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Editorial

Controlling complementary medicine claims

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Key words: advertising, drug industry, drug regulation.

(Aust Prescr 2008;31:142–3)

Despite the widespread and increasing use of complementary medicines, few of these products have been evaluated for efficacy or therapeutic equivalence. There has also been a proliferation of products of dubious efficacy, with promotional claims that cannot be substantiated. However, complaining about them is not straightforward.[1] Complaint procedures are overloaded and the 'sanctions' available may not deter repeat offenders. There is a need for regulatory reform.

Two industry associations agree that certain measures are required to maintain confidence in the regulatory framework. The Australian Self-Medication Industry (ASMI) believes that evidence-based information about the benefits and risks of complementary medicines should be available, that advertising complaint mechanisms need to be adequately resourced and that appropriate penalties and sanctions are required for breaches of the Therapeutic Goods Advertising Code.[2] The Complementary Healthcare Council also supports initiatives to enhance the timeliness of the current complaint process and implement a broader range of sanctions.[3] However, some people believe that increased regulation will damage the complementary medicine industry.

In this issue…

The current global financial crisis shows that markets cannot be left completely to their own devices. While Australia has been innovative in its regulation of complementary medicines, Ken Harvey argues that there needs to be greater scrutiny of the way these products are advertised. A tightening of the code of conduct for the advertising of prescription drugs has resulted in more companies being found in breach of the code.

The top ten drugs show that we spend a lot of money treating an unhealthy lifestyle. Nancy Huang, Karen Duggan and Jenni Harman remind us that lifestyle management is important in hypertension, and Ken-Soon Tan and David Johnson have similar recommendations for renal disease.

I believe that dubious claims, which cannot be substantiated by scientific evidence, would be better dealt with at the time the sponsor of the complementary medicine makes a marketing application, rather than by submitting complaints about its advertising some time later. Currently, sponsors are able to enter their own indications for their products on the Australian Register of Therapeutic Goods (ARTG). As long as the sponsor certifies that it has evidence to back its claims, the ingredients are on the Therapeutic Goods Administration (TGA) 'relatively low risk' list and the necessary fee has been paid, the automated system will list the product on the ARTG. Recent exposure of the ARTG to greater public scrutiny[4] has shown that dubious promotional claims are being entered on the ARTG at the time of listing. This practice should be reviewed.

In addition, a herbal product can be listed using evidence relating to other products. I believe that the TGA should only allow sponsors to do this once the products have been shown to be therapeutically equivalent. This is comparable to the requirement that generic copies of prescription drugs show bioequivalence.

Herbal products consist of a complex mix of ingredients. Just as all red wine is not Grange Hermitage, different products containing the same herbal extract are not necessarily chemically or therapeutically equivalent.[5] Even glucosamine is available as several salts (glucosamine sulfate, glucosamine hydrochloride, and also as N-acetyl glucosamine) in vastly different formulations and with varied evidence of efficacy.[6] However, data specific to each individual glucosamine-derived product are not required by the TGA. Neither health professionals nor consumers can therefore be confident that Australian formulations of glucosamine (or any other complementary medicine) are efficacious.

Following the recall of products made by Pan Pharmaceuticals in 2003, the Australian government set up an expert committee to examine complementary medicines. This committee recommended that sponsors of listed medicines should submit a summary of the evidence to support the efficacy of their products to the TGA.[7] ASMI agreed that there should be access to the ARTG and the summary of evidence submitted by sponsors. However, it recommended that this information should be limited to industry advertising services managers and

the Complaints Resolution Panel. I believe that this information should be publicly available and open to challenge.

The expert committee also recommended that the TGA should increase the level of random auditing of the evidence for complementary medicines.[7] Particular scrutiny could be given to certain categories, such as 'weight loss' products. However, a review of complementary 'weight loss' products was commissioned by the TGA in mid-2007, but is yet to be made public. The TGA also claims to randomly review the labels, product specifications and evidence for listed indications in about 25% of new listings. However, until such time as the TGA is able to conduct audits in a transparent manner there can be little confidence in their value.

The Australian government has provided $7 million for complementary medicine research. However, Australian clinical trials can only evaluate a handful of the 16 000 listed products currently available in the market. Choice (formerly the Australian Consumers' Association) has proposed a pragmatic solution to this problem – an independent evaluation of complementary medicines on an opt-in, cost-recovery basis. Efficacious products, ethically promoted, with appropriate consumer medicine information could be awarded a mark of approval similar to the National Heart Foundation's 'tick' for healthy food. Choice has set up a multidisciplinary working party to explore the practicality of this proposal.

