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Editorial

Compounding in community pharmacy

Mark Feldschuh, Community pharmacist, Caulfield Junction, Victoria

Key words: drug regulation, extemporaneous dispensing.

(Aust Prescr 2008;31:30–1)

When a drug is not available, or is unavailable in a form suitable for a particular patient, compounding may provide a solution to the individual's needs. Compounding is 'the preparation and supply of a single unit of a product intended for immediate use by a specific consumer'.[1] It is also known as extemporaneous dispensing. Compounding may involve modification of a manufactured product or the preparation of a compound from raw ingredients. Although most often associated with pharmacists, other practitioners such as naturopaths and herbalists may compound products.

All medicines were compounded until the expansion and mechanisation of the pharmaceutical industry led to the availability of mass-manufactured drugs. Although now practised to a lesser extent by most pharmacists, compounding is still taught as part of the pharmacy curriculum. All community pharmacies are required to maintain basic compounding equipment for the provision of this service.

Based on experience in the USA where compounding is widely promoted, requests for individualised dosage forms are likely to become more frequent to meet the specific needs of individual patients (see box).

In this issue…

Corticosteroids are effective drugs, but can have serious adverse effects such as osteoporosis. Evange Romas advises on how to limit the loss of bone in patients taking long-term corticosteroids.

Ear drops are commonly prescribed in general practice, but may contain ototoxic drugs. Harvey Coates explains how to reduce the risk of ototoxicity when managing discharging ears.

Some ear drops are not available as commercial preparations and this is where a compounding pharmacy can help. However, Mark Feldschuh tells us that there have been concerns about some of the products that are being compounded.

Some medicines bought from pharmacies can impair driving skills, but Olaf Drummer says that alcohol and illicit drugs remain the biggest threats to road safety.

Which medicines are compounded?

Manufactured medicines are preferable to compounded products as their production is governed by the 'Code of Good Manufacturing Practice for Medicinal Products' and they undergo evaluation by the Therapeutic Goods Administration (TGA). However, many medicines are unavailable in suitable forms for particular patients. The size of the Australian market precludes registration of products required for small but significant patient populations and many products are discontinued or unavailable for economic rather than safety reasons.[2]

Compounding is often needed for paediatric patients. In a review of all products with approved paediatric indications, around 24% were not available in a form suitable for administration to children.[3] The problem of balancing vitamin D deficiency and exposure to sunlight has led to requests to compound high doses of vitamin D as the commercially available products contain insufficient quantities.[4,5] Metronidazole vaginal gel for the treatment of bacterial vaginosis is an example of a manufactured product available overseas that must be compounded by a pharmacist if required by an Australian patient.[6] More controversially, there has been an increase in the prescribing of so-called 'natural' bioidentical hormones following concerns about the risks of hormone replacement therapy with synthetic oestrogen and progestogen.

Compounding concerns

The Therapeutic Goods Regulations 1990 exempt compounded products from registration by the TGA if they 'are dispensed, or extemporaneously compounded, for a particular person for therapeutic application to that person' and they are prepared in a pharmacy 'for supply (other than by wholesale) on or from those premises'. Due to this exemption, extemporaneously dispensed medicines are not subject to evaluation by the TGA. Professional practice is governed by pharmacy boards in each state or territory. Although there have been few confirmed incidents of harm from compounded products in Australia, the potential is great in the absence of enforceable quality control measures. There have been reports of serious adverse events in the USA, mostly associated with improper compounding of sterile parenteral products.[7] In the USA, compounding is also

Reasons for compounding medicines

Different dosage form required, for example liquid form required but only tablets available, ointment required instead of cream

Sensitivity/allergy to excipients and preservatives

Discontinued or unavailable medicine

Different dose or concentration required

Different route of administration required

Compliance problems, for example palatability

regulated by state pharmacy boards, however the federal Food and Drug Administration has taken action against companies that have embarked on large scale manufacture and supply of unapproved drugs under the guise of compounding.

A particular concern of the TGA is batch production (compounding a medicine for more than one patient). Until recently this was mostly undertaken by hospital pharmacies, but now has increased in other areas.

Traditionally, compounded medicines were simple dosage forms, but now some pharmacies are compounding complex dosage forms. Controlled-release formulations are an example that has already caused concern as variations in pharmaceutical performance such as dose dumping are possible. There are usually no or inadequate studies available on bioavailability and hence the compounder has to be aware of their ability and the prescriber has to balance potential harm against clinical need. A triad of informed patient, prescriber and compounder is essential.

Pharmacists are required to provide patient counselling on the appropriate use of compounded medicines. There is no consumer medicine information available for these products, so prescribers and pharmacists must ensure that the patient is aware of this and advise on the correct use, storage, expiry date and possible adverse effects and interactions. This counselling, information and education has to be communicated to each patient.

The way forward

The Pharmaceutical Society of Australia has developed Professional Practice Standards for compounding[1] as well as a specific compounding chapter in the Australian Pharmaceutical Formulary and Handbook. The TGA is currently working with pharmacy professional bodies and health departments to review and improve compounding standards in Australia.

Application and enforcement of practice standards has been inconsistent and under-resourced. A uniform approach to the current regulations and standards would potentially help to address some of the concerns about compounding.[8] The demand for extemporaneously prepared products in pharmacies is low, so the maintenance of compounding skills, equipment, formularies and standard procedures can be difficult and costly. This is leading to the development of specialised compounding practices.

Pharmacy compounding is an important and growing area of professional practice and potentially has a role in the effective treatment of patients with specific needs. Uniform compliance with the standards and regulations is therefore needed. Planning is under way for the development of more comprehensive compounding practice standards which will be critical to ensuring that only the highest quality products are prepared. All compounding activity (not just by pharmacists) should be undertaken to these high standards. Enforcement of these standards should also be uniform to ensure patient health and safety.

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Mr Feldschuh is a shareholder of Professional Compounding Centres of Australia (PCCA) and is a member of PCCA. His current position is Vice President, Pharmaceutical Society of Australia (PSA), Victorian branch. He is the PSA representative on the Pharmacy Manufacturing Technical Expert Reference Group, Therapeutic Goods Administration. He has previously owned two pharmacies.

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.

Antidepressants in pregnancy

Editor, – Current research and information is essential in determining the need for pharmacotherapy of depression during pregnancy and postpartum (Aust Prescr 2007;30:125–7). Therapeutic Guidelines provides a framework for practitioners to address the decision of whether or not to prescribe a psychotropic drug. This includes the risks of prescribing as well as the risks of not prescribing.[1]

Another useful resource is the Therapeutic Advice and Information Service (TAIS), which is funded by the National Prescribing Service. By calling 1300 138 677, health professionals can obtain advice regarding individual patients in a timely manner. This information is provided by drug information pharmacists with access to current medical literature and clinical training to assist with questions relating to drug use during pregnancy and lactation.

Felicity Prior
Director, Hunter Drug Information Service
Calvary Mater Newcastle
NSW
On behalf of the Therapeutic Advice and Information Service

Reference

1. Drug use in pregnancy and breastfeeding. eTG complete. Melbourne: Therapeutic Guidelines Limited; 2007 Nov.

Marine animal injuries

Editor, – I would like to thank Dr Isbister for his excellent review of marine animal injuries (Aust Prescr 2007;30:117–21). One issue not raised is the importance of ensuring adequate tetanus prophylaxis in patients with stingray or venomous fish injuries, as tetanus secondary to the wound is a reported cause of death in stingray injury.[1] Tetanus immunisation status needs to be determined in patients with these penetrating wounds, and prophylaxis used as required.

Michael Corkeron
Senior Staff Specialist
Intensive Care Unit
The Townsville Hospital
Douglas, Qld

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Dr Geoffrey Isbister, author of the article, comments:

I agree that all patients with penetrating marine injuries should have a review of their tetanus prophylaxis, particularly in the interests of keeping tetanus prophylaxis up to date in any patient with a penetrating wound.

Consumer Medicine Information

Editor, – Thank you for publishing the article (Aust Prescr 2007;30:122–4) about some of the concerns surrounding access to and distribution of Consumer Medicine Information (CMI). It has become obvious that many patients are not being offered or receiving any information about the drugs they take, which is unacceptable and unsafe.

We agree that there is a need to increase the provision of CMIs so that health consumers can be properly informed about the drugs they are taking. However, there are a number of other issues identified by health consumer groups which we would like to highlight.

Health consumer groups, including the two which I chair, have approached all relevant stakeholders with the following three-pronged proposal:

1. provision of a central repository for all CMIs for prescribed drugs
2. review of payments to pharmacists for providing CMIs
3. encouragement of pharmaceutical companies to provide printed CMIs with their product.

We are delighted that the TGA has agreed to become the central repository for CMIs, although disappointed that to date consumers do not appear to have been invited to assist in its establishment.

Some pharmaceutical companies have continued to provide package inserts with their product, and some have agreed to restore these. The problem of pharmacists receiving funding to provide CMIs at point of sale and not doing so, remains unaddressed.

We look forward to further productive discussion on how to make a good system work better, for prescribers and for consumers.

Sally Crossing
Chair, Cancer Voices NSW Inc
Greenwich, NSW

The role of drugs in road safety

Olaf H Drummer, Adjunct Professor and Head, Forensic and Scientific Services, Victorian Institute of Forensic Medicine, Department of Forensic Medicine, Monash University, Melbourne

Summary

Drug use is increasingly associated with road accidents. While alcohol and illicit substances dominate, a number of prescription drugs contribute to injury and death. Most drugs do not significantly increase the risks of accidents if they are taken as prescribed, however a number of commonly used drugs can impair the ability to drive safely. Awareness that some drugs affect driving will help to reduce their potential impact on road safety.

Key words: benzodiazepines, drug abuse, road trauma.

(Aust Prescr 2008;31:33–5)

Introduction

Western countries, including Australia, have seen a substantial increase in the availability and use of drugs over the last 30 years. This applies to both medicines and illicit substances. Their use and their increasing prevalence in road trauma have been subject to considerable debate. This debate comes on top of the perennial battle to reduce the road trauma caused by alcohol.

Driving skills

Drugs can affect a number of brain functions that adversely influence the ability to drive safely (see box). These can be best categorised as psychomotor and cognitive functions. Psychomotor skills include reaction times and hand-eye coordination while the ability to make appropriate decisions relates to cognitive skills. Foremost among the skills required for safe driving are vigilance, and the ability to interpret traffic situations and to divide attention between tasks.[1] The driver's behaviour and attitude also contribute to the risk of having an accident.

A large range of substances are known to impair the cognitive or psychomotor skills required for safe driving. Any drug acting on the central nervous system has the potential to adversely affect driving skills. Central nervous system depressants reduce vigilance, increase reaction times and increase errors associated with decision making and speed control in a very similar manner to alcohol. Drugs that affect behaviour may exaggerate adverse behavioural traits and risk-taking behaviour.

Alcohol and illicit drugs

Alcohol continues to be the most prevalent drug causing road trauma. In Australia, its prevalence in road fatalities is 25–30% depending on the jurisdiction. The average blood alcohol concentration in fatal accidents is over 0.15%.

