazole nitrate (2%) as cream, powder, lotion and tincture *
5. Nystatin cream (100 000 units per g) *
6. Terbinafine cream (1%) *
Prophylaxis of thiamine deficiency
7. Thiamine tablet (100 mg) *
Treatment of whipworm infestation
8. Albendazole tablet (200 mg) *
Treatment of chronic suppurative otitis media
9. Ciprofloxacin ear drops (0.3%)
Treatment of a dermatophyte infection where topical treatment has failed
10. Terbinafine tablet (250 mg)

* streamlined authority listing

Restless legs syndrome

Dominic Thyagarajan, Associate Professor and Head of Neurology, Flinders Medical Centre, Adelaide

Summary

Restless legs syndrome is common. While many patients are simply inconvenienced, others suffer greatly from wakefulness and disturbed sleep. The condition is readily recognised by history and examination and perhaps simple investigations. Secondary causes should be excluded. Mild symptoms can be managed without drugs, but severe symptoms may require a dopamine agonist. Treatment is usually effective but may present some practical difficulties.

Key words: dopamine agonists, opioids, pramipexole, ropinirole.

(Aust Prescr 2008;31:90–3)

Introduction

About 5–15% of the population are affected by restless legs syndrome.[1] Probably the earliest description was written in 1683 in 'Two discourses concerning the soul of brutes':

> ... whilst they would indulge in sleep, in their beds, immediately follow leapings up of the tendons in their arms and legs, with cramps, and such unquietness and flying about of their members, that the sick can no more sleep, than those on the rack.[2]

This captures the elements of restless legs syndrome: sensory discomfort ('cramps'), motor restlessness ('unquietness'), the associated involuntary movements during sleep and wakefulness ('flying about of their members'), aggravation by night and rest ('in their beds'), sleep disruption, and the tortured condition of the worst affected ('on the rack').

Restless legs syndrome can begin at any age. Earlier, slower onset suggests hereditary restless legs syndrome and later, abrupt onset, secondary restless legs syndrome. At first exacerbations and remissions occur, but then the tendency is for a static or chronic progressive course. Although some people have severe symptoms, most people do not require drug treatment.

Diagnosis and classification

The clinical evaluation of restless legs syndrome, particularly the patient's history, is very important. The diagnosis is based on criteria proposed at a consensus conference held at the National Institutes of Health in the USA (see box).[1] The condition is classified as 'idiopathic' or secondary to several other conditions (Table 1).

Essential diagnostic criteria

Typically, patients complain of limb (usually leg) discomfort at rest, an urge to move the affected part, and unpleasant sensory symptoms. They often find it hard to describe the sensations, or say 'creeping, crawling, itching, burning, searing, tugging, pulling, drawing, aching, hot and cold, electric current-like, restless or painful'. These sensations are felt deep in muscle or bone, seldom in a joint. The whole limb or part of it may be involved, even unilaterally. In about half the cases, arms and legs are affected, but sole involvement of the arms is uncommon. Occasionally, the sensory symptoms are absent.

Usually, the symptoms begin after the patient has been lying or sitting quietly. Symptoms only on sitting are very uncommon. The more mentally rested and physically quiet the patient is, the more intense the symptoms. They can last for a few minutes or an hour.

Voluntary movement, not necessarily of the affected parts, promptly but only temporarily relieves the symptoms. A characteristic history is that the patient moves about in their chair or bed, gets up and paces about, stretches the limbs or rubs the legs to get relief. Placing the limbs on a cold or hot surface sometimes helps.

The worst times are from the evening to the early hours of the morning, whether or not the patient is asleep. This circadian

Diagnostic criteria for restless legs syndrome [1]

Essential criteria

1. An urge to move the legs (and occasionally the arms or other body parts) usually, but not always, accompanied by uncomfortable or unpleasant sensations
2. The symptoms begin or worsen during periods of rest or inactivity such as lying or sitting
3. Movement such as walking or stretching partially or totally relieves the symptoms at least as long as the activity continues
4. A circadian pattern: the symptoms are worse or only present in the evening or at night and this diurnal variation must have once been present if the symptoms are now so severe as to make diurnal variation unnoticeable

Supportive of the diagnosis

1. Family history
2. Response to dopaminergic therapy
3. Periodic limb movements during wakefulness or sleep

pattern may be lost in severe cases and it is modified by shift work, medication and sleep disorders.

Supportive clinical features

Over 50% of patients have a family history of restless legs syndrome. The pattern is consistent with an autosomal dominant mode of inheritance.

In 80% of patients, repetitive flexing movements of the legs (occasionally the arms), and dorsiflexion and fanning of the toes, for 0.5–5 seconds every 5–90 seconds, occur during sleep or wakefulness. While common, these movements are not required for the diagnosis of restless legs syndrome, nor are they specific to the condition, occurring normally and in a number of other conditions.

Associated features

Over 90% of patients have insomnia – usually trouble initiating or maintaining sleep. The neurological examination is usually normal although there may be signs of neuropathy in some secondary cases. There is an association between restless legs syndrome and cardiovascular disease.[3] Clinical examination is mainly directed at identifying causes of secondary restless legs syndrome (Table 1).

Investigations

Laboratory testing is fairly limited unless a secondary cause is suspected from the history or examination. Measuring iron and ferritin is particularly important as low stores may precipitate and aggravate restless legs syndrome. Recently, measures of ferritin in the cerebrospinal fluid and MRI scans showing reduced iron in the red nucleus and striatum suggest that iron stores in the brain are reduced.[4]

Nerve conduction studies are indicated if the clinical evaluation suggests a neuropathy. They are of doubtful use otherwise, particularly if there is a family history.

Sleep studies for the formal evaluation of sleep quality or periodic limb movements during sleep are neither generally feasible or usually required. They may be considered if excessive daytime somnolence suggests significant sleep disruption.

Table 1

Classification of restless legs syndrome

Primary	Secondary
'Idiopathic'	Iron deficiency
	Pregnancy, especially in third trimester, resolving with delivery
	Uraemia
	Peripheral neuropathies generally, and specifically Charcot-Marie-Tooth type 2 and familial amyloid neuropathy
	Diabetes
	Rheumatoid arthritis
	Vitamin B_{12}/folate deficiency
	Spinocerebellar ataxia, especially type 3
	? Parkinson's disease
	Drugs:
	antiemetics, e.g. metoclopramide
	some anticonvulsants, e.g. phenytoin
	antipsychotic agents, e.g. phenothiazines and haloperidol
	occasionally tricyclic antidepressants, selective serotonin reuptake inhibitors, lithium

Differential diagnosis

Peripheral arterial disease, arthritis and bursitis are easily distinguished by examination. Most painful conditions are not instantly ameliorated by activity.

Restless legs syndrome should be distinguished from akathisia.* The clinical setting may help, for example exposure to an offending drug (such as an antipsychotic or metoclopramide) in akathisia. Patients with restless legs syndrome emphasise the provocative nature of rest and sleep, identify the sensory disturbance as the cause of motor restlessness and have greater relief from activity. On the other hand, repetitive stereotyped movements, like body rocking, are more likely in akathisia, in which such overt motor behaviour is usually evident during the examination. The absence of symptoms while lying down generally excludes a diagnosis of restless legs syndrome.

The association with Parkinson's disease is not established by well-designed studies, but both conditions respond to dopaminergic drugs and are associated with periodic limb movements during sleep. The pathology of Parkinson's disease, however, is quite different.

Treatment

Any underlying causes should be identified and treated. Mild symptoms may respond to good sleep hygiene (Table 2) or simple analgesics. More severe symptoms may need to be managed with dopaminergic drugs, opioids or benzodiazepines. Most trials have used levodopa and dopamine agonists, but other drugs such as amantadine, selegiline and anticonvulsants also have reported efficacy. Initially at least, 90% of patients report relief with levodopa or dopamine agonists. Generally the doses are much smaller than those used in Parkinson's disease.

Opioids or benzodiazepines have a role in drug treatment of occasional symptoms as long as the patient and doctor understand the potential for dependence and withdrawal

* Akathisia: a feeling of inner restlessness which makes the person unable to sit still.

Table 2

Good sleep hygiene

Sleep/wake activity regulation	Establish regular sleep times
	Avoid oversleeping
	Avoid excessive napping (limit to afternoon 'powernap' of 10–15 minutes)
	Exercise regularly (at least six hours before bedtime)
Sleep setting and influences	Avoid bright light exposure in late evening or night, but bright light after rising may be helpful
	Avoid heavy meals within three hours of bedtime
	Sleep in a quiet, dark room (remove TV, stereo)
	Use a suitable mattress and pillow for comfort and support
	Reserve bedroom for sleep and intimacy
	Avoid alerting and stressful ruminations before bedtime (doing jigsaws may help)
	Avoid caffeine after lunch
	Reduce excessive alcohol intake
	Avoid tobacco, especially after dinner
Sleep promoting adjuvants	Have a light snack or warm bath before bed
	Engage in quiet activities before sleep e.g. reading

and restrict their use to only a few days in the month. Of the benzodiazepines, most published experience concerns treatment with clonazepam. This has a modest benefit, but may also be complicated by sedation and confusion. Opioids may be useful when dopaminergic drugs are poorly tolerated or are unhelpful. The advantages of opioids are long half-life and the absence of augmentation as an adverse effect. Another alternative is gabapentin, especially when pain is prominent. The class of drugs shown to be ineffective are anticholinergics; antidepressants with anticholinergic effects may worsen restless legs syndrome.