In conclusion, the current Australian regulatory system neither adequately controls complementary medicine claims nor encourages an evidence-based industry. This is unacceptable given that Australians spend an estimated $1.31 billion on these medicines each year. The challenge for the government is to overcome industry self-interest, and the perception of regulatory 'capture', and to institute the reforms required. This will require continued advocacy by health professional and consumer groups.

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Further reading

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Dr Harvey is a member of the Choice Policy Advisory Group.

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.

Paediatric analgesia

Editor, – The article on paediatric analgesia (Aust Prescr 2008;31:63–5) provides a valuable quick reference on the subject. There is an additional purported mechanism of action for paracetamol, which may have implications in the setting of polypharmacy, especially perioperatively, or associated with chemotherapy.

A serotonergic mechanism of action has been reported for paracetamol.[1,2,3] The inhibition or obliteration of paracetamol-induced analgesia by 5-HT_3 antagonists, commonly used as antiemetics perioperatively, may warrant consideration when prescribing paracetamol concurrently with drugs from this class. Ondansetron, perhaps the most likely drug from the class to be prescribed to a child, may be less likely to inhibit analgesia, particularly in comparison to tropisetron.[4]

Ian Cox
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Concord Hospital, Sydney

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Dr Sean Beggs, author of the article, comments:

The lack of clarity about the mechanism of action for paracetamol is even greater than presented in the article (Aust Prescr 2008;31:63–5). Experimental studies have shown that the analgesic effect of paracetamol can be decreased with the administration of some 5-HT_3 antagonists (tropisetron)[1,4] but not others (ondansetron)[4], while some have been shown to have conflicting effects (granisetron).[3,4] This therefore raises the question of whether it is specifically a 5-HT_3 antagonist effect, or if some drugs in the class are having this effect via another mechanism.[4]

Of importance, however, is the fact that the effects of any of the 5-HT_3 antagonists on paracetamol's action have yet to be shown to be clinically significant. Given this and the fact that ondansetron is the 5-HT_3 antagonist most likely to be used in children, it is difficult to argue that they should not be used in combination. Until clinical trials in children have been undertaken however some doubt remains.

References

As above.

Editor, – Regarding paracetamol dosing for obese children, when using the formula in Dr Beggs' article (Aust Prescr 2008;31:63–5) the predicted lean body weight is 41.8 kg. However, when determining this using the growth charts, the value is 35 kg. Does it matter which method is used?

Would this be the case when calculating dosing of other medicines?

Anderson Leong
Pharmacist
Moorebank, NSW

Dr Sean Beggs, author of the article, comments:

Determining the most appropriate dose of paracetamol and other medications in overweight and obese children is not straightforward. This is because like many issues relating to medications in children there have not been the studies to provide the definitive answer. The formula to calculate lean body weight given in the article is based on adults as there is no validated formula for children. For this reason and for ease of use, the weight-for-height method using growth charts is also outlined. The latter method is slightly more conservative (that is, will give a lower weight) but is not as conservative as if you were to simply use a child's expected average weight for age. For these reasons the weight-for-height method using growth charts is recommended.

Drug information

Editor, – As a retired doctor, I have recently been prescribed various medications about which I wish to obtain more information. I realise that my doctors do not have the time to detail all the side effects, and anticipated finding these in an information sheet within my new packs.

In the case of Patanol eye drops I was not disappointed – just overwhelmed. With Acimax tablets there was no insert, leading me to ask the pharmacist for the drug information sheet. This was dated 2006 and omitted the important facts that it could cause vitamin B_{12} deficiency and that in postmenopausal women taking calcium carbonate, calcium malabsorption might occur. The next disappointment was with Celebrex. No insert in the packet and an inadequate drug information sheet reprinted from MIMS. Next, Mobic to replace the ineffective Celebrex. Again no information included.

As so many patients are admitted to hospital suffering from the ill effects of prescribed drugs, any measure which improves surveillance, even by the patient, should be welcomed. I believe that there is a good case to be made for including an information sheet with **all** prescription drugs listing their common contraindications and side effects accompanied by a caveat saying where further information can be obtained about less common adverse events.

John Martin
Retired general practitioner
Peppermint Grove, WA

Editorial comment:

In addition to talking to their own doctor or pharmacist, consumers can call Medicines Line for independent information on prescription, over-the-counter and complementary medicines. Pharmacists are available on 1300 888 763 between 9 am and 6 pm Eastern Standard Time Monday to Friday. Health professionals can call the Therapeutic Advice and Information Service (TAIS) on 1300 138 677 between 9 am and 7 pm Eastern Standard Time Monday to Friday.