Cannabis (marijuana) is the second most common drug (found in about 15% of fatalities in Victoria), followed by the amphetamine-type stimulants (4%) and opioids (4%). Illicit drugs are present in almost 20% of drivers killed in Victoria.[2] A survey of almost 500 injured drivers admitted to a major road trauma hospital found that cannabis products were present in 46%, opioid analgesics in 11% and amphetamines in 4%.[3]

During the acute phase of activity, central nervous system stimulants such as the amphetamines and cocaine tend to reduce performance on divided attention tasks, cause tunnel vision and increase risk taking. They can also cause rebound fatigue, inattention and hypersomnolence when the stimulatory effects wear off.

There is now substantial evidence to link cannabis and amphetamine use to an increased crash risk.[4] This has led to a number of states in Australia adopting countermeasures, such as random drug testing, to reduce drug-driving.

Prescribed drugs

With the exception of benzodiazepines the evidence for the role of prescribed drugs in road trauma is uncertain. In general, most drugs tend not to be significant risk factors on the road when the drugs are used as prescribed.

Some drugs can cause impairment due to their central nervous system depressant properties, particularly early in treatment

A selection of skills and attributes required for safe driving

Attentiveness and concentration

Vigilance

Divided attention skills (performing two or more functions simultaneously)

Visual fields and acuity

Hand-eye and foot-eye coordination

Reaction time

Tracking (ability to maintain lane control)

Table 1

Medicines that may impair driving skills

Drug	Risk of causing impairment *
Anticonvulsants (such as carbamazepine, gabapentin, phenobarbitone, phenytoin, valproate, vigabatrin)	Moderate to high
Antihistamines	Moderate to high
– sedating (such as azatadine, chlorpheniramine, cyproheptadine, diphenhydramine, promethazine, doxylamine, trimeprazine)	
– less sedating (such as cetirizine, desloratidine, fexofenadine, loratidine)	Low to moderate
Antipsychotics (such as amisulpride, chlorpromazine, haloperidol, pericyazine, clozapine, olanzapine)	Moderate to high
Benzodiazepines and related compounds (such as temazepam, nitrazepam, oxazepam, alprazolam, clonazepam, diazepam, zolpidem, zopiclone)	Moderate to high
Drugs for diabetes	Low to moderate
Muscle relaxants (such as baclofen, dantrolene, orphenadrine)	Moderate
Opioid analgesics (such as codeine, buprenorphine, methadone, morphine, oxycodone, pethidine, tramadol)	Moderate to high
Serotonin, mixed reuptake inhibitors and reversible monoamine oxidase inhibitor antidepressants (such as fluoxetine, sertraline, paroxetine, citalopram, venlafaxine, moclobemide)	Low
Tricyclic and tetracyclic antidepressants (such as amitriptyline, clomipramine, dothiepin, doxepin, imipramine, trimipramine, mianserin, mirtazapine)	Moderate to high
Sympathomimetics (such as pseudoephedrine, phenylephedrine)	Low to moderate

* These risks relate to possible situations when the drug or a member of a drug class is used incorrectly or abused. Risk of significant impairment usually only occurs early in treatment.

before the patient becomes accustomed to the drug, or when the drug is misused.[5] Table 1 shows some prescription drugs and their relative risk of causing impairment. The most common examples seen in road trauma are the anticonvulsants and the antidepressants, but their presence does not necessarily mean that they had a contribution to the crash.

In many cases two or more impairing drugs including alcohol are detected. Combinations of drugs increase the opportunity for impairment and the risk of a serious crash.

Benzodiazepines

Benzodiazepines are well known to increase the risk of a crash.[6,7] They are found in about 4% of fatalities[4] and 16% of injured drivers taken to hospital.[3] In many of these cases benzodiazepines were either abused or used in combination with other impairing substances. When abuse occurs, the drugs may not have been prescribed to the person concerned. The illicit trade in these drugs is significant and they are often obtained by 'doctor shopping'. Medical practitioners do need to be aware of this possibility when prescribing benzodiazepines and the related hypnotics zolpidem and zopiclone. If a hypnotic is needed a shorter-acting drug is preferred. Tolerance to the sedative effects of the longer-acting benzodiazepines used in the treatment of anxiety gradually reduces their adverse impact on driving skills.

Antidepressants

Although the antidepressants are one of the more detected drug groups in fatally-injured drivers, this tends to reflect their wide use in the community. The ability to impair is greater with sedating tricyclic antidepressants, typified by amitriptyline and dothiepin, than with the less sedating serotonin reuptake inhibitors. However, antidepressants can reduce the psychomotor and cognitive impairment caused by depression and return mood towards normal. This can improve driving performance.

Antipsychotics

This diverse class of drugs can improve performance if substantial psychotic-related cognitive deficits are present. However, most antipsychotics are sedating and have the potential to adversely affect driving skills through blockade of central dopaminergic and other receptors. Older drugs such as

chlorpromazine are very sedating due to their additional actions on the cholinergic and histamine receptors. Some newer drugs are also sedating, such as clozapine, olanzapine and quetiapine, while others such as aripiprazole, risperidone and ziprasidone are less sedating. Sedation may be a particular problem early in treatment and at higher doses.

Opioids

There is little direct evidence that opioid analgesics such as hydromorphone, morphine or oxycodone have direct effects on driving behaviour. Cognitive performance is reduced early in treatment, largely due to their sedative effects, but neuroadaptation rapidly sets in. This means that patients on a stable dose of an opioid may not have a higher risk of an accident. This includes patients on buprenorphine and methadone for their opioid dependency, providing the dose has been stabilised after some weeks and they are not abusing other impairing drugs. Driving at night may be a problem due to the persistent miotic effects of these drugs reducing peripheral vision.

Drugs for diabetes

Hypoglycaemia can be a significant problem. The drugs themselves have no major effect on skills, but how well they control blood glucose will affect driving performance.

Advice to patients

The product information of some drugs contains a precaution about driving. This caution may also be given on the label the pharmacist attaches to the prescription. For many drugs, once patients are stabilised, their potential low risk of causing significant impairment is offset by their therapeutic benefit. Nevertheless, it is necessary to appropriately warn patients about the dangers of driving a motor vehicle early in treatment and when the patient is not mentally alert possibly due to persistent drug effects. Moreover, patients driving at night or working shifts where normal sleep patterns are altered are also at an increased risk of fatigue-related crashes. Many drugs can exacerbate the effects of sleep deprivation and increase the risk of a crash. Taking drugs with alcohol increases impairment of driving skills.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 55)

1. Patients taking opioid analgesics for chronic pain should not drive.
2. Prescription medicines are the most common drugs found in road fatalities.

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Treatment of perinatal depression

Anne Buist, Professor of Women's Mental Health, University of Melbourne, Austin Health and Northpark Private Hospital, Melbourne

Summary

If possible, women at risk of depression should be identified during pregnancy. They often do not spontaneously seek help. Early intervention is important for the health of the woman and her baby. Psychological interventions such as support groups are often helpful. Involving the woman's partner can also assist. Antidepressants are required in some cases and women with psychotic symptoms need urgent psychiatric assessment and treatment.

Key words: antidepressants, infants.

(Aust Prescr 2008;31:36–9)

Introduction

Postnatal depression is better termed perinatal depression as it often begins antenatally, although it may not be recognised until the postnatal period. It is a common disorder, with milder adjustment problems and anxiety affecting some 30% of women while about 15% of women have more significant mood disorders, often with anxiety. Women are reluctant to seek help, but early identification and intervention are essential to minimise the long-term complications. These include suicide, chronic depression and marital difficulties, and for the child, cognitive, emotional and behavioural problems.

Identification

Unless women have previously had depression, they rarely recognise it in themselves during the perinatal period. For most, this is their first episode of depression and is unexpected at a time that is anticipated positively. In the antenatal period it is all put down to 'the pregnancy' with the presumption that everything will resolve itself after the baby is born. Historically, pregnancy was thought to be protective against mental illness and suicide, however this is not the case. Mental illness is just less likely to be recognised in pregnancy. Postnatally, there are many reasons why women do not seek help, or at least not for themselves. These include the presence of predominant anxiety rather than depression, a mistaken belief that postnatal depression is somehow linked to not wanting the baby or being a bad mother, the stigma of being seen as a bad mother and the stigma of depression.

Women seek help for the baby, not for themselves. The long waiting lists in mother and baby units and settling facilities are testimony to the very real problem perceived by mothers of their babies having sleeping and feeding difficulties. In some cases this is the primary problem, but often it is the mother's reaction, her high unrealistic expectations and her own depression and anxiety that are the underlying issue.

A key factor in identifying depression is having a suspicion for the condition particularly in women with risk factors (Box 1). Ideally, this risk should be detected during pregnancy. Women with previous perinatal depression or psychosis are particularly at risk of having another episode with future pregnancies. Screening for depression with tools such as the Edinburgh Postnatal Depression Scale can be helpful.[1] Many antenatal clinics and maternal child health nurses do screening and suggest women with high scores (> 12) see a doctor. Adjustment disorders have similar symptoms to depression but fewer, less severe symptoms and with some 'good times' and an ability to see into the future. These disorders usually resolve within three months.

Women with depression have symptoms which last longer than two weeks. They usually have significant anxiety (often related to the baby and their ability to mother), tearfulness, and feel easily overwhelmed and unable to cope with even basic household chores. Biological symptoms (insomnia, appetite changes) not accounted for by disturbed sleep and breastfeeding also suggest a more serious disorder. The severity of symptoms and their impact on the woman's life are the best guides to the need for intervention.

Box 1

Risk factors for perinatal depression

High correlation with increased risk

- Depression in pregnancy
- Past history of affective disorder
- Family history of affective disorder
- Lack of support – partner, mother
- Multiple stressors

Some correlation with increased risk

- Perfectionistic personality
- Low socioeconomic status
- Aboriginal and Torres Strait Islander people
- Childhood abuse

Depression should be distinguished from the less common postpartum psychosis. The latter usually presents in the first few weeks after birth, with confusion, dramatic mood or psychotic symptoms, and requires urgent assessment and inpatient treatment. In all cases if there is a threat to the safety of either the mother or the infant, referral to specialist care or involving protective services may be required. For many women with depression the baby is protective against suicide, but this is not true for women with postpartum psychosis, and suicide remains a leading cause of death.

Engaging

Women are often reluctant to admit how they are feeling and, in some cases, particularly to doctors, who they fear will give them an antidepressant. Women who present frequently to their child health nurse or general practitioner, and do not appear to be their usual selves should be asked again and again about their own health. Talking about normal 'stress' rather than depression, and engineering a view that to get help in fact makes them a good mother, might help break down the barriers over time.

Management

Many women with postnatal depression can be managed, at least initially, without medication. Unless the woman has very significant or long-standing symptoms, it is worth starting with psychosocial management. Antidepressants can be mentioned as one possibility if things do not improve. Although trials have been limited in postnatal depression, evidence suggests that antidepressants do have a role in treatment.[2]

The key to deciding about medication lies largely in diagnosis – is this an adjustment disorder or a major depression? Management must also take into account the woman's particular circumstances (see Box 2). The decision to prescribe is made in conjunction with the woman, and ideally her partner. Some partners are not supportive and may have strong views about the effect of drugs when the woman is pregnant or breastfeeding.