As the condition often fluctuates over time, the mildly affected patient may be able to use medication intermittently. Continuous treatment should be reserved for more severely affected individuals. Generally, idiopathic restless legs syndrome does not resolve.

Dopamine agonists

Low-dose dopamine agonists are largely replacing levodopa as first-line treatment for restless legs syndrome because of ease of management and better efficacy. Cabergoline has the advantage of a very long half-life and had superior efficacy to levodopa in the first large randomised controlled trial comparing two dopaminergic therapies in restless legs syndrome.[5] Of the newer non-ergot derived dopamine agonists, ropinirole has been the most extensively studied[6], followed by pramipexole.[7] If there are significant daytime symptoms, patients may need multiple doses or long-acting preparations. As a general rule, doses should start low and be increased gradually to avoid adverse effects. It is important to keep doses low as there is no extra benefit from the higher doses used in Parkinson's disease, and because of the risk of augmentation with higher doses.

Adverse effects

Several problems may be encountered usually within 3–4 months of starting a dopaminergic drug. The phenomenon of augmentation complicates treatment in up to 80% of patients, as early as 3–4 weeks into treatment. In augmentation, the symptoms are shifted to an earlier time in the day, may be more severe and more easily provoked and may spread to previously uninvolved limbs. Pain and sleeplessness cause severe anxiety and so augmentation is important to recognise. Raising the dose aggravates augmentation, but it resolves on withdrawal of the drug. Risk factors for augmentation are taking the dose well before symptom onset, and doses of levodopa above 200 mg per day. It is primarily a problem with levodopa, but has also been reported with pergolide. So far, it seems that augmentation is less of a problem with cabergoline and non-ergot dopamine agonists. If augmentation occurs, it is best to switch to or between dopamine agonists, or temporarily use opioids while the dose of the dopaminergic drug is lowered.

Another problem is rebound, in which the symptoms of restless legs syndrome reappear after the drug has worn off. This is similar to 'wearing off' in Parkinson's disease and manifests as early morning or late night symptoms. Rebound is related to the half-life of the drug, so it is best to use a long-acting preparation, multiple dosing or switch to cabergoline.

Concerns have arisen over the use of ergot-derived dopamine

agonists (such as cabergoline and pergolide) in the treatment of Parkinson's disease because of the serious complication of restrictive cardiac valvulopathy.[8] The risk could be smaller with bromocriptine and with the lower doses used in restless legs syndrome, but good studies are lacking. Great caution should therefore be used when prescribing cabergoline or pergolide. If they are necessary, regular (six-monthly) echocardiography is recommended, although we still do not know if the valvulopathy is reversible. The non-ergot derived dopamine agonists (such as ropinirole and pramipexole) have not yet been implicated in valvulopathy. There have been no direct comparative studies between cabergoline, pramipexole and ropinirole, therefore no claim for greater efficacy can be made for any of these drugs.

Common adverse effects of dopamine agonists, particularly at the start of treatment, are nausea and dizziness (due to postural hypotension). Impulse control disorders including pathological gambling and hypersexuality are increasingly being recognised. Another concern is pathological daytime somnolence occurring as 'sleep attacks' which may cause motor vehicle accidents. While these adverse effects seem dose related, they may occur with the relatively low doses used in restless legs syndrome, so awareness and caution are necessary.

Opioid treatment may be complicated by sedation and constipation. It has the potential for abuse, dependency and withdrawal, so occasional use is preferable. Caution should be exercised in prolonged treatment.

Conclusion

Restless legs syndrome is a common but under-recognised disorder. For patients with mild symptoms, no drug treatment may be necessary. For patients with severe symptoms, dopamine agonists are the first-line treatment when a drug is needed. Some patients can be managed with intermittent therapy.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false

(answers on page 111)

1. Anticholinergic drugs are an effective therapy for restless legs syndrome.
2. If symptoms of restless legs syndrome come on earlier in the day during treatment with a dopaminergic drug, the dose should be increased.

Preventing foot ulcers

Kerry May, Manager, Podiatry, Diabetic Foot Unit Coordinator, The Royal Melbourne Hospital, Melbourne

Summary

Foot ulceration is an unfortunate complication of a number of chronic diseases, especially diabetes mellitus. Patients with peripheral neuropathy, foot deformity or peripheral vascular disease have an increased risk of developing foot ulcers. Ulceration is often preventable and the general practitioner is in a unique position to ensure timely assessment, education, management and referral for at-risk patients. Most of the evidence for reducing the risk of foot ulcers comes from studies in diabetes. However, it is not unreasonable to apply similar principles to people with other diseases who are also at risk of developing foot ulcers.

Key words: deformity, foot ulcers, peripheral neuropathy, peripheral vascular disease, risk reduction.

(Aust Prescr 2008;31:94–6)

Introduction

Foot ulceration may be defined as the erosion of tissue or a breach of the epidermis at a site distal to the ankle. There are a number of conditions that place a person at risk of developing foot ulceration. These include, but are not limited to, diabetes (see Aust Prescr 2007;30:21–4), peripheral vascular disease, end-stage renal failure, vitamin B_{12} deficiency, gout, rheumatoid arthritis, scleroderma and cerebral palsy, or any other condition that affects the circulation, structure or sensation of the feet. Timely referral to a podiatrist or appropriate specialist may assist these patients to prevent or manage possible foot complications. The general practitioner has an important role in not only identifying people requiring specialist referral, but also educating those at risk about appropriate self-management and risk reduction.

Risk factors

Common risk factors for foot ulceration include peripheral neuropathy, structural deformity of the foot, peripheral vascular disease, trauma and a history of foot ulceration and/or amputation.

Peripheral neuropathy

Many of the conditions that place individuals at increased risk of developing foot ulcers share the common factor of peripheral neuropathy. In patients with peripheral neuropathy, trauma and injury can occur without them knowing. For many people this means that they cannot detect a foreign object in the shoe, or that their shoe does not fit correctly. Undetected trauma is often untreated trauma, and can have potentially limb-threatening consequences. Peripheral neuropathy may also contribute to the development of foot deformity, as well as changes in the skin.

One way to diagnose neuropathy in the clinical setting is with the 10 g Semmes Weinstein monofilament (Fig. 1). Failure to detect the monofilament at any one of the test sites (Fig. 2) indicates the presence of peripheral neuropathy.[1]

Foot deformity

Foot deformity results in increased foot pressures and when combined with an additional risk factor, such as neuropathy, places the patient at significant risk of developing a foot complication.[2] Foot deformity may be congenital, or develop as a consequence of poor footwear or as part of a disease process, especially for those with rheumatoid arthritis and diabetes. The most common foot deformities are claw or hammer toes, bunions, callus, previous surgical sites and a lowered medial longitudinal arch.

Fig. 1

Using a monofilament to assess sensation in the foot

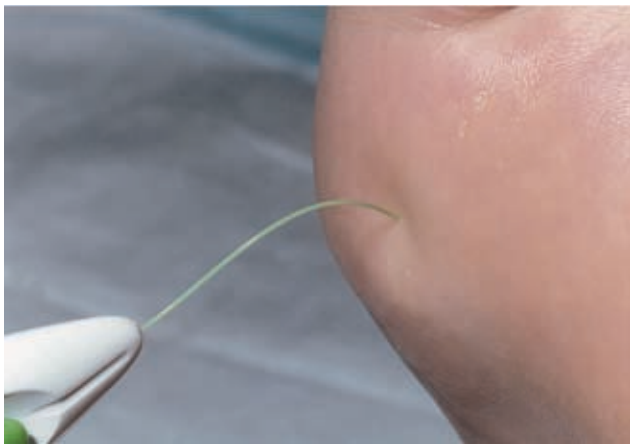
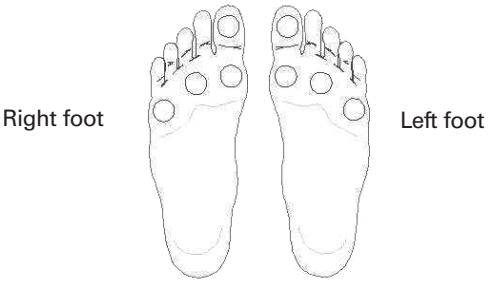


Fig. 2

Monofilament testing sites



Peripheral vascular disease

Peripheral vascular disease is not often the cause of foot ulceration, but is a contributing factor in poor or delayed healing of foot ulcers.[3] A simple clinical test for diagnosing peripheral vascular disease is palpation of the foot pulses. Absence of these pulses indicates a high likelihood of peripheral vascular disease, which may warrant further investigations.[4] Assessment of the microcirculation is more difficult but can be achieved with measurement of toe pressures. A toe pressure of greater than 30 mmHg suggests a wound is likely to heal with conservative therapy.[5]

Trauma

People often think that trauma to the foot is what precipitates foot ulceration, with little credit being given to the contribution of underlying disease process or other risk factors. Certainly, a blister from new shoes or a burn from a hot water bottle are precipitating events in ulcer formation. However, it is the consequences of the underlying disease process that result in the non-healing or problem foot ulcer. Preventing trauma often prevents foot ulceration.