Consumer Medicine Information (CMI) for many medicines is available from the National Prescribing Service at http://www.nps.org.au/search_by_medicine_name

Parenteral drug solutions

Editor, – Many thanks for the excellent article about compatibilities of parenteral drug solutions (Aust Prescr 2008;31:98–101), written from a pharmacy point of view. It certainly contains much practical information for everyday clinical practice, but it might be helpful to add a few extra points from a clinical perspective.

Table 1 shows an incompatibility between lignocaine 2% and sodium bicarbonate solution. In practice, however, the two substances make an excellent marriage; the intense stinging of local anaesthetic injections is markedly reduced by mixing the two. The only problem (in practice) is that left to stand for a few minutes, crystals do form and can block fine needles. The practice is well known and has stood the test of decades.

It is also noted that diazepam precipitates in water. Is this really the case or could the cloudiness be an innocent emulsion? In any case, dilute diazepam (for example 10 mg in 10 mL saline) has been given intravenously for years and works very well. It is standard practice and certainly far easier to titrate than the 10 mg in 1 mL in the ampoule.

The article states that phenytoin must not be diluted as it will precipitate. With its extreme pH of 12, intravenous injection of phenytoin is made easier and less irritating by dilution in saline. Although not described in the product information, it is thankfully normal practice. 'Phenytoin … must be diluted in 0.9% saline (rather than dextrose) to avoid crystallization'.[1]

Andrew Montanari
General practitioner
Merewether, NSW

Reference

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Mr Peter Murney, author of the article, comments:

Lignocaine hydrochloride is an acidic solution (pH = 2.3) which causes pain upon injection. Adding sodium bicarbonate injection to raise the pH and reduce pain is widely practised and supported by a wealth of literature. Nonetheless, the solutions are incompatible and mixing them precipitates lignocaine from its hydrochloride salt. Intradermal injection of suspended lignocaine crystals is of no concern as lignocaine has no local toxicity and will absorb into tissue eventually.

However, intravenous injection of precipitated particulate matter concerns me as I suspect it would many other health practitioners. Diazepam injections are painful, probably because of venous irritation from the propylene glycol/ethanol/water solvent system. Appropriately slow administration of the small volume may also be difficult. There is no component of the mixture which would produce an emulsion and the haze is probably due to precipitated microcrystalline or colloidal diazepam. After 24 hours, the diluted solution clears with deposition of a thin oily film (presumably diazepam) on the syringe barrel. At a total mass of 10 mg, it is unlikely to cause harm upon injection and should rapidly redissolve in plasma. Larger amounts of precipitated drug may result in an embolism of precipitated drug sludge although I could find only one report of an associated fatality.

While some references support addition of phenytoin to normal saline infusion solution for short periods, the diversity of stability studies is disconcerting with some reporting presence of suspended crystals immediately after addition to the bag. Contrary to the current product information, a number of institutional protocols permit addition to a saline infusion bag but generally specify use of an in-line filter to remove crystals.

Slow administration of undiluted injection solutions can be facilitated with spring-loaded devices which, with a flow restrictor fitted to the syringe, allow administration of a specified volume over a specified time.

Restless legs syndrome

Editor, – Restless legs syndrome occasionally occurs in pregnancy, but no mention was made of how this condition should be treated in Professor Thyagarajan's article on the topic (Aust Prescr 2008;31:90–3).

Benzodiazepines and antiepileptic medication have been advocated in the past. Usually the symptoms are not severe and women can cope until pregnancy is over. Are there any studies concerning the effectiveness and safety of low-dose dopamine agonists in pregnancy?

Douglas Johnson
General practitioner
Mornington, Vic.

Professor Thyagarajan, author of the article, comments:

There are very few studies of pharmacotherapy for restless legs syndrome in pregnancy and none of these involve dopaminergic drugs. However, Dr Johnson points out that it is a common problem in pregnancy, usually mild and resolves with the completion of pregnancy. Iron status should first be determined by measurement of the serum ferritin.

The teratogenicity of dopamine agonists is unknown and they cannot be recommended at present; nor is it likely that future trials will address this safety and efficacy question. If pharmacotherapy is needed, opioids, anticonvulsants such as gabapentin or carbamazepine, or benzodiazepines, all have a better safety track record during pregnancy and should be tried first.