Psychosocial interventions

While postpartum psychosis (a probable variant of bipolar disorders) may have a clear biological aetiology, perinatal depression appears to begin at least as a stress response, in someone predisposed through personality or genetics. While the end result may be biological changes that will respond to medication, unless the stress is dealt with, recovery is likely to be delayed or prevented. In many cases, stress reduces as the baby ages, becomes more predictable, and life develops a routine. Women can be helped as they adapt to their new lifestyle. They need an opportunity to talk about their feelings and experiences. Although there are common themes, they will vary among women. For some a traumatic birth may be an issue, for others not being 'in control' or loss of lifestyle may be crucial to their feelings.

Box 2

When to consider use of antidepressants for perinatal depression

Severe or significant number of symptoms, particularly biological symptoms (e.g. sleep and appetite disturbance)

Persistent symptoms

Response to psychosocial management nil or inadequate

Unable to offer psychosocial management because of cost, distance, or other practical factors

Family or past history of good response to medication

Woman's preference

Therapeutic groups can be effective[3], but new mother groups can be counterproductive with depressed women feeling they are failures compared to the 'normal' mothers around them. A specific group can target the common anxieties of these depressed mothers, such as needing to be perfect and always there for their child, as well as focusing on the relationship with their infant. Many groups also include the partner for at least some sessions as the advent of parenthood and coping with a depressed woman can have a significant effect on the partner's mental health, as well as on the relationship.

It is important to look at the available supports and try to enhance these. Childcare to give the woman a break to have time for herself is often something women desperately need, but feel guilty about. If her main support is her mother or partner and there is conflict in the relationship, it is important to deal with this. Extra stress does not constitute support even if the intention is there.

Specific cognitive behavioural or interpersonal strategies in an individual setting can be helpful, although more research is needed.[4] Referral to a psychologist is worth considering. Relaxation, yoga and meditation can all have benefits, but are difficult for many women to implement. Website-based interventions can be useful such as those provided by the Centre for Clinical Interventions (www.cci.health.wa.gov.au).

Antidepressants in pregnancy

There are risks with antidepressants in pregnancy[5,6], but it is important to balance these largely unknown and seeming relatively low risks with the risks of **not** treating depression. Anxiety and depression in pregnancy can affect the fetus, for example a higher cortisol concentration at birth can be maintained for 10 years.[7] Depressed women are also more likely to smoke, and have poor nutrition and a risk of suicide.

Antidepressants in lactation

The harmful effect of taking antidepressants during lactation needs to be balanced against the benefits for each woman.[6,8] For some women being given permission to cease breastfeeding can be a relief, particularly when anxiety has resulted in decreased milk supply or care of the baby is overwhelming. The risks of antidepressant drugs seem quite low, with the exception of venlafaxine, which appears to be concentrated in the breast milk. Smaller, premature and unwell infants could be more at risk and any subtle effects of drugs in breast milk are unknown.

Mother-infant interaction

There is now extensive literature on the association of maternal depression with an increased risk of poorer mental health outcomes in children.[9,10] While this is clear, the association is not straightforward, and includes a biological influence through genes and stress hormones in pregnancy, as well as the mother's own parenting, her attachment to the child, and her social circumstances.

Research suggests that treating the depression alone does not in itself bring about change in the mother-infant relationship. Depressed and anxious women more often than not want to be good mothers, but their illness, and their own attachment experience may interfere with this, making them less responsive, or over-intrusive or inconsistent. Early intervention is important because in the first year of life, infants form an attachment which is the building block for all later relationships.[11]

General practitioners can think of and watch the relationship between mother and baby. If there are concerns, ask the mother about her feelings and her own experience of being mothered. Suggest ways of making things easier for her that will be better for baby. The 'circle of security', which shows diagrammatically the needs of the child, can be downloaded (www.circleofsecurity.org) and used with women. It is a simple way of showing what young babies need, and a useful talking point. Consider if there is anyone else that could be involved in the child's care. If the mother is very withdrawn, then engage her partner or mother and point out the importance of them providing stimulation to the infant. While this may not seem much, it is important to remember that infants have their own resilience factors. Anything that can enhance these can potentially bring about a better outcome.

When to refer

While most women with perinatal depression can be managed in general practice, referrals can be considered in a number of key situations. Firstly, if there are risks of harm, referral should be made urgently to a parent-infant unit, psychiatric hospital or crisis team depending on local availability and protocol.

An opinion from a psychiatrist specialising in the area can be particularly useful when medication is being contemplated in pregnancy and lactation.

A psychiatry referral for a management plan (Medicare item 291) can be considered when women have not responded to psychosocial management and at least one antidepressant, or when they have not improved and are reluctant to use antidepressants. Referral to a psychologist is also useful in this scenario, and when anxiety is a key feature.

Referral for assessment, or for ongoing care, should be considered for women with comorbid disorders, significant impairment in the mother-infant interaction and where the mother's childhood issues and personality factors are contributing significantly to presentation and poor progress.

Conclusion

Perinatal mood and anxiety disorders are common and have potential long-term negative outcomes for the woman and her infant. Although there is a limited evidence base, medication, cognitive behavioural and interpersonal strategies and support may be of use. Early identification through careful assessment of the patient, her infant and risk factors, awareness of the difficulties women have in recognising and accepting a diagnosis of depression, and specific issues related to the baby, all need consideration in managing women in the perinatal period.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 55)

3. Maternal depression has no effect on the future mental health of the child.
4. Perinatal depression is often underrecognised.

Patient support organisations

Perinatal depression

beyondblue

beyondblue is an Australian independent not-for-profit organisation working to address issues associated with depression, anxiety and related substance misuse disorders. The beyondblue website has informative sections on depression, postnatal depression, anxiety and bipolar disorder. It has recommended links to additional information and contacts in every state and territory.

Website: www.beyondblue.org.au
Telephone information line: 1300 22 4636

Post and Ante Natal Depression Association (PANDA)

PANDA is a Victorian not-for-profit self-help organisation that provides confidential information, support and referral to those affected by post- and antenatal mood disorders, including partners and extended family members. PANDA produces and distributes accurate information about post- and antenatal mood disorders to health professionals and the wider community, in the form of:

- resources and information on antenatal and postnatal depression and postpartum psychosis, on the website and in paper copy
- telephone support and information
- information and referral details for supports and services in your area
- newsletters for members.

Website: www.panda.org.au

Telephone: 1300 726 306 Victoria, (03) 9481 3377 outside Victoria

Book review

Therapeutic Guidelines: Analgesic. Version 5.

Melbourne: Therapeutic Guidelines Limited; 2007. 285 pages. Price $39, students $30, plus postage

Simon Vanlint, Assistant Dean (students) and Lecturer, Discipline of General Practice, University of Adelaide

Version 5 updates the previous version of this therapeutic guideline, published in 2002. Its stated aim is 'to provide clear, practical, authoritative and succinct therapeutic information for busy health practitioners'. Although it is not explicitly stated, the target audience appears to be students, junior doctors (including specialist trainees) and general practitioners. In the subject area of analgesia, successive versions have seen an increase in detail about the theoretical and pathophysiological considerations which underpin clinical practice, reflecting the considerable growth in knowledge since the first version appeared in 1988.

The book discusses the mechanisms and pathophysiology of pain, followed by both general and specific information about pharmacology. Non-pharmacological methods are also covered in some detail. Guidelines are provided for assessing pain (including pain in children), managing chronic pain and for a range of specific clinical situations. Despite its compact size, the book is very comprehensive and covers a wide range of situations where pain will need to be assessed and managed. Although much will be very familiar to experienced practitioners, there is still value in reviewing basic knowledge, especially when that knowledge has been added to in the recent past. This book would be invaluable for students and junior doctors, and is likely to be helpful for rural practitioners, given the very wide range of clinical scenarios that they will encounter. It will also be helpful for those who find that the management of chronic pain is becoming more prominent in their day-to-day practice. In short, a useful update of a trusted tool.

Ear drops and ototoxicity

Harvey Coates, Clinical Associate Professor, School of Paediatrics and Child Health, University of Western Australia, and Senior Otolaryngologist, Princess Margaret Hospital for Children, Perth

Summary

Ototoxicity is a rare but potentially serious complication of the use of aminoglycoside and other cochleo-toxic ear drops. This risk is increased when there is a perforation of the tympanic membrane or a patent grommet. Until recently, no alternatives to potentially ototoxic antibiotic ear drops were approved in Australia. The approval of fluoroquinolone ear drops means that an alternative to the aminoglycosides is now available for use in the open middle ear. Guidelines from the Australian Society of Otolaryngology Head and Neck Surgery state that non-ototoxic antibiotic ear drops are preferable for the management of a discharging middle ear.

Key words: aminoglycosides, antibiotics, fluoroquinolones, hearing.

(Aust Prescr 2008;31:40–1)

Introduction

The risks of systemic ototoxicity from various drugs, such as the aminoglycosides, are well known. Less well known is the potential for ototoxicity when these drugs are prescribed as ear drops for patients with tympanic membrane perforations. Although some antibiotic ear drops have been used for 40 years in Australia, ototoxicity has become an increasing concern globally over the last ten years. Aminoglycoside ototoxicity can affect not only the cochlea (hearing) but also the vestibular (balance) system.

Aminoglycoside ototoxicity

The most frequently prescribed antibiotic ear drops in Australia are a combination of framycetin (an aminoglycoside), gramicidin and dexamethasone. Aminoglycoside ear drops may cause hearing loss or balance disorder in about 1 in 10 000 patients, but the true incidence of topical ototoxicity is unknown. It may be much more common, but not recognised for various reasons, including:

- lack of pre- and post-treatment audiograms or balance assessment
- lack of audiologic testing for frequencies greater than 8000 Hz
- attribution of any hearing loss to the underlying disease process.

There is no doubt that some ingredients of older ear drops, especially but not limited to aminoglycosides, have the potential to cause severe cochlear and vestibular ototoxicity. Neomycin is probably the most toxic of the aminoglycosides followed by gentamicin and tobramycin. (Framycetin is a major component of neomycin.) Repeated and prolonged courses of treatment increase the risk of toxicity.

In a survey of 2235 American otolaryngologists, 3.4% reported having seen a patient with probable ototoxicity secondary to the use of potentially ototoxic ear drops in the presence of a tympanic membrane perforation or open mastoid cavity.[1] In a Canadian series of nine patients prescribed gentamicin drops (not generally used in Australia except for deliberate ablation of vestibular function in Ménière's disease) four developed balance symptoms that were so incapacitating that they required mechanical aids to help them walk.[2]

Factors affecting topical ototoxicity

A clinician may prescribe ototoxic ear drops for an apparent otitis externa or wax-obstructed ear canal, but if there is an undetected tympanic membrane perforation a profound sensori-neural hearing loss may result. In the presence of a tympanic membrane perforation, open mastoid cavity or patent grommet, topical antibiotics can cause ototoxicity within a few days, although most cases follow prolonged therapy. The absorption of drops is affected by the presence or absence of thickened middle ear mucosa and round window membrane (the latter being the portal of entry of the drops to the inner ear). The presence of granulation tissue, webs or polypoid tissue can also prevent ear drop access to the round window. There are genetic factors in some patients of Asian or Arabic origin causing them to be uniquely sensitive to the ototoxic effects of ear drops.