History of foot ulceration or amputation

Previous ulceration or amputation are recognised as the most significant risk factors for developing further ulceration.[6] This probably represents the underlying limb pathology, and may also be related to gait changes that result from an amputation.[7,8] A person with diabetes and a history of foot ulceration or amputation must be considered at ongoing high risk for developing further ulceration and be referred to a podiatry service for monitoring and management. There is evidence to support reduced re-ulceration and amputation rates in people with diabetes who access regular podiatry care.[9,10,11]

Preventative measures

It is important to optimise the treatment of underlying conditions, such as peripheral neuropathy, which can increase the risk of developing foot ulcers. Regular foot inspections by a general practitioner are a good opportunity to check that the feet are free from injury, but also to reiterate advice and discuss any concerns the person may have.

Patients should be educated about how to reduce their risk of developing foot ulcers (Table 1). This is especially important for people with peripheral vascular disease who are more likely to require a referral for expert assessment, monitoring and management than those with neuropathy. People with early stage vascular disease should be encouraged to 'move it or lose it' to maintain their circulation, with the exception of people who currently have an active foot problem.

Table 1

Foot care for patients at risk of foot ulcers [12]

Advice	Points to highlight
Daily foot inspection	Check between the toes and underneath the feet Look for any breaks in the skin, areas of rubbing or signs of infection
First aid for injuries	Apply antiseptic (e.g. povidone-iodine) to the injury, followed by a protective cover (e.g. dry dressing such as cutiplast) Seek expert assistance when an injury is not healing
Self-care	Wash feet daily and dry thoroughly, especially between toes Daily use of an emollient to prevent drying and cracking of the feet, such as sorbolene Filing in preference to cutting of nails. If nails are cut this should be straight across and the nail edge should be left longer than the most distal aspect of the nail sulcus (see Fig. 3). Use of a pumice to reduce callus development. This should only be undertaken when a person has no neuropathy and has had a safe technique demonstrated to them by their podiatrist or general practitioner.
Risk reduction	Never walk barefoot Beware of sources of heat (heaters, hot water bottles) as a cause of trauma Treat tinea infections promptly with an appropriate topical antifungal such as terbinafine preparations. Any breach of the epidermis increases the risk of bacterial infection.
Well-fitting footwear	Wear shoes with a wide and deep toe box (should be able to freely move toes inside) Shoes should have leather upper, minimal internal seams, firm fastenings (laces or velcro), a firm heel counter (the rear of a shoe should be able to hold its shape under firm pressure) and a cushioning sole New shoes should be worn in slowly to minimise the risk of the shoe causing a foot ulcer. A podiatrist usually recommends starting at one hour a day, increasing the time the shoe is worn by an hour each day as long as no problems are detected.

The most basic but important advice for individuals with neuropathy is to inspect their feet daily for signs of trauma. This can be difficult for some people with visual or physical disabilities. Where a family member or carer is not available, most people are able to adequately perform this function using a good quality magnifying mirror to inspect the plantar surface of the foot. Patients should also be advised to inspect their footwear for foreign objects before wearing, and check their shoes are a good fit.

People with foot deformity should be educated on the importance of purchasing well-fitting footwear, and for more severe cases that are affecting day-to-day function, a referral to a podiatrist or orthotist for pressure-relieving orthoses and/or specialist footwear may be of assistance.

The best advice people can be given is to seek professional help as soon as a foot problem develops, or is not resolving. Any person identified as being at high risk for ulceration should not only receive detailed education on risk reduction, but should also be referred for podiatry care.

Conclusion

Foot ulceration is preventable with suitable assessment, management and education. The regular access and individual relationships that people with a chronic disease have with their general practitioner provide excellent opportunities to reduce the risk of foot ulceration. When individuals at high risk develop a foot complication, they should be promptly referred to specialist health professionals with expertise in managing these conditions to maximise wound healing and reduce the risk of lower limb amputation.

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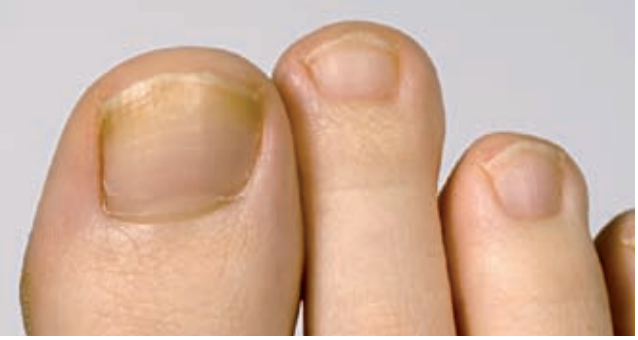
Fig. 3

Correctly cut big toenail



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Patient resource:

Australasian Podiatry Council. Your podiatrist talks about diabetes. http://www.feet.org.au/images/publications/Diabetes.pdf [cited 2008 Jul 10]

Conflict of interest: none declared

Self-test questions

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

3. Peripheral vascular disease is often the cause of foot ulceration.
4. Daily foot inspection is advisable for patients with peripheral neuropathy.

Medicinal mishap

Severe hyponatraemia due to mirtazapine

Prepared by Dr Chan Cheah, Medical Registrar, and Ms Bronwyn Ladhams, Senior Clinical Pharmacist, Fremantle Hospital and Health Service, Perth

Case

A 79-year-old woman was admitted with new onset confusion. Her past medical history included heart failure and depression. On admission she was taking ramipril, metoprolol and frusemide. She had started mirtazapine 10 days previously.

The patient was euvolaemic. Her initial investigations revealed a low serum sodium of 113 mmol/L, low serum osmolality 243 mmol/kg (normal range 275–295 mmol/kg) and inappropriately high urine osmolality of 170 mmol/kg (normal range 50–1200 mmol/kg). Tests showed normal renal, thyroid and adrenal function. A diagnosis of inappropriate antidiuretic hormone secretion was suspected. Her chest X-ray and CT of the head did not show evidence of lesions potentially responsible for inappropriate secretion of antidiuretic hormone.

The patient's fluid intake was restricted, and frusemide and mirtazapine were ceased. Her confusion began to resolve after four days. Her serum sodium improved to 132 mmol/L by day 10. Frusemide was reintroduced, without a fall in serum sodium over the next few weeks. We therefore suspected that mirtazapine had caused her hyponatraemia.

Comment

Mirtazapine is a tetracyclic analogue of mianserin used to treat major depression. It is well documented that many psychotropic drugs can cause hyponatraemia, but there are only two published case reports involving mirtazapine.[1,2] The Adverse Drug Reactions Advisory Committee has received 18 reports since the drug became available in Australia.

Mirtazapine exerts its therapeutic effect by increasing the release of noradrenaline and serotonin by blockade of alpha$_2$ adrenoceptors. This increases the level of both substances within the brain. There are animal data suggesting that serotonin acts on the hypothalamic supraoptic nucleus to increase secretion of antidiuretic hormone. This results in impaired free water excretion and hypo-osmolar hyponatraemia[3], and might be a mechanism by which mirtazapine has this effect.

Patients who may be at risk of drug-related hyponatraemia are the elderly, those who have comorbidities (such as chronic congestive cardiac failure, alcoholic liver disease, intracranial pathology) or those taking other drugs (thiazides, ACE inhibitors) which are associated with hyponatraemia (see box).

We consider that measurements of serum and urine osmolality, urine sodium, thyroid, adrenal and renal function are indicated when severe (sodium < 125 mmol/L) and symptomatic hyponatraemia develops, even if the patient has just started a new drug. Complete and prompt reversal on cessation of the drug and the exclusion of other causes support the diagnosis. Confirming the diagnosis would require a rechallenge with mirtazapine, but this may be inappropriate given the risks to the patient and the availability of many alternative antidepressants.

Conclusion

Symptoms of severe hyponatraemia include confusion, weakness, lethargy, convulsions and coma. Hyponatraemia may be an under-reported adverse effect of mirtazapine which can result in hospitalisation. Clinicians should be aware of the possibility, particularly as early symptoms may mimic those of the patient's depression. We suggest patients with risk factors (see box) have a serum sodium measured before and 1–2 weeks after starting mirtazapine, or at any time if symptoms suggestive of hyponatraemia develop.