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Hypnotic hazards: adverse effects of zolpidem and other z-drugs

LG Olson, Sleep Disorders Physician, France

Summary

Zolpidem, zopiclone and zaleplon are hypnotics with similar pharmacology to benzodiazepines. In addition to the usual adverse effects of sedative drugs, there have been unusual reactions associated with the 'z-drugs', particularly zolpidem. It is unclear why there have been so many reports of bizarre behaviour in Australians taking zolpidem. Some of the cases may be the result of other conditions or drugs. As many patients with insomnia can be managed without drugs, limiting the use of hypnotics will limit any harmful effects.

Key words: benzodiazepines, insomnia, zopiclone.

(Aust Prescr 2008;31:146–9)

Introduction

The 'z-drugs', zolpidem, zopiclone and zaleplon, are sedatives, marketed as hypnotics. Zopiclone was marketed in Australia in 1994 with zolpidem following in 2000. Zaleplon is not currently available in Australia. The z-drugs have been promoted as being safer than benzodiazepines, and in many countries they are the most widely prescribed drugs for insomnia. As the drugs have never been listed on the Australian Pharmaceutical Benefits Scheme, there are no readily available data on how widely they have been used here.

Pharmacology

The z-drugs are sedatives which act at GABA receptors in the brain. They are not chemically related to benzodiazepines but their pharmacology is similar. (They bind to a receptor subtype known as the benzodiazepine-1 subtype.) At standard doses, in sleep laboratory tests, they do not impair memory and cognition as much as benzodiazepines. Their half-lives are relatively short (1 hour for zaleplon, 2–3 hours or so for zolpidem and about 5 hours for zopiclone). At standard doses, they are less likely to cause marked residual daytime sedation than benzodiazepines.

Unusual adverse effects

In the 1990s there were sporadic published case reports of visual hallucinations, and later of amnesia and compulsive behaviour associated with zolpidem. After the first year of marketing in Australia, the Adverse Drug Reactions Advisory Committee (ADRAC) noted a significant number of reports of visual hallucinations and a smaller number of reports of amnesia with zolpidem. By 2007 ADRAC had received 104 reports of hallucinations, 62 of amnesia, and 16 of unusual or inappropriate behaviour of which the patient had no memory.[1] Television and newspaper reports, on the other hand, state that there have been 'more than 400' adverse event reports and 'up to 14 deaths' related to zolpidem.[2] Despite the numerical dominance of hallucinations in ADRAC reports, it has been inappropriate behaviour with amnesia which has created most media interest and which has dominated direct reports from consumers.[3] Similar events related to zaleplon and zopiclone have rarely been reported, but media stories have often referred to problems with z-drugs as a group. There have been reports in other countries, but the rate of adverse events relating to zolpidem appears to be much higher in Australia.[4]

Although the media have been impressed with the outlandish adverse events reported with zolpidem, these events are not unprecedented. Amnesia, hallucinations and bizarre behaviour were also seen frequently in patients taking the short-acting benzodiazepine, triazolam, for insomnia.[5]

Nocturnal activity with amnesia

Complex behaviour with amnesia is a common and non-specific effect of sedative drugs. Alcohol is the prototype drug causing disinhibition, inappropriate behaviour and amnesia, but all sedative drugs can have similar effects. Z-drugs do cause sedation and amnesia, especially in higher doses.[6,7] This effect is little different from that of the benzodiazepines – although advertisements for the z-drugs may not have conveyed this clearly. The frequency of reports of amnesia with zolpidem, with or without abnormal behaviour, may be related to a mistaken belief that it would not cause sedation and amnesia at all. Taking zolpidem with alcohol or other psychoactive drugs is common, and exaggerates the sedative and amnesic effects. Many overseas reports of bizarre behaviour with zolpidem have involved patients taking multiple psychoactive drugs as well as alcohol, but it is not clear how often this has been the case in Australia.

Sleepwalking

Many of the 'unusual behaviour with amnesia' events reported with zolpidem have been called sleepwalking, but electroencephalographic confirmation of this diagnosis is lacking, and it may not be correct. Sleepwalking occurs when

the cortex is asleep, but areas of the brain concerned with motor control are active. Z-drugs do not prevent sleepwalking in the way benzodiazepines do, but their pharmacology as it is currently understood does not suggest that they would worsen sleepwalking or cause it to start. No drug has ever been shown in laboratory studies to cause sleepwalking or even to precipitate events in known sleepwalkers. However, the reported ability of zolpidem (but not zopiclone or zaleplon) to activate the cortex in patients with anoxic brain injury does raise the possibility that it has unusual effects on the cortex.[8] These effects could, conceivably, precipitate sleepwalking in patients predisposed to it. Since about 10% of children and 2% of adults sleepwalk there is a large pool of patients predisposed to sleepwalking, so a small effect of the drug could possibly account for what has been reported.