Ototoxic ear drops – overseas recommendations

The British[3], Canadian[4] and US[5] guidelines or protocols for the use of ototoxic ear drops in the open middle ear recommend against the use of aminoglycosides with a tympanic membrane perforation. The evidence-based recommendations of the expert consensus panel of the American Academy of Otolaryngology – Head and Neck Surgery regarding efficacy and safety of topical antibiotics in the treatment of ear disease have been adopted, with minor variations, by the Australian Society of Otolaryngology Head and Neck Surgery pharmaceutical sub-committee (see box).[6]

The Australian situation

The majority of prescriptions for antibiotic ear drops in Australia have been for potentially ototoxic aminoglycoside-containing drops. Six cases of deafness in patients using combination ear drops have been reported to the Adverse Drug Reactions Advisory Committee. The product information states the drops are contraindicated in the presence of tympanic membrane perforations yet they are still used as first-line management of discharging middle ears. In children with chronic suppurative otitis media, particularly Aboriginal and Torres Strait Islander children, repeat courses of potentially ototoxic drops have been used for prolonged periods, placing these often audiologically unmonitored children at risk of sensorineural hearing loss. The Therapeutic Guidelines: Antibiotic recommends aural toilet for chronic suppurative otitis media and limits any aminoglycoside drops to seven days of treatment. If there is no response after seven days a topical fluoroquinolone is recommended.

A study by the National Aboriginal Community Controlled Health Organisation compared fluoroquinolone ear drops with a combination of framycetin, gramicidin and dexamethasone. In 111 children with ears infected by the usual organisms isolated in chronic suppurative otitis media (*Pseudomonas aeruginosa*, *Staphylococcus aureus*), the efficacy of ciprofloxacin was significantly greater.[7] There was a clinical cure in 42 of the 55 children given ciprofloxacin, compared with 29 of the 56 children given the combination.

The recommended duration of ciprofloxacin therapy is nine days, and safety and efficacy are unknown beyond 14 days. There is concern about bacterial resistance to the fluoroquinolones, but no controlled studies with pre- and post-treatment minimum inhibitory concentration/sensitivity testing have detected fluoroquinolone resistance in the absence of previous systemic fluoroquinolone treatment. The local high concentration of topical drops ensures that they are bactericidal to bacteria in the middle ear and mastoid, although a bacterial biofilm may persist.

Ciprofloxacin drops as an ear preparation have been approved by the Therapeutic Goods Administration, and the Pharmaceutical Benefits Scheme subsidises them for use in chronic suppurative otitis media in Aboriginal and Torres Strait Islander patients over the age of one month. A private prescription is necessary for other patients.

Australian Society of Otolaryngology Head and Neck Surgery recommendations [6]

1. Non-ototoxic eardrops are preferable in the presence of tympanic membrane perforations.
2. If potentially ototoxic drops are used for discharging middle ears, they should be ceased immediately the infection resolves.
3. Patient's/parental informed decision making should be documented for use of potentially ototoxic eardrops.
4. If hearing loss, vertigo, or tinnitus develop while using potentially ototoxic ear drops the patient should be instructed to return to their doctor.
5. If the tympanic membrane is known to be intact and the middle ear and mastoid are closed, then the use of potentially ototoxic preparations presents no risk of ototoxic injury.

Conclusion

The ototoxicity of commonly prescribed aminoglycoside ear drops, although rare, poses a therapeutic dilemma for the prescribing physician. The use of ototoxic ear drops should be avoided in patients with perforations of the tympanic membrane. The Australian recommendations provide a clear plan of management for the discharging middle ear and raise awareness of an alternative therapeutic option using non-ototoxic fluoroquinolone rather than potentially ototoxic ear drops.

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Further reading

For a list of further references see this article online at www.australianprescriber.com in Vol. 31 No. 2.

Dr Coates has attended scientific and educational meetings sponsored by Alcon Laboratories and Daiichi.

Therapeutic drug monitoring: which drugs, why, when and how to do it

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Summary

Therapeutic drug monitoring of concentrations of drugs in body fluids, usually plasma, can be used during treatment and for diagnostic purposes. The selection of drugs for therapeutic drug monitoring is important as the concentrations of many drugs are not clearly related to their effects. For selected drugs therapeutic drug monitoring aims to enhance drug efficacy, reduce toxicity or assist with diagnosis. Despite its apparent advantages, it has inherent limitations. Some large hospitals have services which provide support with drug monitoring and interpretation of results.

Key words: pharmacokinetics.

(Aust Prescr 2008;31:42–4)

Introduction

The monitoring of therapeutic drugs involves measuring drug concentrations in plasma, serum or blood. This information is used to individualise dosage so that drug concentrations can be maintained within a target range.[1]

Drug concentration at the site of action cannot be routinely measured, but the desired or adverse effects may correlate better with plasma or blood concentrations than they do with dose. For a few drugs, concentration measurements are a valuable surrogate of drug exposure, particularly if there is no simple or sensitive measure of effect.

When there is a large inter-individual variation between dose and effect, for example when there is large pharmacokinetic variation, individualising drug dosage is difficult.[1] This is particularly relevant for drugs with a narrow target range or concentration-dependent pharmacokinetics. Similarly, variations within an individual can occur over time for a range of reasons with some drugs, and therapeutic drug monitoring could then be useful.

Therapeutic drug monitoring involves not only measuring drug concentrations, but also the clinical interpretation of the result. This requires knowledge of the pharmacokinetics, sampling time, drug history and the patient's clinical condition.

Which drugs?

When an effect, such as changes in blood pressure, pain or serum cholesterol is readily measured, the dose of a drug should be adjusted according to the response. Monitoring drug concentration is more useful when drugs are used to prevent an adverse outcome, for example, graft rejection or to avoid toxicity, as with aminoglycosides. A drug should satisfy certain criteria to be suitable for therapeutic drug monitoring. Examples include:

- narrow target range
- significant pharmacokinetic variability
- a reasonable relationship between plasma concentrations and clinical effects
- established target concentration range
- availability of cost-effective drug assay.

The most commonly monitored drugs are probably carbamazepine, valproate and digoxin. However, there is little evidence that monitoring concentrations of anticonvulsants improves clinical outcomes when the drugs are used to treat mood disorders.

Table 1 shows some of the drugs that meet these criteria.

Indications ('why do it')

Drug assays are costly, so the reason for monitoring and the additional information to be gained (if any) should be carefully considered. For some drugs, therapeutic drug monitoring helps to increase efficacy (vancomycin), to decrease toxicity (paracetamol) and to assist diagnosis (salicylates). Routine monitoring is not advocated for most drugs. Only clinically meaningful tests should be performed.[1]

The appropriate indications for therapeutic drug monitoring (and examples) include:

- toxicity
  - diagnosing toxicity when the clinical syndrome is undifferentiated (unexplained nausea in a patient taking digoxin)
  - avoiding toxicity (aminoglycosides, cyclosporin)

- dosing
  - after dose adjustment (usually after reaching a steady state)
  - assessment of adequate loading dose (after starting phenytoin treatment)
  - dose forecasting to help predict a patient's dose requirements[1] (aminoglycosides)
- monitoring
  - assessing compliance (anticonvulsant concentrations in patients having frequent seizures)
  - diagnosing undertreatment (particularly important for prophylactic drugs such as anticonvulsants, immunosuppressants)
  - diagnosing failed therapy (therapeutic drug monitoring can help distinguish between ineffective drug treatment, non-compliance and adverse effects that mimic the underlying disease).

The target concentration may depend on the indication. For example, the recommended concentration for digoxin depends on whether it is being used to treat atrial fibrillation or congestive heart failure.[2]

Table 1

Drugs suitable for therapeutic drug monitoring

Drug	Target range *
Drugs regularly monitored in clinical practice	
digoxin	0.8–2 microgram/L and < 0.01 microgram/L in refractory heart failure
lithium – acute mania	0.8–1.2 mmol/L
– maintenance	0.4–1.0 mmol/L
perhexiline	0.15–0.6 mg/L
phenytoin	10–20 mg/L
cyclosporin	50–125 microgram/L (serum or plasma) 150–400 microgram/L (whole blood) Concentrations differ for various clinical settings
sirolimus	5–15 microgram/L (whole blood)
tacrolimus	5–20 microgram/L (whole blood)
Drugs for which monitoring may be useful	
amiodarone	1–2.5 mg/L
carbamazepine	5–12 mg/L
flecainide	0.2–0.9 mg/L
lamotrigine	1.5–3 mg/L
salicylate	150–300 mg/L
sodium valproate	50–100 mg/L
vancomycin	Trough 10–20 mg/L

* Concentrations may vary between laboratories

Timing of the plasma sample ('when to do it')

Unless therapeutic drug monitoring is being used to forecast a dose or there are concerns about toxicity, samples should be taken at steady state (4–5 half-lives after starting therapy).[1,3]

At steady state, plasma concentration is usually proportional to receptor concentration. Some drugs, such as perhexiline, which has a very long half-life in patients who are 'poor metabolisers', should be monitored before steady state is achieved to prevent toxicity developing after the first few doses. Another example where early monitoring may be useful is after phenytoin loading, where measurement of the plasma concentration can give a preliminary indication of adequate dosing.

The timing of the collection of the sample is important as the drug concentration changes during the dosing interval. The least variable point in the dosing interval is just before the next dose is due. This pre-dose or trough concentration is what is usually measured. For drugs with long half-lives such as phenobarbitone and amiodarone, samples can be collected at any point in the dosage interval.[1,3]

Correct sample timing should also take into account absorption and distribution. For example, digoxin monitoring should not be performed within six hours of a dose, because it will still be undergoing distribution and so plasma concentrations will be erroneously high.[1,3]

Occasionally, sampling at the time of specific symptoms may detect toxicity related to peak concentrations of, for example, carbamazepine and lithium.

For once-daily dosing of aminoglycosides, the timing of the blood sample is determined by the method of monitoring. For example, it is collected 6–14 hours post-dose when a nomogram is used, or twice within the dosing interval to calculate the area under the concentration-time curve.[4,5] When aminoglycosides are prescribed in multiple daily doses to treat, for example, enterococcal endocarditis, then trough samples are measured to minimise toxicity and assess whether concentrations are adequate for efficacy.

Therapeutic drug monitoring request ('what to document')

Drug assays may be requested for therapeutic drug monitoring or for clinical toxicology purposes.[5] For therapeutic drug monitoring the information required to allow interpretation of the result should include the time of the sample collection, the time of the last dose, the dosage regimen and the indication for drug monitoring.[1,3]

Interpretation

Drug concentrations need to be interpreted in the context of the individual patient without rigid adherence to a target range. For example, if a patient has an anticonvulsant drug concentration just below the target range, but is not having seizures, an

increase in dose is probably not required. For a few drugs, monitoring drug concentration is a helpful adjunctive measure. Before making dose adjustments, it is important to consider if the sample was taken at the correct time with respect to the last dose, if a steady state has been reached and whether the patient has adhered to their treatment. There are other considerations, for example, the serum potassium should be noted when interpreting digoxin concentrations as toxicity can occur at a therapeutic concentration if there is hypokalaemia.