Risk factors for mirtazapine-induced hyponatraemia [4]

Advanced age

Female gender

Pre-existing hyponatraemia or comorbidities associated with hyponatraemia

Concurrent drugs which can cause hyponatraemia

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To mix or not to mix – compatibilities of parenteral drug solutions

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Summary

Many injectable drugs cannot be mixed together in syringes or infusions. Some cannot be safely diluted in infusion bags. Incompatibility can involve precipitation, ionic reactions, evolution of gas and denaturation of biological molecules. Knowledge of drug compatibility is needed before mixing drugs. Reference texts can provide information, but data are often unavailable for new drugs. If drugs are mixed together, the mixture should be inspected for precipitates, turbidity or changes in colour, however not all incompatibilities are visible.

Key words: diazepam, injections, phenytoin, precipitation.

(Aust Prescr 2008;31:98–101)

Introduction

Mixing solutions of parenteral drugs is generally not recommended because of the potential for incompatibility and consequent loss of activity of one or both drugs. However, in some circumstances there may be compelling reasons for mixing two or more parenteral drug solutions in the same infusion bag, in the same syringe or at a Y-site junction where two or more intravenous lines meet. Such circumstances include:

- difficulties with venous access limiting the number of intravenous lines available for continuous administration of multiple drugs
- multiple drugs requiring parenteral administration within a short time frame such as in a home visit by a general practitioner
- patients at home requiring many drugs by simultaneous continuous infusion where multiple intravenous lines are not feasible, for example, use of a syringe driver during palliative care.

The decision to mix drugs should not be made without knowledge of their compatibility. If intravenous drugs are not mixed but are given consecutively, the infusion line should be flushed through with compatible fluid between each administration.

Mechanisms of incompatibility

Incompatibility problems are more likely to arise when small concentrated volumes are mixed in a syringe rather than in the larger volume of an infusion bag. This is because of higher mutual drug concentrations and potentially greater pH changes in the more concentrated solution. The absence of any visible change to a solution upon mixing does not automatically exclude degradation of either or both components.

Drugs that precipitate upon dilution

Precipitation of a drug from its concentrated injection solution when it is diluted with water or saline is counter-intuitive. However, a small number of injection solutions are formulated in non-aqueous solvents to allow dissolution of a poorly water soluble substance in a small volume. In these formulations, dilution of the non-aqueous injection vehicle with water or saline may precipitate the drug.

The problem is frequently observed when diazepam injection is diluted. Diazepam is very poorly water soluble so it is formulated as an injection solution in a vehicle comprising 50% propylene glycol and 10% ethanol. At first, dilution produces a slight turbidity which clears upon mixing, but dilution beyond fourfold produces an opaque white precipitate which does not clear until substantial further dilution.

Other drugs which demonstrate solubility problems and which are formulated in injection vehicles other than simple aqueous solutions include digoxin, clonazepam, phenytoin, amiodarone and phytomenadione. In some cases, the manufacturer recommends administration of the undiluted drug. In other cases, care needs to be taken to ensure that if the injection solution is diluted, the dilution is adequate to ensure continuing solubility over the duration of the infusion.

Precipitation of drugs due to pH change upon mixing

The water solubility of any drug is enhanced by ionisation of the molecule. For a drug molecule which acts as a proton acceptor (a Lowry-Bronsted base), ionisation is achieved by formulation in a low pH solution usually as a hydrochloride or hydrogen sulfate salt (for example, amiodarone hydrochloride or adrenaline acid tartrate). Conversely, for a drug molecule which can lose a proton or hydrogen ion (a Lowry-Bronsted acid – usually a weak organic acid), ionisation is achieved

Table 1

Examples of drug compatibilities

Drug	Compatible in syringe	Incompatible in syringe	Comments
Benzylpenicillin 600 mg powder for reconstitution	No common drugs listed in published data	Prochlorperazine, promethazine, chlorpromazine, sodium bicarbonate	
Dexamethasone sodium phosphate 4 mg/1 mL	Metoclopramide, ondansetron, ranitidine	Glycopyrrolate, midazolam, prochlorperazine, promethazine	
Diazepam 10 mg/2 mL	Nil	Widely incompatible – do not mix with other drug solutions	Poorly water soluble drug marketed in a complex solvent system
Frusemide 20 mg/2 mL	No common drugs listed in published data	Buprenorphine, chlorpromazine, droperidol, metoclopramide, midazolam, morphine sulfate, prochlorperazine, promethazine	pH of solution is 8.0–9.3. Frusemide is unstable in acidic media which may include glucose 5% solution.
Haloperidol 10 mg/2 mL	Hydromorphone	Benztropine, ketorolac	
Hydrocortisone sodium succinate 100 mg powder for reconstitution	Metoclopramide	Prochlorperazine, promethazine, midazolam	
Lignocaine hydrochloride 2% in 5 mL	Glycopyrrolate, metoclopramide	Ampicillin, sodium bicarbonate solution	
Metoclopramide hydrochloride 10 mg/2 mL	Chlorpromazine, dexamethasone, droperidol, fentanyl, hydrocortisone sodium succinate, lignocaine, midazolam, morphine, pethidine, promethazine	Ampicillin, frusemide, sodium bicarbonate	
Morphine sulfate, morphine tartrate (various strengths)	Stability of at least 15 minutes published for atropine, bupivacaine, droperidol, fentanyl, glycopyrrolate, hyoscine butylbromide, ketamine, prochlorperazine, and up to 24 hours for metoclopramide	Aminophylline, flucloxacillin, frusemide, phenytoin, promethazine, sodium bicarbonate	Is less soluble in alkaline conditions
Prochlorperazine edisylate	Atropine, hydromorphone, hyoscine hydrobromide, morphine sulfate (may vary with brand), pethidine	Aminophylline, amphotericin, ampicillin, benzylpenicillin, calcium gluconate, cephalothin, dexamethasone sodium phosphate, frusemide, heparin, hydrocortisone sodium succinate, midazolam	The bulk of the published data refer to the edisylate salt which is marketed overseas. The salt marketed in Australia is mesylate which is similar, and for which extrapolation of data is considered reasonable.
Promethazine hydrochloride 50 mg/2 mL	Atropine, droperidol, fentanyl, glycopyrrolate, metoclopramide, midazolam, pethidine	Aminophylline, benzylpenicillin, dexamethasone sodium phosphate, frusemide, hydrocortisone sodium succinate, morphine, phenytoin, sodium bicarbonate	Locally irritant and unsuitable for subcutaneous injection. Avoid extravasation in intravascular injection.
Tramadol hydrochloride 100 mg/2 mL	No common drugs listed in published data	Diazepam, midazolam	This is a relatively recently marketed drug on which there is a paucity of published compatibility data

by formulation in a high pH solution, usually as a sodium or potassium salt (for example, benzylpenicillin sodium). Any change in pH towards the other end of the pH scale will reduce the proportion of ionised to un-ionised drug in solution and will therefore reduce the water solubility of the drug.

The most prominent example of a pH-related reduction in solubility is dilution of phenytoin sodium injection. The drug is formulated with non-aqueous solubilising agents and the solution is adjusted to a pH of 12. Dilution of injectable phenytoin by adding it to an infusion bag lowers its pH and therefore reduces its solubility resulting in precipitation of the drug. Glucose 5% infusion solution, which has a pH of 4.3–4.5, will precipitate phenytoin almost immediately. Indeed, phenytoin injection is so incompatible that it should generally not be mixed with any other solution.

Ionic reactions forming insoluble substances

The salts of monovalent cations, such as sodium and potassium, are generally more soluble than those of divalent cations, such as calcium and magnesium. Mixing solutions containing calcium or magnesium ions has a substantial risk of forming an insoluble calcium or magnesium salt. Mixing magnesium sulfate 50% and calcium chloride 10% results in precipitation of insoluble calcium sulfate. The mixing of drug salts of calcium, and to a lesser extent magnesium, with phosphates, carbonates, bicarbonates, tartrates or sulfates should also be avoided. A recent warning has been issued about mixing calcium-containing solutions, including Hartmann's solution, with ceftriaxone causing the formation of the insoluble ceftriaxone calcium salt.[1]

Denaturation of biological molecules

Biological substances including blood products and insulin are prone to denaturation when exposed to variations in pH and osmolality. While published compatibility data exist for insulins and some of the blood products, most recently marketed biological drugs such as infliximab, interferons and recombinant coagulation factors have no such data available and mixing with other drugs is not recommended.

Evolution of gas

Addition of an acidic drug solution to a solution containing a carbonate or bicarbonate may result in production of carbon dioxide gas. However, the evolution of gas is a normal part of the reconstitution of some drugs, notably ceftazidime.

Use reliable reference material

Some incompatibilities are eminently predictable from simple chemical knowledge, but most compatibilities and incompatibilities are not so easily predicted. For this reason, the decision to mix any two injection solutions whether in a syringe, in an infusion bag or at a Y-site should be based on a reliable reference. However, published data are specific to the concentration, solvent, ambient temperature and sometimes the composition of the syringe or infusion bag. A number of references, in addition to the manufacturer's product information, are available. These include the Australian Injectable Drugs Handbook.[2] Table 1 shows some of the compatibility and incompatibility data currently available.