The spectrum of behaviour in sleepwalking is wide, from muttering and talking to getting up and walking about, but it is confined to what can be done with no cortical input: purposive or adaptive behaviour is not likely to be sleepwalking. In contrast, many reports of abnormal behaviour with zolpidem are of complex and apparently adaptive behaviour inconsistent with sleepwalking. There is a wide differential diagnosis for unusual nocturnal activity with amnesia. As well as sleepwalking, common causes are epilepsy, REM (rapid eye movement) behaviour disorder, micro-sleeps, confusional arousals and dissociative states associated with mental illness.

Normal sleep causes antegrade amnesia for the 5–10 minutes before sleep onset, and micro-sleeps (intrusions of sleep, lasting seconds, into wakefulness) also do this. Severely fatigued individuals can have frequent micro-sleeps, and thus quite long periods of amnesia, although the person is awake between the micro-sleeps and can carry out complex actions. This is relatively common in severe obstructive sleep apnoea, in parents of babies who sleep poorly, and in shift workers.

Confusional arousals are arousals from sleep with disorientation, amnesia and sometimes automatism, which can involve inappropriate or aggressive behaviour. Mild events are common in fatigued individuals, such as long distance travellers (waking up in hotel rooms with no idea where they are) and shift workers. Sedatives of all kinds can also cause these events, and the combination of fatigue and sedative drugs makes them more frequent and worse.

Bizarre and compulsive behaviour

Many reports of behaviour with amnesia related to zolpidem have emphasised its bizarre or inappropriate character. Sleep-eating, sleep-sex and sleep-driving have been reported. However, in no case is there electroencephalographic evidence that the patient was asleep at the time, that is, evidence to distinguish sleepwalking from, for example, confusional arousal. Often, it is said that the behaviour was compulsive or irresistible, but it is unclear what is meant by this when amnesia is reported as well.[9] For example, the ADRAC Bulletin has spoken of patients with 'uncontrollable urges to eat while asleep'[1], but if the patients were asleep, how did they know they had uncontrollable urges?

While these forms of behaviour seem outlandish, there are case series of sleep-eating and sleep-sex in patients who have not taken z-drugs which are larger than those in patients who have. Nocturnal eating is common, and although it can occur during sleepwalking, when there are feelings of compulsion the eating occurs during wakefulness.[10,11]

Reports, or claims, of having sex while asleep are also common.[12] The difficulty is to distinguish sex during sleep from (what is far more likely) sex with amnesia for the event caused by subsequent sleep (assisted, perhaps, by alcohol or another drug). The great majority of carefully studied cases of sex with amnesia have been found to represent sex after partial or confusional arousal rather than sex during sleep.[13,14]

Sleep-driving is a more difficult problem because it cannot be studied in the sleep laboratory in the way that sleep-sex and sleep-eating can. Carefully studied cases of sleep-driving are rare, and are actually cases of patients who have histories of driving with amnesia and well-documented sleepwalking.[15] Wakeful driving with amnesia caused by drugs is a far more likely cause of reports of sleep-driving, and is certainly the cause of the great majority of cases of sleep-driving reported with zolpidem in the USA.

Zolpidem has been linked to suicide, although in one widely publicised Australian case zolpidem had been withdrawn and replaced by zopiclone a week before death.[2] Database evidence shows clearly that z-drugs are not associated with a higher risk of suicide from poisoning[16,17], and although an effect on other means of suicide is not excluded it must be unlikely.

Hallucinations and psychosis

The most frequent unusual adverse effect of zolpidem reported in Australia has been visual hallucinations. In published reports the hallucinations usually last 30 minutes or so, although there are reports of hallucinations lasting several hours in patients taking both zolpidem and serotonin reuptake inhibitors.[18] In most reported cases the hallucinations have been an isolated phenomenon, but there are reports of psychotic reactions to zolpidem.[19]