Most drug assays measure total drug concentration (bound and unbound drug), but only the unbound drug interacts with its receptor to produce a response. The unbound fraction may be affected by factors such as serum albumin concentration, displacement by an interacting drug and renal failure. This is important for drugs like phenytoin. If phenytoin's unbound fraction doubles from 10% to 20%, the target range based on total phenytoin concentration should be halved. If dose adjustments are made according to the usual target range, toxicity may result.

Measuring and monitoring

Drug concentrations should be measured within a clinically useful timeframe in laboratories with appropriately trained staff and subject to quality assays.[3] The ideal laboratory turnaround time should be shorter than the dosing interval, however, due to cost, assays are performed in batches which may lengthen the turnaround time.

Plasma drug concentrations are reported either in mass or molar units. Reporting in mass units with attached conversion formulas may assist with interpretation of results.[3]

Differences exist between laboratories and validated target ranges should accompany results to assist clinicians with safe and effective prescribing.[3]

Some institutions provide drug monitoring and interpretive services which may help to improve the safety, efficacy and cost-effectiveness of clinical services. These therapeutic drug monitoring services also have an educational role by promoting the principles of rational prescribing and quality use of medicines.[3]

Limitations

Apart from the limited number of drugs amenable to therapeutic drug monitoring, there are also inherent limitations, including the scientific accuracy of the drug assays, laboratory variability in reporting, limited accessibility in rural Australia and the validity of suggested target ranges.[1,3]

The target range describes a range of drug concentrations associated with a reasonable probability of efficacy without undue toxicity in the majority of patients. It is not well described for most drugs and is often based on a very limited number of data points.[1,2]

Active metabolites (for example carbamazepine-10,11-epoxide) may contribute to the therapeutic response but are not routinely measured.

Conclusion

The drug concentration is complementary to and not a substitute for clinical judgement so it is important to treat the individual patient and not the laboratory value. Drug concentrations may be used as surrogates for drug effects so therapeutic drug monitoring may assist with dose individualisation. It can also be used to detect toxicity, so therapeutic drug monitoring can optimise patient management and improve clinical outcomes. Careful selection of drugs to be monitored should occur. Regular monitoring of many drugs is not required in a clinically stable patient.

Professor Peter Pillans is acknowledged for his assistance in the preparation of this article.

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Conflict of interest: none declared

National Medicines Symposium 2008

Wednesday 14 – Friday 16 May 2008, National Convention Centre, Canberra

The theme for the fifth biennial symposium is 'QUM: what does it really mean for you? The science, the policy and the practice'. Co-hosted by the National Prescribing Service and Pharmaceutical Health And Rational use of Medicines (PHARM) Committee, the symposium will cover a variety of perspectives and views from health professionals, the pharmaceutical industry, academics, policy makers and regulators, consumers and community organisations. NMS 2008 will be a platform for sharing expertise and experience, and exploring international and national best practice in QUM.

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Corticosteroid-induced osteoporosis and fractures

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Summary

Corticosteroids can cause fractures by reducing bone formation and the viability of osteoblasts and osteocytes. The heightened fracture risk is dose dependent and occurs within months of starting therapy. Daily doses of more than 2.5 mg prednisolone or equivalent are associated with a higher fracture risk. Randomised studies reveal adverse skeletal effects with daily doses as low as 5 mg. After treatment stops, the fracture risk rapidly falls towards baseline unless the patient was taking long-term therapy. Patients who start corticosteroid therapy should routinely receive calcium and vitamin D supplementation. Those with a higher risk of fracture should also be offered a bisphosphonate. Repeated efforts should be made to reduce the dose of corticosteroids or discontinue long-term therapy if possible.

Key words: bisphosphonates, bone, vitamin D.

(Aust Prescr 2008;31:45–9)

'All they had to offer were calcium and bed rest… '

Patrick White: Letters.*

Introduction

Fragility fractures are a serious complication of long-term treatment with corticosteroids. The high frequency and rapid onset of corticosteroid-related fractures necessitates prompt identification of at-risk patients.

A meta-analysis of more than 42 000 patients compared outcomes for patients who had taken oral corticosteroids with those who had not. The relative risk for osteoporotic fracture was 2.63 at the age of 50 and 1.71 at 85 years. For hip fracture the respective relative risks were 4.42 and 2.48. Overall, the reported fracture risk was similar in men and women, independent of prior fracture, and only partially explained by losses in bone mineral density.[1]

In a retrospective study of a general practice database (244 235 people taking oral corticosteroids were compared with the same number of controls) the relative rate was 1.61 for hip fracture and 2.60 for vertebral fracture. The fracture risk increased with daily prednisolone doses greater than 2.5 mg/day and no truly 'safe dose' of corticosteroid was identified. Importantly, fracture rates decreased rapidly (within one year) after cessation of oral corticosteroid therapy, indicating reversibility of the risk.[2]

Mechanisms

Bone loss is usually higher at skeletal sites rich in trabecular bone, particularly the vertebral bodies, ribs and distal radius, but it also occurs in cortical bone in the upper femur. The mechanisms of increased bone fragility are not completely understood, but the inhibitory effects of corticosteroids on osteoblasts are likely to be critical. Corticosteroids inhibit replenishment of osteoblasts, reduce the synthesis of bone collagen and osteocalcin by existing osteoblasts, and promote osteoblast and osteocyte apoptosis. Osteoblast inhibition leads to a reduction in the amount of bone replaced in each remodelling cycle. However, the role of osteoclastic bone resorption in fracture risk is less certain as study results have been inconsistent and markers of bone resorption are often unchanged during short-term corticosteroid treatment.

Corticosteroids reduce intestinal calcium absorption and increase renal calcium excretion. This may contribute to hyperparathyroidism and bone loss. These negative effects on calcium balance can be reversed with oral calcium and vitamin D_3 supplementation, or by treatment with active vitamin D metabolites such as 1,25-dihydroxyvitamin D_3 (calcitriol). In some patients, corticosteroids also reduce gonadal function, which may further contribute to bone fragility.

The role of steroid-induced myopathy on fractures is unknown. The increase over time of both vertebral and non-vertebral fractures without an increase in forearm fractures suggests that the direct effects of corticosteroids on bone strength predominate over any effects on falls.

Effects of dosage and timing

Short-term studies show that daily doses of prednisolone as low as 5 mg cause markers of bone formation (for example osteocalcin) to fall rapidly. Both the daily dose and treatment duration, and therefore cumulative dose, are considered responsible for the skeletal adverse effects. However, as

* The Nobel Prize winning Australian author, Patrick White, suffered osteoporotic fractures due to prolonged oral corticosteroid therapy. White's lament for the lack of therapy is no longer true. [White P. Patrick White: Letters. Sydney: Random House; 1994]

fractures often occur rapidly after starting corticosteroids, the effects on fractures are probably more closely related to the daily dose rather than to the duration of therapy or cumulative dose.

When high doses (prednisolone > 20 mg/day or equivalent) are used, the annual rate of loss of spinal bone density is 5–15%. The rate of bone loss is most marked in the first six months after starting corticosteroids and can be as high as 27%. Bone loss may slow irrespective of whether or not the dose is tapered as the patient's underlying condition improves. The relationship of dose to fracture risk and bone mineral density is different. The daily dose is the single most important determinant of fracture, whereas there is a strong inverse relation between cumulative dose and bone mineral density.[3] Patients with high cumulative doses (more than 10 g prednisolone equivalent) show marked deterioration in trabecular micro-architecture characterised by thinning and loss of connectivity, compared to short-term treatment.[4] Hence, fracture risk reduction after withdrawal of corticosteroids is less certain after long-term therapy than after short-term therapy.

In contrast to premenopausal women, people aged over 50 years and postmenopausal women are more susceptible to osteoporosis even with low doses (prednisolone < 7.5 mg/day or equivalent). At doses greater than 20 mg/day, corticosteroids have a devastating effect on bone mineral density irrespective of age, gender or menopausal status. At high doses, trabecular bone connectivity (not merely thickness) is severely compromised, leading to vertebral fractures.

Intermittent oral corticosteroids (in men) and inhaled corticosteroids increase vertebral fracture risk, but patients taking intermittent corticosteroids are less likely to sustain fractures than those taking continuous therapy. Taking corticosteroids on alternate days may preserve growth in children, but does not prevent bone loss in children, or in adults. Pulsed intravenous high dose corticosteroids (that is 1 g methylprednisolone) are less deleterious to bone mineral density, but increase the risk of osteonecrosis. The rapid reduction in systemic inflammation after pulsed therapy might be protective, as the underlying diseases for which corticosteroids are prescribed (for example rheumatoid arthritis, Crohn's disease) often contribute to the increased risk of fractures, independently of corticosteroid therapy.

Risk assessment

Each patient's risk factors should be carefully appraised before prescribing corticosteroids (Fig. 1). Readily identified factors that influence bone loss and fracture risk include the dose, the underlying condition, and factors such as age, female gender, menopausal status and low bone mineral density. In practice, postmenopausal women are those at highest risk for corticosteroid-induced osteoporosis.

The effects of corticosteroids on bone mineral density can be measured precisely and accurately using dual energy X-ray absorptiometry. Early changes are seen in the lumbar spine. Dual energy X-ray absorptiometry of the lumbar spine and femoral neck is recommended for all patients starting long-term (> 3 months) corticosteroids. Repeated measurements at 1–2 year intervals are recommended to monitor bone loss. The T-score can help guide management, but there is no consensus on an appropriate or cost-effective threshold for intervention in patients taking corticosteroids. T-scores of less than –1.0 (USA) or less than –1.5 (UK) have been suggested. The use of these low intervention thresholds in oral corticosteroid users reflects the fact that fracture rates are considerably higher in corticosteroid users than in non-users.