Palliative care

There are a number of drugs that are commonly delivered via syringe driver to patients having palliative care in the community (see box). Combinations of two, three or more of these drugs occasionally need to be co-administered via syringe driver. Specialist references dealing with their mutual compatibilities need to be consulted.[3,4]

Combinations of drugs commonly used in palliative care *

Haloperidol and midazolam
Hydromorphine and clonidine
Metoclopramide and atropine
Metoclopramide and midazolam (and morphine)
Metoclopramide and morphine
Morphine and clonidine
Morphine and glycopyrrolate
Morphine and midazolam

* In palliative care settings and in chronic pain control, combinations of as many as four of these drugs may be mixed in the same syringe for use in a syringe driver over 24 hours.

Conclusion

While some general principles can be applied to the mixing of injection solutions, they are fraught with exception and applicability varies with circumstance. Mixing is best avoided. If circumstances are so compelling as to warrant mixing any two or more solutions, there should be support from published compatibility data. A visual check for precipitation, turbidity or colour change should be carried out before administering the mixture, but does not guarantee compatibility.

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Conflict of interest: none declared

Self-test questions

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

5. When two drug solutions are mixed together the absence of a visible reaction does not exclude degradation of either drug.
6. Injectable diazepam should be diluted with four parts water to ensure it does not precipitate in the syringe.

New guidelines for endocarditis prophylaxis

The Australian recommendations for the use of antibiotics in the prevention of endocarditis have been revised by Therapeutic Guidelines. These changes are consistent with new international guidelines for endocarditis prophylaxis, which have generally reduced the indications for using antibiotics.

The revised guidelines are available free of charge on the Therapeutic Guidelines website www.tg.com.au and in the electronic publications eTG complete and miniTG. The booklet versions of Therapeutic Guidelines: Antibiotic and Therapeutic Guidelines: Oral and Dental will be updated when new editions are published.

Incretin mimetics and enhancers: mechanisms of action

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Summary

The incretins are peptide hormones secreted from the gut in response to food. They increase the secretion of insulin. The incretin response is reduced in patients with type 2 diabetes, so drugs acting on incretins may improve glycaemic control. Incretins are metabolised by dipeptidyl peptidase, so selectively inhibiting this enzyme increases the concentration of circulating incretins. A similar effect results from giving an incretin analogue that cannot be cleaved by dipeptidyl peptidase.

Key words: diabetes, dipeptidyl peptidase, glucagon-like peptide, glucose-dependent insulinotropic polypeptide.

(Aust Prescr 2008;31:102–4)

Introduction

It has been known for many decades that an oral glucose load causes a greater release of insulin than a similar glucose load given intravenously. This difference (40–60% in the area-under-the-curve of the insulin time-concentration graph) is due to the 'incretin effect'. By increasing insulin secretion, the incretins lower blood glucose.

Physiology

The incretins are peptide hormones. They are released into the circulation, in response to luminal nutrients, within minutes of eating. In humans, the major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 is secreted by the L cells in the ileum and colon, while GIP is secreted by the K cells in the duodenum.

Both incretins have hormonal effects on multiple organs, notably the endocrine pancreas, the gut and the brain (Table 1). Their predominant role is regulation of energy homeostasis. They stimulate insulin secretion in a glucose-dependent manner, delay gastric emptying and suppress appetite. This combination of effects makes a significant contribution to glucose homeostasis, particularly the control of postprandial glucose. Subsequent studies have identified other actions including improvement in pancreatic β cell glucose sensitivity and, in animal studies, promotion of pancreatic β cell proliferation and reduction in β cell apoptosis.

The circulating incretins act via specific G-protein-coupled receptors. There are clinically important differences in the tissue distribution of these receptors. The GLP-1 receptor is expressed in pancreatic islet α and β cells, heart, central nervous system, kidney, lung and gastrointestinal tract. The GIP receptor is expressed predominantly in the pancreatic islet β cells and less so in the central nervous system and adipose tissue.

Table 1

Incretins and their actions

Glucagon-like peptide-1 (GLP-1)	Glucose-dependent insulinotropic polypeptide (GIP)
Secreted by L cells in the distal gut (ileum and colon)	Secreted by K cells in the proximal gut (duodenum)
Stimulates glucose-dependent insulin release	Stimulates glucose-dependent insulin release
Suppresses hepatic glucose output by inhibiting glucagon secretion in a glucose-dependent manner	
Enhances β cell proliferation and survival in animal models and isolated human islets	Enhances β cell proliferation and survival in islet cell lines
Delays gastric emptying	Delays gastric emptying
Cleared by dipeptidyl peptidase 4 inactivation and renal elimination	Cleared by dipeptidyl peptidase 4 inactivation and renal elimination
Anorexic	
Controls fasting glycaemia	

The incretin response to a meal lasts approximately 2–3 hours because, despite rapid metabolism and the short half-life (1–2 minutes) of each incretin molecule, the stimulus of nutrients in the gut persists and so there is ongoing production of incretins. The major mechanism of metabolism of the incretins is cleavage by dipeptidyl peptidase 4 (DPP4), an enzyme that is ubiquitously expressed, including in endothelial cells.

Incretins in diabetes

The clinical relevance of the incretin system came to light when it was recognised that the incretin response is markedly attenuated in people with type 2 diabetes. The lack of nutrient-induced release of GLP-1 contributes significantly to hyperglycaemia in these patients through a relative reduction in postprandial insulin response, the subsequent failure of glucagon suppression and a lack of appetite suppression. The concentration of GIP is near normal, but its effect on insulin secretion is diminished. These observations uncovered a new therapeutic strategy for type 2 diabetes – that of promoting the activity of the incretin system.

Two pharmacological approaches have been taken to enhance the incretin effect in type 2 diabetes. One approach is to administer GLP-1 'analogues' (GLP-1 receptor agonists) that are resistant to cleavage by DPP4. The other approach is to inhibit DPP4 activity. This effectively increases the half-life and therefore the circulating concentrations of the incretins. The effectiveness of both approaches suggests that there is no significant reduction in GLP-1 sensitivity in subjects with diabetes.

GLP-1 receptor agonists

The administration of an incretin analogue resistant to cleavage by DPP4 has been successfully pursued by a number of pharmaceutical companies. Two drugs are now in clinical use or late stage clinical trial. As they are peptides they need to be given by subcutaneous injection, but long-acting formulations are being developed to see if once-weekly injections are possible.

Exendin is a peptide with approximately 50% homology to GLP-1. It is found in the saliva of a lizard known as the Gila monster. The molecule is a potent activator of the GLP-1 receptor and is resistant to cleavage by DPP4 and other peptidases so it has a long circulating half-life. The clinical formulation (exenatide) is in use in many parts of the world.

Another analogue of human GLP-1 has been made by adding a C-16 fatty acid. The resultant compound (liraglutide) is resistant to DPP4 cleavage and has a long circulating half-life. It maintains normal activity at the GLP-1 receptor.

The incretin effect on insulin secretion is glucose-dependent; insulin production is only enhanced by GLP-1 in the presence of hyperglycaemia. This is therapeutically highly advantageous because hypoglycaemia is not an effect of treatment.

A therapeutically beneficial additional effect of the GLP-1 analogues is significant weight loss (of up to 3 kg in clinical trials). This results from the combined effect of delayed gastric emptying and central effects to induce anorexia and (possibly) nausea. Additionally, the delayed gastric emptying causes nausea and vomiting in some patients.

The incretin analogues show direct effects which preserve β cell mass in animal models. They also have *in vitro* and *in vivo* effects which promote β cell proliferation and reduce β cell apoptosis.

The 'downsides' of the analogue approach are that there is no alteration or restoration in GIP concentrations or activity, administration is via injection, and the long-term consequence (if any) of prolonged GLP-1 receptor activation is unknown.

Inhibition of dipeptidyl peptidase 4

DPP4 is a member of a large family of peptidases which have a wide range of actions. As GLP-1 and GIP are the only known substrates of DPP4, it is important for drugs to selectively inhibit this enzyme and not the other peptidases to limit adverse effects on other systems. Of particular relevance is the need to avoid inhibiting DPP8 and 9 as this can cause renal and skin toxicity, and immunosuppression.

Sitagliptin and vildagliptin are two DPP4 inhibitors that are highly specific for DPP4. They have long half-lives, allowing once-daily oral therapy. Two hours after a single dose there is almost complete inhibition of DPP4 and at 24 hours there is approximately 85% inhibition. In patients with type 2 diabetes, the drugs effectively restore GLP-1 circulating concentrations and the postprandial response of GLP-1 to that of a non-diabetic person. Fasting incretin levels remain low, but detectable, and the drugs also reduce fasting blood glucose in patients with type 2 diabetes, predominantly by reducing glucagon secretion. They also return the impaired β cell glucose sensitivity towards normal, an action that contributes to postprandial glucose control.

In animal models of type 2 diabetes, sitagliptin and vildagliptin preserve β cell mass (and function). If this effect also occurs in patients, then the drugs may delay or prevent the characteristic β cell deterioration seen in type 2 diabetes.

Future directions

The development of drugs to manipulate the incretin system is fascinating. It teaches us much about the pathophysiology of glucose homeostasis and type 2 diabetes. Based on currently available evidence, these drugs will provide additional therapies for type 2 diabetes.