Comparative incidence of adverse effects

Whether abnormal behaviour with amnesia and hallucinations are commoner with z-drugs than with other sedatives cannot be determined from the available data. Systematic reviews of controlled trials of z-drugs have not revealed the adverse effects reported by patients in Australia. However, adverse events occurring in less than 1% of patients would not be expected to be revealed in trials.[20] Systematic reviews do show that in

older people adverse cognitive and psychomotor effects are common with all sedatives, but they are not obviously more common with z-drugs.[21] Motor vehicle accidents are increased by use of z-drugs (relative risk 2.3), but somewhat less than by use of benzodiazepines (relative risk for nitrazepam 2.7 and for flunitrazepam 4.0).[22]

Postmarketing surveillance outside Australia has not revealed a high prevalence of behavioural adverse events with z-drugs. For example, a survey of 14 029 patients treated with zolpidem for four weeks found 20 patients who reported nightmares, 19 who reported agitation, and one who developed paranoid ideation during treatment.[23] A French regional study of prescriptions for hypnotics, anxiolytics and antidepressants given to adolescents found that of 3286 prescriptions issued in one year, 2724 were for zolpidem, but there were only three reports of adverse drug reactions.[24]

Available data also do not answer the question of whether the frequency or severity of adverse effects of z-drugs may relate to particular patient characteristics. Psychiatric illnesses, particularly anxiety and depression, are common in patients with insomnia, but it is not clear that this plays a role in the adverse event reports.

Recommendations

Z-drugs are effective for insomnia – in a manner of speaking. 'In a manner of speaking' because the effect on the deficits complained of by patients with insomnia is small. Across all hypnotic drugs there is a mean increase in total sleep time of 25 minutes.[21] Only for zopiclone is there evidence from randomised controlled trials of sustained improvements in self-reported work performance and quality of life. These effects were small and there is, obviously, a problem with blinding in placebo-controlled trials of a drug with zopiclone's action.[25]

Z-drugs are no better for insomnia than benzodiazepines. They cause sedation and increase the risk of motor vehicle accidents, and are not a safe alternative to benzodiazepines in patients who need to drive. Z-drugs do cause dependency[20], and are not a safe alternative for patients who have had problems with dependence on benzodiazepines.

It is possible to manage insomnia without ever using hypnotic drugs and this approach should be the rule rather than the exception. Insomnia is commonly caused by delayed sleep phase syndrome*, constitutional short sleep need†, or the effects of caffeine or alcohol, and sedative drugs should not be used for these patients. Some patients with depression and others with significant psychiatric illness may need drug treatment specifically for poor sleep, but most patients seen in general practice do not.

At present, there is no good evidence that z-drugs should be prescribed with unique precautions. On the other hand, it is seldom a good idea to prescribe any sedative drug for insomnia in patients over 60 years of age, for patients who may need or choose to drive or make important decisions within eight hours of taking a dose, or who live alone. These cautions apply with special force to patients taking another psychoactive drug.

If patients are prescribed z-drugs they should be made aware that sedation, confusion and disinhibition may occur. They should be advised to avoid alcohol. The hypnotic should be taken once the patient is in bed, not on the way to bed. Simple changes to the home environment, such as securing the bedroom door and windows, can reduce the risk of harm from sedation, disinhibition and confusion. It may be prudent to advise patients to make these changes, especially if they have a psychiatric illness that may predispose them to suicide or are taking multiple psychoactive drugs.

Conclusion

Evidence that z-drugs, especially zolpidem, commonly cause adverse effects not predictable from their pharmacology is weak. Zolpidem may cause hallucinations relatively frequently (as triazolam did), but reports of 'abnormal behaviour with amnesia' probably reflect predictable effects. Z-drugs have few advantages over benzodiazepines, and there is no good reason for their use in insomnia. If there were fewer prescriptions there would be fewer adverse events.

* 'Delayed sleep phase' refers to otherwise normal individuals whose natural sleep pattern is to go to sleep late – midnight or later – and wake up late – 9 am or later. If for social or occupational reasons getting up this late is unacceptable, the person typically attempts to go to sleep earlier in order to get up earlier, but when they are unable to go to sleep before their natural sleep time they may complain of insomnia.

† 'Constitutional short sleep need' refers to otherwise normal individuals who habitually sleep only a few hours a night (often four or five) but do not feel the need of more. This may cause a complaint of insomnia, typically when the person retires and no longer values their ability to study until midnight and then be up at 5 am to exercise before going to work.

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Further reading

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Dr Olson has no pecuniary or other interest relevant to the subject of this paper. He has received no research grants, honoraria, speaker's fees or other considerations from companies manufacturing z-drugs or from companies competing with them.

Self-test questions

The following statements are either true or false
(answers on page 167)

1. Sedative drugs are likely to cause sleepwalking in people who have not previously sleepwalked.
2. Amnesia may be caused by micro-sleeps.