> The importance of reducing or stopping corticosteroids, whenever possible, cannot be overemphasised

Determining the absolute fracture risk for individual patients is difficult. Scoring systems to ascertain this risk are now emerging, but are not yet in routine use. In one study, a woman aged 65 years with rheumatoid arthritis, low body mass index, and a previous history of fracture and falls who took 15 mg prednisolone daily had a five-year fracture risk of 47% compared with a man with a similar history whose risk was 30.1%.[5]

Management

The importance of reducing or stopping corticosteroids, whenever possible, cannot be overemphasised. The general practice research database study reported that the excess risk of fracture diminished within one year of stopping therapy and this was most obvious for vertebral fractures. The risk of hip fracture also fell towards baseline levels after treatment stopped.[2]

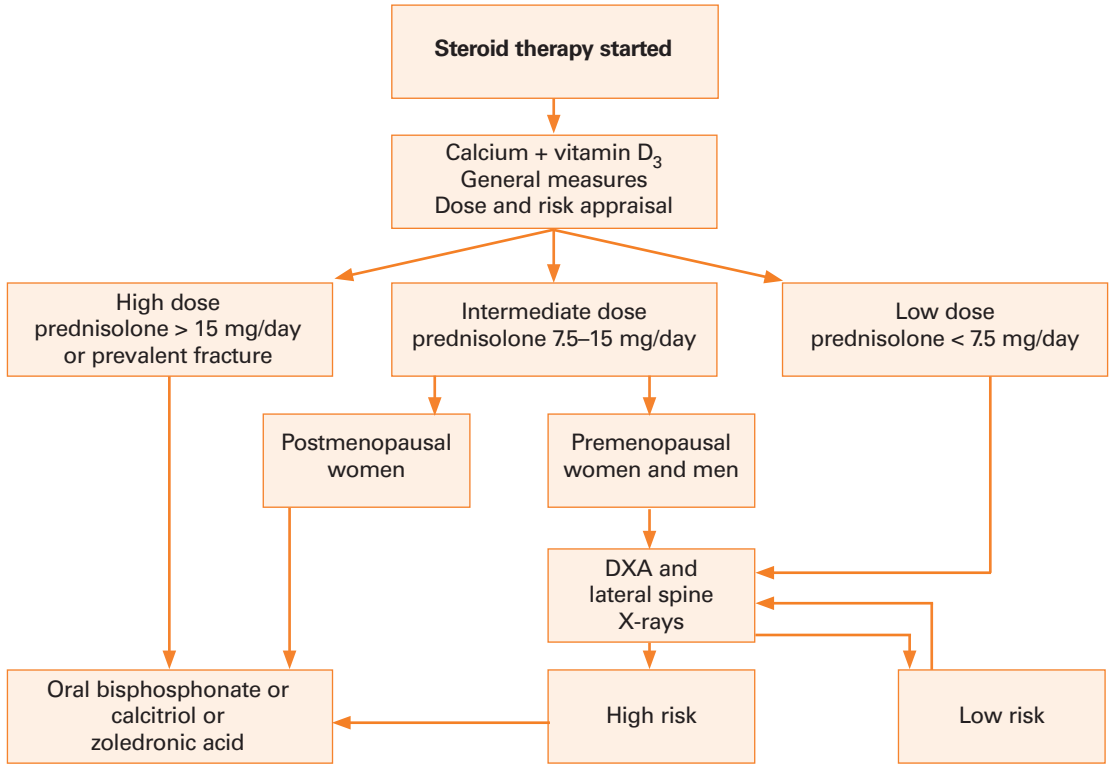
There are sparse data on the effects of lifestyle interventions in patients using oral corticosteroids. Patients should be advised not to smoke or abuse alcohol. Although proximal muscle weakness is a complication of oral corticosteroids, the possible effects of physical exercise on muscle mass or fracture rates have not been systematically evaluated.

Calcium and vitamin D

Calcium alone is insufficient to prevent rapid bone loss in patients starting corticosteroids. However, calcium and vitamin D_3 (cholecalciferol) may blunt the continuing loss during long-term use of corticosteroids. A Cochrane meta-analysis compared patients taking calcium and vitamin D_3 to patients using calcium alone or placebo.[6] The studies were underpowered to detect statistically significant reductions in fracture risk, but revealed a trend towards a lower risk of fracture in patients treated with calcium and vitamin D_3. All patients starting oral corticosteroid therapy are advised to take calcium (1000 mg/day) and

Fig. 1

Fracture prevention for patients starting corticosteroids



DXA dual energy X-ray absorptiometry

vitamin D_3 (at least 500 IU/day). In practice, the aim should be to maintain serum 25-hydroxyvitamin D_3 levels greater than 50 ng/mL to prevent secondary hyperparathyroidism.

In addition to vitamin D_3, randomised controlled trials demonstrated that the hydroxylated derivatives of vitamin D_3, for example 25-hydroxyvitamin D_3 (calcidiol), 1-hydroxyvitamin D_3 (alfacalcidol) or 1,25-dihydroxyvitamin D_3 (calcitriol) administered together with calcium, were superior to calcium alone in reducing bone loss after corticosteroid therapy (Table 1). The risk of hypercalciuria or hypercalcaemia is higher with the hydroxylated vitamin D_3 metabolites than with plain vitamin D_3, especially when combined with calcium, and this must be monitored. Apart from calcitriol, vitamin D metabolites are not routinely available to Australian prescribers. Studies comparing the vitamin D metabolites in corticosteroid users have not been reported. Alendronate (10 mg/day) is more effective than alfacalcidol (1 microgram/day) in the prevention of costicosteroid-induced bone loss.[7] However, calcitriol is at least as effective as alendronate in preventing bone loss in corticosteroid users.[8]

Table 1

Vitamin D metabolites for prevention of corticosteroid-related bone loss

Vitamin D derivative	Dose range
Cholecalciferol (vitamin D_3)[11]	500 IU/day–100 000 IU/week
Calcidiol (25-hydroxyvitamin D_3)[12] *	35–40 microgram/day
Alfacalcidol (1-hydroxyvitamin D_3)[7, 13] *	0.5–1.0 microgram/day
Calcitriol (1,25-dihydroxyvitamin D_3)[14]	0.5–1.0 microgram/day

* not generally available in Australia

Antiresorptive drugs

Although the effects of corticosteroids on bone formation predominate, antiresorptive drugs appear to reduce fracture risk both by reducing their effects on osteoclast-mediated bone remodelling and preventing the negative effects of corticosteroids on osteoblast and osteocyte viability. The active metabolites of vitamin D_3, such as calcitriol (0.25–0.5 microgram/day), may effectively slow the rapid bone loss in patients starting corticosteroids. Bisphosphonates, such as alendronate and risedronate, also prevent bone loss in these patients and in those already taking chronic therapy.

A meta-analysis attempted to rank various antiresorptive drugs according to their effect on bone mineral density. It found that bisphosphonates had greater efficacy than no therapy or

calcium (4.6% difference in percent change in the bone mineral density of the lumbar spine after one year). The efficacy of bisphosphonates was also enhanced when used in combination with vitamin D_3 (6% difference in bone mineral density).[9]

While bisphosphonates are currently the most effective therapies for the management of corticosteroid-induced osteoporosis, few studies have measured fracture outcomes. The overall reduction in risk of morphometric (X-ray detected) vertebral fractures with bisphosphonates, such as risedronate, is approximately 37%, but there are no efficacy data about hip and other non-vertebral fractures in patients taking corticosteroids. The assumption is that the efficacy is similar to the 30–50% reduction in non-vertebral fractures seen in patients treated for postmenopausal osteoporosis, although this has not been rigorously tested. Further, no study has examined symptomatic vertebral fractures or back pain as a primary end point.

The intravenous bisphosphonates (pamidronate and zoledronic acid) are often used in patients who are intolerant of oral bisphosphonates. Zoledronic acid is effective in reducing vertebral and hip fractures in postmenopausal osteoporosis, and randomised studies in corticosteroid users are under way.

Anabolic drugs

Intermittent injections of parathyroid hormone have a bone anabolic effect. A randomised clinical trial showed that recombinant human parathyroid hormone injections could override corticosteroid-induced suppression of bone formation and increase bone mass.[10] However, the precise role and cost-effectiveness of recombinant parathyroid hormone in postmenopausal and corticosteroid-induced osteoporosis has not been defined.

Recommendations

Postmenopausal women taking oral corticosteroids have the highest risk of bone loss and vertebral fracture so prophylaxis should be considered. In men and premenopausal women, the decision to intervene is less clear and depends on factors such as the baseline bone mineral density and the anticipated duration and dose of corticosteroid therapy (Fig. 1).

Oral bisphosphonates, such as alendronate and risedronate, are the drugs of choice for primary prevention of corticosteroid-related osteoporosis. Patients who are intolerant of oral bisphosphonates may be offered calcitriol, or intravenous pamidronate or zoledronic acid. Although many patients will not qualify for therapy under the Pharmaceutical Benefits Scheme, they should be offered treatment if considered to be at higher risk of fractures.

While calcium alone is ineffective in preventing osteoporosis in patients starting high-dose corticosteroids, all patients should receive calcium and those on bisphosphonates should take vitamin D.

In patients on long-term low-dose prednisolone (< 7.5 mg/day or equivalent), calcium and vitamin D_3 therapy may be sufficient to prevent continuing bone loss and reduce falls. However, patients who continue to lose bone or those at high risk of fracture (previous fragility fracture, bone density < –1.5) should also be offered oral bisphosphonates. Although most clinical trial data are limited to 1–2 years, it is rational to maintain fracture prophylaxis for as long as corticosteroids are taken at a daily dose of more than 5 mg prednisolone or equivalent.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 55)

5. The effectiveness of bisphosphonates in preventing hip fracture in patients taking corticosteroids is unknown.
6. Calcium prevents the rapid loss of bone mineral density in patients starting corticosteroids.

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.

Lenalidomide

Revlimid (Celgene)

5 mg, 10 mg, 15 mg and 25 mg capsules

Approved indication: multiple myeloma

Australian Medicines Handbook section 14.3

Multiple myeloma is a cancer of plasma cells in bone marrow. This disease is characterised by increased levels of paraprotein, an abnormal type of immunoglobulin produced by tumour cells. Multiple myeloma is incurable with conventional treatments and the median survival time after diagnosis is 3–5 years.[1] Modern treatments such as bone marrow transplant, bortezomib (Aust Prescr 2006;29:84-7) and thalidomide (Aust Prescr 2003;26:146-51) have improved the prognosis.

Lenalidomide is an analogue of thalidomide. Its mechanism of action is not clearly understood although it is thought to modulate the immune system. It inhibits proliferation of certain haematopoietic tumour cells, prevents the growth of blood vessels within tumours and induces proliferation of specialised immune cells that attack cancerous cells.

Following oral administration in patients with multiple myeloma, lenalidomide is rapidly absorbed and maximum plasma concentrations are reached within 0.5–4 hours. In healthy volunteers, its elimination half-life increases with dose from about three hours with 5 mg up to nine hours with 400 mg. Most of the drug is excreted unchanged in urine. Lenalidomide should be taken at least one hour before or two hours after food.

In studies of multiple myeloma, patient responses are generally judged by changes in concentrations of paraprotein. In an open-label trial, the efficacy of lenalidomide was investigated in patients with relapsed or relapsed and refractory multiple myeloma. Responses were observed in 1 of 5 patients given 10 mg/day lenalidomide, 2 of 3 patients given 25 mg/day and 12 of 13 patients given 50 mg/day.[2]

In another trial, patients with relapsed or relapsed and refractory multiple myeloma received either 30 mg lenalidomide once daily (67 patients) or 15 mg lenalidomide twice daily (35 patients) for 21 days of a 28-day cycle. Patients with stable or progressive disease after two cycles of treatment had dexamethasone added. Overall, 25% of patients responded to lenalidomide treatment. Four patients had a complete response in the once-daily group, whereas there were no complete responses in the twice-daily group. During the trial, 68 of the 102 patients had dexamethasone added and 20 of these patients responded to the addition. The median progression-free survival time was 7.7 months with the single dose of lenalidomide and 3.9 months with the twice-daily dose.[3]

In two phase III trials totalling 704 patients with relapsed or refractory multiple myeloma, lenalidomide (25 mg once daily for 21 days of a 28-day cycle) or placebo was added to dexamethasone treatment (40 mg). Results were similar in each trial with more patients taking lenalidomide plus dexamethasone responding to treatment compared to those taking dexamethasone alone (approximately 61% vs 22%). Median time to progression was around 11 months with combination therapy compared to just under 5 months with dexamethasone alone.[4,5]

Monitoring of complete blood counts is recommended because neutropenia and thrombocytopenia are very common with lenalidomide (especially when used with dexamethasone) and patients often need their dose to be reduced or interrupted. Growth factors may be needed for patients with neutropenia.