A key set of data that will become available over the next few years will highlight the effect of these drugs on the pancreatic islet, with particular emphasis on their ability to prevent or delay secondary β cell failure. Should this be apparent in patients with type 2 diabetes, a strong case could be made for starting these

drugs very early in the disease, perhaps even in the pre-diabetic phase. This therapy would depend on favourable outcomes in long-term studies.

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Professor Prins has received research funding and/or honoraria for lectures or Advisory Board membership from Merck Sharp & Dohme, NovoNordisk and Novartis.

Self-test questions

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

7. Stimulating the receptor for glucagon-like peptide causes weight gain.
8. Incretin analogues cause hypoglycaemia in patients with type 2 diabetes.

Experimental and clinical pharmacology

Incretin mimetics and enhancers: clinical applications

Anne T Reutens, Endocrinologist and Clinical researcher, and Jonathan E Shaw, Deputy Director, International Diabetes Institute, Melbourne

Summary

Mimicking or enhancing the actions of incretin can help to control type 2 diabetes. Exenatide and liraglutide are injectable glucagon-like peptide-1 receptor agonists, while vildagliptin and sitagliptin are oral dipeptidyl peptidase 4 inhibitors. These drugs have their main effects on postprandial glucose, but also lower fasting glucose concentrations. Glucagon-like peptide-1 agonists lower glycated haemoglobin by about 1–1.7% and induce weight loss, but frequently cause transient nausea. Dipeptidyl peptidase 4 inhibitors reduce glycated haemoglobin by 0.5–1%. They have infrequent adverse effects, but no effect on weight. Longer-term data are required to establish their full adverse event profile and their efficacy in reducing the macro- and microvascular complications of diabetes.

Key words: dipeptidyl peptidase, glucagon-like peptide, exenatide, liraglutide, sitagliptin, vildagliptin.

(Aust Prescr 2008;31:104–8)

Introduction

The incretin effect is a normal physiological response involving gut hormones. These incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), stimulate pancreatic β cells to increase insulin secretion in response to oral carbohydrates. In type 2 diabetes, the secretion of GIP remains normal but the insulin response to it is impaired. GLP-1 concentrations are reduced in type 2 diabetes but the pancreatic response is relatively preserved. Using agonists to mimic the action of incretin, or inhibiting incretin metabolism to enhance the effect, are new strategies to treat type 2 diabetes.[1] The main effect of the drugs is to lower postprandial glucose. This is particularly attractive, as postprandial glucose concentrations are more strongly linked to cardiovascular disease than is fasting glucose.[2]

GLP-1 receptor agonists (mimetics)

GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP4), so its potential as a drug is very limited. However, drugs which are synthetic agonists at the GLP-1 receptor resist cleavage by DPP4.

Exenatide

Exenatide is an agonist which is administered twice daily before meals by subcutaneous injections from a pre-filled pen. The

starting dose is 5 microgram twice daily, increasing if tolerated after one month to 10 microgram twice daily. A long-acting release formulation of exenatide that is injected subcutaneously once a week has been studied.

Exenatide is cleared by glomerular filtration and while no dose adjustment is needed for mild renal impairment, exenatide probably should not be used in patients with a creatinine clearance less than 30 mL/min or on dialysis. There have been no studies in patients with liver disease and the effects on human pregnancy are unknown.

Efficacy of exenatide in combination with oral hypoglycaemic drugs

Randomised placebo-controlled clinical trials have enrolled 1689 patients with suboptimally controlled type 2 diabetes despite treatment with metformin, sulfonylureas or thiazolidinediones. The metformin and/or sulfonylurea studies lasted 30 weeks and the thiazolidinedione study lasted 16 weeks. Patients were randomised to add placebo, low- (5 microgram) or high-dose (10 microgram) exenatide twice daily. The mean effects of exenatide, in comparison to placebo, were:

- a reduction in glycated haemoglobin (HbA1c) of approximately 0.6% with low dose and 1.0% with high dose (both doses resulted in significantly greater proportions of patients achieving an HbA1c of 7% or less)
- a reduction in fasting plasma glucose of approximately 1.0 mmol/L with low dose and 1.4 mmol/L with high dose
- reductions in postprandial glucose of approximately 2.0 mmol/L with low dose and 3.0 mmol/L with high dose
- progressive weight loss during the trial period, with a reduction in body weight of approximately 0.8 kg with low dose and 1.4 kg with high dose.

A total of 974 patients opted to continue exenatide in uncontrolled open-label extensions to these trials. For 283 patients follow-up lasted for two years.[3] During the two years the HbA1c reduction (approximately 1.0% from baseline) was sustained and weight loss continued (4.7 kg below baseline). Other statistically significant effects were increased high density lipoprotein cholesterol (0.12 mmol/L), decreased triglycerides (0.4 mmol/L) and decreased diastolic blood pressure (2.7 mmHg). The alanine transaminase concentration returned to normal in 39% of the patients who had elevated baseline concentrations.[3] This reduction probably reflects a decrease in liver inflammation in patients with non-alcoholic fatty liver disease.

The long-acting release formulation of exenatide has been used in a randomised placebo-controlled study of 45 patients with type 2 diabetes.[4] After 15 weeks of once-weekly subcutaneous injections the mean changes were:

- a reduction in HbA1c of 1.4% to 1.7% from baseline (with 0.8 mg and 2.0 mg/week respectively) compared to a rise of 0.4% with placebo
- a reduction in fasting plasma glucose of 2.4 mmol/L and 2.2 mmol/L from baseline (with 0.8 mg and 2.0 mg/week respectively) compared to a rise of 1.0 mmol/L with placebo
- weight loss of 3.8 kg in the 2.0 mg/week arm, but no change in the 0.8 mg/week or placebo arms.

Efficacy of adding exenatide or insulin

In patients with suboptimally controlled diabetes despite maximal doses of metformin and a sulfonylurea, adding twice-daily exenatide was compared with adding once-daily insulin glargine.[5] After 26 weeks HbA1c had fallen by 1.1% in both groups. Exenatide reduced postprandial glucose more effectively and produced less nocturnal hypoglycaemia than insulin, whereas insulin reduced fasting plasma glucose more than exenatide did. Body weight decreased with exenatide (2.3 kg) but increased (1.8 kg) with insulin glargine.

Similar results were found in a 52-week open-label study comparing the addition of exenatide with the addition of twice-daily insulin aspart in patients with suboptimally controlled diabetes despite taking maximal doses of metformin and sulfonylurea.[6] The HbA1c reduced by approximately 1% and fasting plasma glucose by approximately 1.7 mmol/L in both groups. Exenatide produced a greater reduction in postprandial glucose and caused weight loss, whereas the patients given insulin gained weight (between-group difference 5.4 kg).

Safety

GLP-1 agonists appear not to cause hypoglycaemia directly. When exenatide is added to metformin, the rates of hypoglycaemia are no different from those of adding placebo. However, when exenatide is added to a sulfonylurea, there is an increase in hypoglycaemia.

Gastric emptying is slowed by exenatide, and this may be an important part of its glucose-lowering mechanism, as it slows the absorption of carbohydrate. Gastrointestinal symptoms are common. Mild to moderate nausea is the most frequent adverse effect. The duration of nausea was not formally reported but was described as intermittent in a 16-week study. Analysis of the two-year follow-up data showed that when treatment-emergent adverse events were examined in 10-week intervals from baseline, the incidence of nausea was highest initially (39% of patients) and remained above 10% for subsequent 10-week intervals until 100 weeks had passed. However, only 3% of patients stopped exenatide because of nausea.[2] Weight loss was independent of the presence of nausea.

Anti-exenatide antibodies occurred in approximately 40% of patients. The antibody titre did not affect clinical efficacy, but the long-term significance of having antibodies is unknown. Injection site reactions are uncommon.

There is a possible association between exenatide use and acute pancreatitis. The incidence of acute pancreatitis with exenatide was 1.7 cases/1000 patient years in clinical development studies

and 0.2/1000 patient years during postmarketing surveillance. By comparison, the incidence was 3.0/1000 patient years with placebo and 2.0/1000 patient years with insulin.

Liraglutide

Liraglutide is the second GLP-1 receptor agonist to be developed, and, like exenatide, is injectable.

Efficacy

The published randomised controlled clinical trials of liraglutide monotherapy enrolled 745 patients with type 2 diabetes. These studies were phase II dose-ranging studies which lasted 5–14 weeks. Patients were randomised to use placebo, once-daily liraglutide at various doses, metformin or glimepiride. The mean effects of liraglutide, in comparison to placebo, were:

- a reduction in HbA1c at doses of at least 0.6 mg/day. This reduction was approximately 0.9% at low dose (0.6–0.75 mg/day) and 1.7% at high dose (1.9–2.0 mg/day).
- a reduction of fasting plasma glucose of approximately 2.2 mmol/L with low doses and 3.4 mmol/L with high doses
- significantly greater proportions of patients achieving postprandial glucose less than 10 mmol/L with high doses
- a weight loss from baseline of 2.5 kg with high doses.