Lifestyle management of hypertension

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Summary

Recently updated Australian guidelines recommend that advice on smoking, nutrition, alcohol use, physical activity and body weight should be part of routine management of hypertension for all patients, regardless of drug therapy. Smoking cessation is recommended to reduce overall cardiovascular risk. Healthy eating, reducing dietary sodium and alcohol intake, regular physical activity and achieving a healthy body weight are all effective in lowering blood pressure.

Key words: alcohol, cardiovascular disease, diet, physical activity, smoking cessation.

(Aust Prescr 2008;31:150–3)

Introduction

Hypertension is a major risk factor for stroke and coronary heart disease, and is a major contributor to the onset and progression of chronic heart failure and chronic kidney failure. Guidelines by the National Heart Foundation of Australia[1] recommend that doctors caring for patients with hypertension should routinely provide advice on smoking, nutrition, alcohol use, physical activity and body weight.

Lifestyle modification is indicated for all patients with hypertension, regardless of drug therapy, because it may reduce or even abolish the need for antihypertensive drugs. In addition to the immediate goal of lowering blood pressure, the recommended lifestyle changes confer a range of health benefits, including better outcomes of common chronic diseases. Effective approaches to promoting lifestyle changes in primary care are listed in Box 1.

Smoking

Smoking is a strong independent risk factor for cardiovascular disease. Quitting is acknowledged to be one of the most effective lifestyle interventions for preventing cardiovascular disease and premature deaths.

Smoking causes an immediate increase in blood pressure and heart rate that persists for more than 15 minutes after one cigarette. People who smoke show higher ambulatory blood pressure levels than non-smokers.[2]

Elevated blood pressure and smoking are the two most important risk factors for subarachnoid haemorrhage in the Asia-Pacific region. The risk of myocardial infarction is 2–6 times higher and the risk of stroke is three times higher in people who smoke, compared with non-smokers.[1]

Smoking cessation markedly reduces overall cardiovascular risk, including the risk of coronary heart disease and stroke, compared with continued smoking. In patients with coronary heart disease, smoking cessation is associated with a 36% reduction in the risk of all-cause mortality.[3] Although smoking is known to increase the risk of developing hypertension, there is currently no evidence that smoking cessation directly reduces blood pressure in people with hypertension.[2]

Nutrition

Determining the influence of various nutrients on blood pressure and cardiovascular risk is a complex and evolving research area. While some relationships between food and cardiovascular health have not yet been clearly quantified, there is sufficient evidence to recommend that people with hypertension should avoid salty foods and aim for a healthy eating pattern.

Restricting salt intake

High dietary sodium intake is associated with an increased incidence of stroke, and with increased risk of death due to coronary heart disease or cardiovascular disease.[4] Reducing dietary sodium by approximately 1700 mg (75 mmol) per day can lower systolic blood pressure by 4–5 mmHg in hypertensive individuals and 2 mmHg in normotensive individuals.[4,5] This may reduce the need for antihypertensive drugs. Responses vary between individuals and are generally greatest among the elderly and those with severe hypertension.

There is weak evidence suggesting that weight loss combined with reduced dietary sodium may be more effective at lowering blood pressure than salt avoidance alone.[4] Reduced-salt diets in combination with thiazide diuretics may predispose elderly patients to hyponatraemia, so electrolytes should be monitored regularly.

Dietary potassium

Some clinical trials suggest that increasing dietary potassium by approximately 2100 mg (54 mmol) per day can reduce systolic

Box 1

Lifestyle recommendations for lowering blood pressure

Smoking

Give all patients clear, unambiguous advice to stop smoking. Assess for nicotine dependence (e.g. time of last cigarette, withdrawal symptoms) and offer counselling, support services and pharmacotherapy as appropriate.

Nutrition

Advise patients to limit salt intake to 4 g/day (65 mmol/day sodium) or less by choosing foods normally processed without salt, foods labelled 'no added salt' or 'low salt' (or 'reduced salt' products when other options are unavailable). High-salt processed foods (ham, bacon, sausages, canned or packet soups, stock cubes), salty snacks, takeaway foods high in salt, or salt added during cooking or at the table should be avoided.

Advise patients to eat a diet that includes mainly plant-based foods (e.g. fruits, vegetables, pulses and a wide selection of wholegrain foods, moderate amounts of low-fat or reduced-fat dairy products), moderate amounts of lean unprocessed meats, poultry and fish, moderate amounts of polyunsaturated and monounsaturated fats (e.g. olive oil, canola oil, reduced-salt margarines).