There is also an increased risk of deep vein thrombosis and pulmonary embolism in patients taking lenalidomide with

dexamethasone so patients and doctors should be vigilant for symptoms. Erythropoietic drugs or drugs that increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution. Prophylactic measures may be needed in high-risk patients.

Other adverse events associated with lenalidomide (30 mg once daily) include constipation (25% of patients), anaemia (16%), peripheral neuropathy (10%), fatigue (7%) and diarrhoea.[3] Lenalidomide is renally excreted, so the risk of adverse events is expected to be greater in patients with impaired renal function.

Lenalidomide increases the plasma exposure of digoxin, so it is advisable to monitor digoxin concentrations if these drugs are taken concomitantly. As fatigue, dizziness, somnolence and blurred vision have been reported with lenalidomide, caution is recommended when driving or operating machinery.

Due to its structural similarity with thalidomide, lenalidomide is a potential teratogen and should be avoided during pregnancy. Male patients should use condoms throughout treatment and for one week after cessation. Lenalidomide is only available under a restricted distribution program. Doctors and pharmacists must be registered in the program before they can prescribe or dispense the drug.

Lenalidomide is indicated for the treatment of multiple myeloma in patients who have received at least one prior therapy, and who have progressive disease. Its effectiveness seems to be higher when used in combination with dexamethasone and investigations are under way for its use in combination with other treatments such as doxorubicin and vincristine. Using lenalidomide with dexamethasone for newly diagnosed multiple myeloma is also being studied.[1]

☒ manufacturer declined to supply data

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Nilotinib

Tasigna (Novartis)

200 mg capsules

Approved indication: chronic myeloid leukaemia

Australian Medicines Handbook section 14.2.2

Most patients who develop chronic myeloid leukaemia have an abnormal chromosome called the Philadelphia chromosome (Ph) (Aust Prescr 2006;29:76–9). This is caused by a genetic translocation of chromosomes 9 and 22. The presence of this mutation leads to the production of an abnormal tyrosine kinase which causes cells to become malignant.

The majority of patients with newly diagnosed chronic myeloid leukaemia benefit from treatment with the tyrosine kinase inhibitor imatinib. However, resistance to imatinib can arise, for example from point mutations in the tyrosine kinase which cause interference with imatinib binding.

Nilotinib is a new tyrosine kinase inhibitor which has been rationally designed to have a more selective action than imatinib. It prevents proliferation of malignant cells by binding to the abnormal tyrosine kinase. In *in vitro* studies, nilotinib has been shown to inhibit the growth of 32 out of 33 imatinib-resistant cell lines. However, it is not effective against cell lines carrying the T3151 mutation.

After oral administration, peak concentrations of nilotinib are reached within three hours. Nilotinib should be taken on an empty stomach and food should not be eaten for at least two hours before and one hour after the dose. This is because the bioavailability of nilotinib is increased with food therefore the risk of toxicity is increased. The drug is metabolised mainly by cytochrome P450 3A4 and is excreted in the faeces unchanged and as metabolites.

Cytochrome P450 3A4 inhibitors (such as ketoconazole, erythromycin and grapefruit products) and inducers (such as corticosteriods, rifampicin and St John's wort) may alter serum levels of nilotinib and should be avoided. Nilotinib increases the risk of toxicity from other cytochrome P450 3A4 substrates such as simvastatin. Caution should be used with warfarin. Drugs that prolong the QT interval, such as clarithromycin and haloperidol, should be avoided with nilotinib.

An initial dose-escalation trial of nilotinib showed benefits in patients with chronic myeloid leukaemia who were resistant to imatinib therapy. Nilotinib was found to be less effective in patients with blastic-phase chronic myeloid leukaemia than those in the chronic or accelerated phase of the disease.[1]

Two open-label phase II trials of nilotinib (400 mg twice daily) have been conducted in patients with either chronic-phase[2] or accelerated-phase[3] chronic myeloid leukaemia who had failed to respond or were intolerant to imatinib therapy.

In the chronic-phase disease trial, around half of the patients (134 of 280) had a major cytogenetic response (0–35% Ph-positive cells in the bone marrow) to nilotinib. The median time

for this response was 2.8 months. A complete haematologic response (measured by counting white blood cells, platelets, blasts, myelocytes and metamyelocytes in peripheral blood) was achieved by 74% of evaluable patients.[2]

In the trial of accelerated-phase disease, about a third of patients (35 of 119) had a major cytogenetic response to nilotinib and 26% (31 of 119) had a complete haematologic response after a median of seven months treatment.[3] (In this trial, a third of the 119 patients had not been assessed for a haematologic response at the time of data collection.)

Nilotinib appeared to overcome imatinib resistance in many patients in these trials. However, as predicted from *in vitro* studies, almost all of the patients (7 of 8) carrying the T3151 mutation were resistant to nilotinib treatment.[1,2,3]

During the clinical trials, neutropenia and thrombocytopenia were seen in up to a third of patients. These were usually managed by reducing or interrupting the nilotinib dose with some patients requiring haematopoietic growth factors or platelet transfusions. As myelosuppression is common with nilotinib, complete blood counts should be performed every two weeks for the first two months and then monthly after that.

Rash, pruritus, nausea, constipation, fatigue and headache were commonly reported.[1,2,3] Elevations in bilirubin, aspartate aminotransferase and alanine aminotransferase have been observed at daily doses of 600 mg or more. Increased concentrations of serum lipase and amylase have also been reported and caution is recommended in patients with a history of pancreatitis.

Nilotinib can potentially prolong the QT interval and sudden deaths with this drug have occurred, therefore it should not be used in patients with prolonged QT interval. Electrolyte abnormalities, such as hypokalaemia and hypomagnesaemia, should be corrected before a patient starts nilotinib.

For patients who are resistant to imatinib or cannot tolerate it, nilotinib offers a second-line treatment option along with another recently approved drug, dasatinib (see New drugs, Aust Prescr 2007;30:50–5). However, like dasatinib, nilotinib is not effective for patients carrying the T3151 mutation. It is not known how nilotinib directly compares with dasatinib, but a trial of 23 patients showed that dasatinib may be effective when nilotinib therapy has failed.[4]

T manufacturer provided only the product information

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Paliperidone

Invega (Janssen-Cilag)

3 mg, 6 mg and 9 mg modified-release tablets

Approved indication: schizophrenia

Australian Medicines Handbook section 18.2.2

Risperidone is an antipsychotic drug which is at the end of its patent. Its manufacturer is now marketing one of its metabolites, paliperidone.

When risperidone is metabolised by cytochrome P450 2D6 it produces 9-hydroxy-risperidone (paliperidone) which exists as two enantiomers. The activity of paliperidone is similar to that of risperidone because it binds to dopamine (D_2) and serotonin ($5HT_{2A}$) receptors.

The tablets of paliperidone are designed to slowly release the drug into the gut. They should not be crushed or broken to assist swallowing. Although food increases bioavailability, the once-daily dose does not have to be taken with meals. However, patients are advised not to alternate taking the drug with or without food. It takes 24 hours to reach the peak plasma concentration and the elimination half-life is of a similar duration. Most of the drug is excreted unchanged in the urine. Lower doses are needed if renal function is reduced.

In a six-week trial, 628 patients with acute schizophrenia were randomised to take a placebo, 10 mg olanzapine or one of three doses of paliperidone (6 mg, 9 mg, 12 mg). The atypical antipsychotics had a significantly larger effect than placebo on the patients' scores on the Positive and Negative Syndrome Scale (PANSS). The mean baseline score of 94 was reduced by 4.1 with placebo, 19.9 with olanzapine, and by 17.9, 17.2 and 23.3 with 6 mg, 9 mg and 12 mg paliperidone respectively.[1] Two other six-week studies produced similar results. As it is unclear that higher doses are significantly more effective, the recommended dose of paliperidone is 6 mg taken each morning.

A double-blind, randomised trial looked at paliperidone in the prevention of symptom recurrence. After 207 patients with schizophrenia were stabilised on paliperidone they either continued treatment or were switched to a placebo. The trial was stopped prematurely because a significant difference in efficacy emerged. At the time of the halt the median duration of treatment was 29 days with placebo and 45 days with paliperidone. Schizophrenia symptoms had recurred in 53% of

the placebo group and 25% of the paliperidone group.[2]

The adverse effects of paliperidone are similar to those of risperidone. Extrapyramidal symptoms common to both drugs include tremor, akathisia and dystonia. Other frequent adverse events include headache, somnolence, tachycardia and orthostatic hypotension. The six-week study was too short to show significant changes in metabolism, but a weight increase of 7% or more was seen in 5% of the patients taking paliperidone 6 mg compared with 2% of the placebo group.[1] In the recurrence study 20% of the paliperidone group and 12% of the placebo group added at least 7% of their body weight.[2] This will add to the risk of developing diabetes.[3] An increase in serum prolactin with paliperidone may have the same effect as risperidone, which is associated with an increased risk of tumours in animal studies. As paliperidone can cause a small increase in the QT interval it is not recommended for use with drugs which have a similar effect on the ECG.

While paliperidone is better than placebo in short-term studies, schizophrenia is a long-term illness. Much more is known about risperidone. As paliperidone is a product of the cytochrome P450 system it is not expected to cause interactions with other drugs metabolised by this system. While dose titration is not required at the start of therapy, any advantage of paliperidone over risperidone would be unlikely to justify a higher price. Paliperidone is not approved for patients with dementia-related psychosis.

T T manufacturer provided additional useful information

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Raltegravir

Isentress (Merck Sharp & Dohme)

400 mg tablets

Approved indication: HIV infection

Australian Medicines Handbook section 5.4

The main classes of antiretroviral drugs inhibit viral enzymes such as reverse transcriptase and protease. Combinations of reverse transcriptase inhibitors and protease inhibitors are effective, but this treatment eventually fails. Drugs acting on other parts of the HIV life cycle are therefore needed to regain control of the patient's viraemia.

The replication of HIV requires viral DNA to be inserted into the genome of the host cells. This process involves HIV integrase, so inhibiting this enzyme should impede viral replication. Raltegravir is the first integrase inhibitor to be approved in Australia.