Comparison of the effect of adding liraglutide 2.0 mg/day or adding glimepiride 4 mg to treatment with metformin showed:

- no difference in amount of HbA1c reduction
- a greater reduction in fasting serum glucose (1.2 mmol/L more than glimepiride)
- a greater reduction in postprandial glucose (1.1 mmol/L less excursion than with glimepiride)
- a reduction in body weight (1.2 kg weight loss versus 0.8 kg weight gain with glimepiride).

Unlike exenatide, there are no published studies of liraglutide combined with sulfonylureas or thiazolidinediones. No significant changes in lipids were observed with liraglutide treatment.

Safety

The most frequent adverse effects of liraglutide are generally transient and include nausea, diarrhoea, vomiting and headache. With liraglutide 2.0 mg used as monotherapy or combined with metformin, the median duration of gastrointestinal events was 1–3 days, with most events reported in the first 23 days of treatment. Nausea led to withdrawal of 4% of patients from trials.

The incidence of confirmed hypoglycaemia associated with liraglutide use in clinical studies was extremely low. No antibody formation has been reported so far and injection site reactions are uncommon.

DPP4 inhibitors (enhancers)

The highly selective DPP4 inhibitors vildagliptin and sitagliptin prevent the normal rapid degradation of GLP-1. They are selective because they inhibit DPP4 significantly more than the related enzymes, DPP8 and DPP9. DPP4 inhibitors have similar clinical effects to GLP-1 receptor agonists, but generally do not slow gastric emptying or lead to weight loss.

Vildagliptin and sitagliptin are administered orally once daily. Sitagliptin is 79% renally excreted, and dosage reduction is required with renal failure. Vildagliptin is mainly hydrolysed and only 22% is excreted unchanged by the kidneys, hence dose adjustments are unlikely to be needed in renal failure. No dose adjustment is required in patients with hepatic impairment.

Efficacy

Published studies have examined DPP4 inhibitors as monotherapy or combined with metformin or thiazolidinediones.[1]

Vildagliptin

The published randomised controlled trials of vildagliptin as monotherapy or add-on therapy enrolled 5165 patients with type 2 diabetes. Most trials ran for 24 weeks (range 12–52 weeks). The mean effects of daily vildagliptin monotherapy when compared to placebo were:

- a reduction in HbA1c of 0.6% with vildagliptin 50 mg/day and 0.7% with vildagliptin 100 mg
- a reduction of fasting plasma glucose of approximately 0.9 mmol/L with vildagliptin 50 mg and 1 mmol/L with vildagliptin 100 mg. (The change from baseline fasting plasma glucose ranged from 0.4 to 0.97 mmol/L with 50 mg and from 0.8 to 1.1 mmol/L with 100 mg.)
- a placebo-adjusted reduction in 4-hour postprandial plasma glucose of 1.5 mmol/L with 50 mg and 0.9 mmol/L with 100 mg (only two studies examined this effect)
- no significant reduction in weight.

When used as add-on therapy to metformin, vildagliptin reduced HbA1c significantly when compared to placebo (by 0.7% with 50 mg and 1.1% with 100 mg). Daily doses also significantly reduced fasting plasma glucose (by 1 mmol/L with 50 mg and 1.5 mmol/L with 100 mg).

When vildagliptin was added to pioglitazone treatment, combination therapy was significantly more efficacious in improving glycaemic control than either drug alone. The combination decreased HbA1c by 0.7% (with 100 mg vildagliptin).

A single study added vildagliptin to the treatment of patients with diabetes poorly controlled by insulin. The combination only decreased HbA1c by 0.3% relative to placebo.

In active comparator studies, 100 mg vildagliptin:

- failed the statistical non-inferiority test when compared to 2 g metformin in previously untreated patients (HbA1c fell by 1.0% vs 1.4%)
- was statistically non-inferior when compared to treatment with rosiglitazone 8 mg (HbA1c fell by 1.1% vs 1.3%).

Sitagliptin

The trials of sitagliptin included 6315 people with type 2 diabetes and mostly ran for 24 weeks (range 12–52 weeks). Doses ranged from 10 mg to 200 mg/day with 100 mg/day the most common dose. The mean effects of sitagliptin 100 mg/day monotherapy when compared to placebo were:

- a reduction in HbA1c of 0.8%
- a placebo-adjusted reduction in fasting plasma glucose of 1.1 mmol/L. (The change from baseline in fasting plasma glucose with sitagliptin was 0.8 mmol/L (range 0.7–0.94 mmol/L))
- a reduction in 2-hour postprandial plasma glucose of 3.2 mmol/L (range 2.6–4.5 mmol/L)
- no significant weight change.

When used as add-on therapy to metformin, sitagliptin 100 mg reduced HbA1c by 0.7% and fasting plasma glucose by 1.5 mmol/L, significantly more than placebo. Adding sitagliptin to metformin was not inferior to adding glipizide to metformin.

Compared to placebo, adding sitagliptin to pioglitazone treatment decreased HbA1c by 0.7% and fasting plasma glucose by 1 mmol/L. When added to glimepiride, sitagliptin 100 mg reduced HbA1c by 0.89% and by 0.6% when added to glimepiride plus metformin.

Safety

The collective data show that vildagliptin and sitagliptin are well tolerated, with a low incidence of gastrointestinal effects or hypoglycaemia.[1] Adverse events reported in the clinical trials had no specific pattern and were not generally increased relative to the comparator groups. DPP4 inactivates many peptides and is identical to the T cell activation antigen CD26, so its inhibition potentially can affect many pathways. Long-term safety is unknown. Post-marketing reports of anaphylaxis, angioedema, rash, urticaria and exfoliative skin conditions such as Stevens-Johnson syndrome have occurred with sitagliptin, up to 3 months after starting treatment.

Treatment of type 2 diabetes

Aggressive treatment of type 2 diabetes typically requires the use of multiple hypoglycaemic drugs. For type 2 diabetes that is not controlled by a sulfonylurea and metformin, or for patients unable to tolerate a sulfonylurea or metformin, the GLP-1 agonists or DPP4 inhibitors offer options for third-line therapy.

These drugs reduce postprandial and fasting glucose concentrations with sustained improvement in HbA1c, without weight gain or significant hypoglycaemia. They potentially preserve β cell function with chronic use and have favourable safety profiles. GLP-1 receptor agonists lead to weight loss, but frequently cause nausea, although this is often transient. Neither weight loss nor nausea occurs with DPP4 inhibitors. Until long-term data are available to confirm safety and explore the potential for cardiovascular protection, these new drugs will inevitably be restricted to add-on therapy, with metformin remaining the first choice oral hypoglycaemic drug.

Further research

Promising orally active GLP-1 receptor agonists include substituted quinoxalines and cyclobutanes. Long-acting GLP-1 receptor agonists, which use microspheres or albumin bioconjugates to make them suitable for once-weekly injection, are being developed.

Conclusion

The GLP-1 receptor agonists and DPP4 inhibitors are important and promising additions to diabetes therapy which will help more patients with type 2 diabetes achieve their glycaemic targets. The results of long-term studies are required to determine adverse effects with chronic use as well as outcomes for cardiovascular events and the incidence of microvascular complications.

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Dr Reutens has received conference sponsorship from Novo Nordisk. Dr Shaw has received research funding, and honoraria for lectures and consultancies, from Lilly Pharmaceuticals, Novo Nordisk, Merck Sharp & Dohme and Novartis.

Self-test questions

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

9. The nausea associated with exenatide can persist for more than a year.
10. The main effect of drugs acting on the incretin system is a reduction in postprandial glucose concentrations.

New drugs

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

Fosaprepitant dimeglumine

Emend IV (Merck Sharp & Dohme)

vials containing 115 mg as powder for reconstitution

Approved indication: chemotherapy-induced nausea and vomiting

Australian Medicines Handbook section 12.3.4

Aprepitant is an oral antiemetic which was marketed for use in chemotherapy in 2004 (see 'New drugs' 2004;27:76–9). Fosaprepitant is an intravenous formulation of aprepitant which can be given on the first day of chemotherapy. The dose is infused over 15 minutes, 30 minutes before chemotherapy.

Fosaprepitant is a prodrug. It is rapidly converted by many tissues into aprepitant. An intravenous dose of 115 mg fosaprepitant is equivalent to an oral dose of 125 mg aprepitant.[1] Although the concentrations are similar after 24 hours, the maximum concentration of aprepitant is higher when fosaprepitant is used.

There appear to be few published clinical trials of fosaprepitant. Its product information only contains pivotal efficacy studies of aprepitant. The adverse effects of the two drugs are similar, but fosaprepitant has some extra warnings: the intravenous formulation is incompatible with Hartmann's or Ringer's lactate solution.