In a dose-ranging study, 35 patients took raltegravir or a placebo for 10 days. The concentration of viral RNA declined significantly more with the drug than with placebo, paving the way for phase II trials.[1]

One trial randomised 179 patients to take a placebo or one of three doses of raltegravir twice daily. These patients had been treated for a median of 10 years, but their viral RNA load was greater than 5000 copies/mL. They took an 'optimised background regimen' of 2–7 antiviral drugs in addition to their randomised therapy. After 24 weeks 13% of the placebo group had less than 50 copies/mL. This response was achieved by significantly more of the patients taking raltegravir; 65% with 200 mg, 56% with 400 mg and 67% with 600 mg. There was also a significant increase in CD4 cell counts. With the recommended dose of 400 mg twice daily, there was a mean increase of 113 cells/microlitre compared with an increase of 5 cells/microlitre with placebo.[2]

The approval of raltegravir is based mainly on the interim results of two phase III trials. These trials had the same design and enrolled previously treated patients infected with HIV resistant to three different classes of antiretroviral drugs. In total, 462 patients added raltegravir to their optimised background regimen and 237 added a placebo. After 16 weeks 436 patients had been treated or discontinued. HIV RNA had fallen below 50 copies/mL in 61–62% of the patients taking raltegravir compared with 33–36% of the placebo group. CD4 cell counts increased by 83–86 cells/mm^3 with raltegravir and by 31–40 cells/mm^3 with placebo. These differences remained at the 24-week analysis.

Adverse events in patients taking multiple drugs are common. Adding raltegravir did not appear to cause more adverse effects than adding a placebo. Only 2% of patients discontinued treatment because of adverse events. Serious adverse events occurring in the trials included hypersensitivity reactions, hepatitis, anaemia, myocardial infarction and renal failure.

The pharmacokinetics of raltegravir are variable and its bioavailability is unknown. Raltegravir is probably cleared by glucuronidation with most of the dose being eliminated in the faeces. The terminal half-life is approximately nine hours. Atazanavir inhibits glucuronidation so it will increase concentrations of raltegravir, however no dose adjustment has been recommended for patients taking raltegravir with a combination of atazanavir and ritonavir. The combination of tipranavir and ritonavir reduces concentrations of raltegravir, but no dose adjustment is recommended.

Although the final results of the phase III trials are currently unpublished, raltegravir has a significant effect on the markers

of HIV infection. Whether this improves the patient's prognosis remains to be seen. Longer-term follow-up is also needed to assess the development of viral resistance and long-term adverse events such as cancer. Although raltegravir has been studied in previously untreated patients[3], this indication is not approved.

X manufacturer did not respond to request for data

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Rotigotine

Neupro (UCB Pharma)

transdermal patches releasing 2 mg, 4 mg, 6 mg or 8 mg per 24 hours

Approved indication: Parkinson's disease

Australian Medicines Handbook section 16.2

Parkinson's disease is characterised by a progressive loss of dopaminergic neurons in the brain, causing patients to develop tremor, rigidity and bradykinesia. Symptomatic treatment using drugs such as levodopa and dopamine agonists (Aust Prescr 2001;24:92–5) aims to restore dopaminergic stimulation of the striatal neurons.

Rotigotine is a new non-ergot dopamine agonist which acts at dopamine receptors D_3, D_2 and D_1. In Australia, it has been approved as a monotherapy or in combination with levodopa for early to advanced Parkinson's disease.

This drug comes in the form of a skin patch which is applied once a day. About 45% of the rotigotine in the patch is released within 24 hours and steady state plasma concentrations are reached by 1–2 days. After being extensively metabolised, rotigotine is mainly excreted in the urine as metabolites. Once the patch is removed, plasma concentrations decrease with a terminal half-life of 5–7 hours.

In an eleven week dose-finding trial of 242 patients with early Parkinson's disease, there was a significant improvement in activities of daily living and motor function of patients who received rotigotine 6 mg/24 hours or 8 mg/24 hours compared to placebo.[1] In a six-month study of 272 similar patients, the proportion of participants who had a 20% improvement was higher with rotigotine (2 mg, 4 mg or 6 mg/24 hours) than with placebo (48% vs 19%).[2]

Rotigotine has been compared with ropinirole in 561 patients with early Parkinson's disease. Ropinirole is also a dopamine agonist, but is not currently approved for Parkinson's disease in Australia. Although rotigotine was better than placebo (with 52% vs 30% of patients responding), it did not appear to be as effective as ropinirole (to which 68% of patients responded).[3]

Rotigotine has also been tested in patients with advanced Parkinson's disease who were already taking levodopa (≥ 200 mg/day) and had poorly controlled symptoms with at least 2.5 hours of 'off' time a day.[4,5] After 24 weeks of maintenance treatment, there were more responders (patients with 30% or more reduction in 'off' time) with rotigotine (8 mg/24 hours or 12 mg/24 hours) than with placebo (56% vs 35%).[4] In another trial, rotigotine (up to 16 mg/24 hours) appeared to be as effective as pramipexole (up to 4.5 mg/day orally) after 16 weeks of maintenance treatment. Responder rates were 60% for rotigotine (120 of 201 patients), 67% for pramipexole (134 of 200 patients) and 35% for placebo (35 of 100 patients).[5]

Rotigotine's safety profile is generally typical of a dopamine agonist. In a trial of early Parkinson's disease, the most commonly reported adverse events with doses of 2–8 mg/24 hours were nausea (47% of patients), application-site reactions (39%), dizziness (24%), somnolence (22%), insomnia (19%), headache (17%), vomiting (16%) and fatigue (15%). Nausea, application-site reactions, somnolence and insomnia appeared to be dose-related.[1] Approximately 13% of 649 patients receiving rotigotine discontinued treatment because of adverse events. The most common reasons were application site reaction (5%), nausea (2%) and vomiting (1%). When tested as an adjuvant to levodopa in patients with advanced Parkinson's disease, rotigotine was associated with an increase in hallucinations and dyskinesia compared to placebo.[4,5]

Patients should be warned about the potential sedating effects of rotigotine, which include somnolence and falling asleep suddenly. Some patients have reported sudden sleep or loss of consciousness while driving. Compulsive behaviours such as pathological gambling and increased sexual urges have occurred in patients taking rotigotine.

Rotigotine can elevate heart rate and blood pressure and cause orthostatic hypotension. Monitoring of blood pressure is advisable, especially at the beginning of treatment. Peripheral oedema has been reported in some patients on rotigotine. Patients should be monitored for skin cancers because of an increased risk of melanoma. Cardiac valvulopathy and retinal degeneration may also be a risk with rotigotine.

Dopamine antagonists such as antipsychotics or metoclopramide could potentially reduce the effectiveness of rotigotine and should be avoided.

Rotigotine should be started at 2 mg/24 hours for early Parkinson's disease and 4 mg/24 hours for advanced disease. The dose should be increased weekly depending on the clinical response and tolerability. Likewise, when stopping treatment the dose of rotigotine should be decreased gradually to avoid precipitating neuroleptic malignant syndrome. After removal, the patch is to be folded over so that it sticks to itself before being disposed of safely, and patients or carers should wash their hands to remove any drug.

Rotigotine offers another treatment option for patients with Parkinson's disease. A once-a-day skin patch may be preferable to taking tablets for some patients.

T manufacturer provided only the product information

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Sitagliptin

Januvia (Merck Sharp & Dohme)

25 mg, 50 mg and 100 mg tablets

Approved indication: type 2 diabetes

Australian Medicines Handbook section 10.1.3

Incretins stimulate the release of insulin after meals. They are rapidly metabolised by dipeptidyl peptidase 4 (DPP4) so inhibiting this enzyme prolongs their effect (see Experimental and clinical pharmacology, Aust Prescr 2008. In press).

Sitagliptin is an inhibitor of DPP4 which can be given once a day. The drug is rapidly absorbed and its action leads to lower blood glucose concentrations. Its half-life is approximately 12 hours and most of the dose is excreted unchanged in the urine. While people with liver disease may be able to take sitagliptin, it is not recommended for patients with renal impairment.

Several doses of sitagliptin were compared to placebo and glipizide in 743 patients with type 2 diabetes. The patients' mean glycated haemoglobin (HbA1c) at the start of the study was 7.9%. After 12 weeks a total daily dose of sitagliptin 100 mg had reduced the HbA1c by 0.54%, while there had been a 0.23% increase with placebo. Glipizide reduced HbA1c by 0.76%.[1]

Another placebo-controlled study gave sitagliptin to 741 patients for 24 weeks. The mean HbA1c was reduced from 8.0% to 7.39% in the patients who took sitagliptin 100 mg. It fell below 7% in 41% of those taking this dose, compared with 17% of the placebo group.[2]

A trial involving patients whose type 2 diabetes was inadequately controlled by metformin randomised 464 to add sitagliptin and 237 to add a placebo. The HbA1c declined in the first 12 weeks of sitagliptin therapy then plateaued. After 24 weeks the mean HbA1c had declined from 7.96% to 7.26% with sitagliptin while it was almost unchanged in the placebo group. The HbA1c fell below 7% in 47% of the sitagliptin group, but in only 18% of the placebo group.[3]

Another study tried starting the treatment of 1091 patients with sitagliptin, metformin or a combination of both. The drugs were given in a variety of doses all of which significantly reduced the mean HbA1c (8.8%) over 24 weeks. The reductions were 0.66% with sitagliptin 100 mg, 0.82% with metformin 500 mg twice daily and 1.13% with metformin 1 g twice daily. In combination therapy, sitagliptin 50 mg twice daily reduced HbA1c by 1.4% with metformin 500 mg twice daily and by 1.9% with metformin 1 g twice daily.[4]

Patients whose diabetes was not controlled by metformin were enrolled in a trial comparing sitagliptin with a sulfonylurea. Glipizide was added to the treatment of 584 patients while 588 added sitagliptin. After a year the average HbA1c declined by 0.56% with glipizide, and 0.51% with sitagliptin. There was a difference in the effect of treatment on the patients' weights. People taking glipizide gained 1.1 kg while those taking sitagliptin lost 1.5 kg.[5]

Sitagliptin has also been added to the treatment of 353 patients taking pioglitazone. At the start of the placebo-controlled trial these patients had mean HbA1c concentrations of approximately 8%. In the 175 randomised to add sitagliptin 100 mg daily for 24 weeks the HbA1c fell by 0.85%. The fall in the placebo group was 0.15%. By the end of the trial 45% of the patients taking sitagliptin and pioglitazone had HbA1c concentrations below 7% compared with 23% of the patients taking pioglitazone and a placebo.[6]

During the trials of sitagliptin the main adverse events were gastrointestinal upsets and musculoskeletal complaints. There were slightly more infections in the patients given sitagliptin. This could be a concern as DPP4 is found in T-lymphocytes. Serious hypersensitivity reactions have also been reported. Hypoglycaemia can occur, but is more likely to happen if sitagliptin is used in combination with a sulfonylurea. Approximately 12% of patients reported hypoglycaemia when sitagliptin was used in combination with glimepiride, with or without metformin.

Sitagliptin has little effect on lipids and its influence on cardiovascular disease in diabetes is unknown. It has an effect

on the surrogate outcome of HbA1c, but its role in therapy is currently unclear. In the comparison with glipizide more patients taking sitagliptin discontinued treatment, mainly because of a lack of efficacy.[5] Although sitagliptin has a greater effect than placebo, it has not been approved for monotherapy in Australia. It is also not approved as an add-on therapy when a patient's diabetes has not been controlled by the standard therapy of metformin and a sulfonylurea.

X manufacturer did not respond to request for data

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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

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