A dose of fosaprepitant does not stop vomiting, immediately after cisplatin-based chemotherapy, in as many patients as ondansetron, but it does reduce delayed emesis.[2] A similar result occurred when intravenous fosaprepitant and dexamethasone, followed by oral aprepitant, were compared to ondansetron and dexamethasone, followed by placebo.[3]

As aprepitant is metabolised by the cytochrome P450 system, especially 3A4, fosaprepitant can interact with other drugs with similar metabolism such as cyclosporin and tacrolimus. Aprepitant can reduce concentrations of warfarin and oral contraceptives. Inhibition of P450 3A4 by ketoconazole will increase concentrations of aprepitant.

T T manufacturer provided additional useful information

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Idursulfase

Elaprase (Genzyme)

5 mL glass vials containing 2 mg/mL concentrate solution for infusion

Approved indication: Hunter syndrome

Australian Medicines Handbook Appendix A

Hunter syndrome is a very rare lysosomal storage disease. Patients have a deficiency of the enzyme iduronate sulfatase and this leads to an accumulation of mucopolysaccharides. (Hunter syndrome is also known as mucopolysaccharidosis II.) Early onset of this X-linked disorder results in developmental delay, coarse facial features, impaired vision, deafness, stiff joints, hepatosplenomegaly and cardiorespiratory problems.

Idursulfase is a genetically engineered form of iduronate sulfatase. A solution of the enzyme is diluted and infused over 1–3 hours. Although it only has a half-life of approximately 45 minutes, idursulfase only needs to be infused once a week.

The efficacy of enzyme replacement therapy was assessed in 96 patients with a median age of approximately 14 years (range 5–31 years). These patients were randomised to receive a weekly infusion of idursulfase or placebo or an infusion of idursulfase every other week. After a year, liver volume had decreased by approximately 25% with enzyme replacement. Lung function (absolute forced vital capacity) improved, but was only significantly better than placebo with weekly infusions. From a baseline mean of 396 metres, the distance the patients could walk in six minutes increased by 44 metres with weekly infusion, 30 metres with infusions every other week and 7 metres with placebo.[1]

Adverse reactions which occurred more frequently with idursulfase than with placebo included headache, abdominal pain, arthralgia and rashes. Many reactions were infusion-related so the infusion may need to be slowed or stopped. Life-threatening anaphylaxis has been reported and these reactions may have a delayed onset. Patients who develop antibodies to idursulfase have an increased incidence of infusion reactions.

While the evidence shows that weekly infusions improve walking capacity, more research is needed to show if idursulfase has any effect on the progression of Hunter syndrome. The main trial of idursulfase did not report on the neurological aspects of the syndrome.[1] It is also unclear if the development of antibodies will eventually lead to a loss of efficacy. Although idursulfase replaces the deficient enzyme, it cannot be regarded as a cure for Hunter syndrome.

T manufacturer provided only the product information

Reference *†

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Paricalcitol

Zemplar (Abbott)

1 microgram, 2 microgram and 4 microgram capsules

5 microgram/mL in 1 mL and 2 mL ampoules

Approved indication: secondary hyperparathyroidism

Australian Medicines Handbook section 10.3.2

In chronic renal failure there is reduced production of calcitriol, the active form of vitamin D. This affects calcium homeostasis and leads to increased secretion of parathyroid hormone. High concentrations of parathyroid hormone increase bone resorption leading to renal osteodystrophy. Secondary hyperparathyroidism can be treated with calcitriol, but it may cause hypercalcaemia and hyperphosphataemia. This has led to research into vitamin D analogues, such as paricalcitol.

The dose and frequency of paricalcitol are determined by the patient's concentrations of parathyroid hormone, calcium and phosphorus. The oral formulation is well absorbed whether or not it is taken with food. Paricalcitol is extensively metabolised by several enzymes including cytochrome P450 3A4. Most of the metabolites are excreted in the faeces. In healthy people the half-life of paricalcitol is 4–7 hours, but this increases to 14–20 hours in patients with chronic kidney disease. Haemodialysis has little effect on the elimination of paricalcitol.

Three placebo-controlled trials enrolled a total of 220 patients with secondary hyperparathyroidism due to chronic kidney disease. In one study patients took capsules once a day, in the others patients took them three times a week. The treatment period was 24 weeks and 83% of patients took the drug for at least 16 weeks. The trial end point (two consecutive decreases in parathyroid hormone greater than 30% of the baseline concentration) was achieved by 91% of the patients randomised to paricalcitol compared with 13% of the placebo group. Only two patients given paricalcitol developed hypercalcaemia.[1]

An open-label study has followed 164 patients, with end-stage renal failure, for up to 13 months. Intravenous doses of paricalcitol given two or three times a week at the end of haemodialysis decreased the concentrations of parathyroid hormone. Mean concentrations of calcium and phosphorus were controlled, but hypercalcaemia occurred in 10% of the patients. Drug-related adverse events affected 26% of patients and 9% withdrew from the study because of adverse events.[2]

Adverse events which occur more frequently with paricalcitol than with placebo include fever, chills, sepsis, pneumonia, oedema, nausea and vomiting. Patients require regular monitoring for hypercalcaemia.

Although the main trials of paricalcitol gave several doses a week this may not be essential. A small study has found that a weekly intravenous dose may be effective in reducing concentrations of parathyroid hormone.[3]

The advantages of paricalcitol over calcitriol, seen in an historical study, need confirmation. In approximately 67 000 patients having haemodialysis the mortality rate was 0.223 per person-year in patients receiving calcitriol and 0.18 per person-year in patients receiving paricalcitol.[4]

T manufacturer provided only the product information

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Temsirolimus

Torisel (Wyeth)

vials containing 25 mg/mL concentrate

Approved indication: advanced renal cell carcinoma

Australian Medicines Handbook section 14.2.3

About 30% of patients with renal cell carcinoma have advanced or metastatic disease at the time of diagnosis. Chemotherapy is generally ineffective and nephrectomy is the mainstay of treatment for disease confined to the kidney. Treatment with drugs such as interferon alfa, interleukin-2 and the tyrosine kinase inhibitors sunitinib and sorafenib may benefit some patients.[1]

Temsirolimus is a kinase inhibitor derived from sirolimus (rapamycin) (Aust Prescr 2002;25:97–8). It works by inhibiting the action of an enzyme called 'mammalian target of rapamycin' or mTOR. Inhibition prevents the division of cancerous cells, slowing the growth and spread of the cancer.

Following intravenous administration, temsirolimus is extensively metabolised by CYP3A4, with the main metabolite being sirolimus. The half-life is 17 hours for temsirolimus and 55 hours for sirolimus. Metabolites are primarily eliminated in the faeces.

The efficacy of temsirolimus in advanced renal cell carcinoma was first assessed in a dose escalation trial of 111 previously treated patients. After a weekly dose of 25, 75 or 250 mg (for a median of 5.6 months), 7% of the patients had a complete or partial response to temsirolimus, but this was not dose-dependent.[2] In a larger trial of 626 previously untreated patients, median overall survival was longer in patients treated with temsirolimus (25 mg each week) than those treated with interferon alfa (10.9 months vs 7.3 months). Adding interferon alfa to temsirolimus did not improve the overall survival time and was associated with more serious adverse events than temsirolimus alone.[3]

In the trials, rash, fatigue, mucositis, nausea, oedema, anaemia and anorexia were common adverse events in patients receiving temsirolimus. The most frequent laboratory test abnormalities were hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, thrombocytopenia, leucopenia and elevated alkaline phosphatase, serum creatinine and aspartate aminotransferase.[2,3]

Approximately 5% of the participants in the larger trial had a hypersensitivity reaction to temsirolimus so patients should be given intravenous antihistamine approximately 30 minutes before temsirolimus is administered. If a hypersensitivity reaction develops, the temsirolimus infusion should be stopped.

Cases of interstitial lung disease have occurred in patients taking temsirolimus and patients should be advised to seek medical attention if they develop worsening respiratory symptoms. Other rare but serious adverse events that have been reported include fatal bowel perforation and renal failure. Patients with central nervous system tumours and/or taking anticoagulants may have an increased risk of intracerebral bleeding.

Immunosuppression may occur with temsirolimus, so be vigilant for infections. Also, live vaccines and contact with people who have recently had them should be avoided. Temsirolimus may delay wound healing and should not be given to patients in the peri-surgical period.

Drugs that induce or inhibit the CYP3A4 enzyme should be avoided in patients taking temsirolimus. Concomitant use of sunitinib can result in dose-limiting toxicities such as serious maculopapular rash and gout or cellulitis requiring hospitalisation. Angioneurotic oedema-type reactions have been observed in patients who were receiving temsirolimus concomitantly with an angiotensin converting enzyme inhibitor. Some patients on temsirolimus and interferon alfa have developed cataracts.

Temsirolimus provides another option for patients with advanced renal cell carcinoma. However, its relative efficacy compared to tyrosine kinase inhibitors is not known.

T T T manufacturer provided clinical evaluation

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

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

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

Answers to self-test questions

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

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Typesetting
Barnes Desktopping and Design

Printed in Australia by
Blue Star Print Group, ACT
22 Pirie Street, Fyshwick, ACT 2609

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

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Print Post Approved PP349181/00151 • ISSN 0312-8008