Patients with hypertension who are not taking potassium-sparing diuretics and have normal renal function can be advised to increase potassium intake by eating a wide variety of fruits and vegetables, plain unsalted nuts (limit quantity and frequency to avoid excess kilojoules), and legumes (e.g. beans, lentils, dried peas).

Alcohol

Advise patients to limit alcohol intake to a maximum of two standard drinks per day (men) or one standard drink per day (women) and have at least two alcohol-free days per week.

Physical activity

Advise patients to become physically active. Aim for 30 minutes of moderate intensity* physical activity on most, if not all, days of the week.[1] The daily dose can be accumulated in shorter bouts (e.g. three 10-minute walks). Advise against isometric exercise routines that may raise blood pressure (e.g. weightlifting), except within professionally supervised programs.

Body weight

Advise patients with hypertension how to achieve and maintain a healthy body weight target†: waist circumference less than 94 cm (men) or less than 80 cm (women) and body mass index (BMI) less than 25 kg/m^2.

* 'Moderate' means any activity sufficiently intense to cause a slight increase in breathing and heart rate, and may cause light sweating (e.g. brisk walking, lawn mowing, low-paced swimming, cycling, gentle aerobics).

† Targets are based on data from European populations and may not be appropriate for all ages and ethnocultural groups. Compared with Europeans, the BMI cut-point associated with increased risk of type 2 diabetes and cardiovascular disease is typically higher for Polynesian populations and lower for Aboriginal and Torres Strait Islander populations and some Asian populations.

blood pressure by 4–8 mmHg in hypertensive individuals and 2 mmHg in normotensive individuals. Potassium-rich whole foods, such as bananas, kiwi fruit, avocado, potatoes (with skin), nuts and yoghurt, are more effective in reducing blood pressure than potassium supplements, which are potentially toxic.[4]

High potassium intake can produce hyperkalaemia in people with impaired renal function. It should be recommended only for those with known normal renal function.

Healthy eating

Blood pressure reductions in people with and without hypertension can be achieved by a healthy eating pattern based on the Dietary Approach to Stop Hypertension (DASH) diet, in addition to reduced salt intake.[4] The DASH diet emphasises fruits, vegetables, whole grains, low-fat dairy products and dietary fibre, while being low in dietary sodium, cholesterol and saturated fat.[6]

High-dose (at least 3 g/day) omega-3 polyunsaturated fatty acid supplement (fish oil) may also lower blood pressure in hypertensive individuals.[2] Evidence is insufficient to recommend calcium and magnesium supplements or increasing dietary fibre intake alone (for example, taking supplemental fibre rather than increasing fruit and vegetable intake) to reduce blood pressure.

Alcohol

Evidence for cardiovascular benefits of light drinking has been challenged by a recent meta-analysis.[2] Regardless of this debate, evidence is emerging that all levels of alcohol intake increase blood pressure. Moderate drinking can increase blood pressure, while binge drinking appears to increase the risk of hypertension.[1] Epidemiological data show a linear relationship between alcohol consumption and hypertension prevalence.[2] Reducing alcohol consumption can lower systolic blood pressure by an average of 3.8 mmHg in patients with hypertension.[7] The Heart Foundation recommends that patients with hypertension limit their alcohol intake to a maximum of two standard drinks per day for men, and one standard drink per day for women.[1]

Physical activity

It is clear that physical activity lowers resting and daytime ambulatory blood pressure.[1] In clinical trials of people with hypertension, regular aerobic activity reduced systolic blood pressure by an average of 6.9 mmHg and diastolic blood pressure by 4.9 mmHg.[8]

Regular physical activity has an independent cardioprotective effect.[1] Regular exercise is associated with an increase in high-density lipoprotein cholesterol and with reductions in body weight, waist circumference, percentage body fat, insulin resistance, systemic vascular resistance, plasma noradrenaline and plasma renin activity.[8]

Body weight

There is a direct association between blood pressure and body weight and/or abdominal adiposity. Weight loss studies show that clinically significant blood pressure reductions can be achieved by modest weight loss in people with and without hypertension and that blood pressure reduction is proportional to weight loss.[2] Every 1% reduction in body weight lowers systolic blood pressure by an average of 1 mmHg.[1] Losing 4.5 kg reduces blood pressure or prevents hypertension in a large proportion of overweight people, while losing 10 kg can reduce systolic blood pressure by 6–10 mmHg.[1] In overweight patients with hypertension, weight-reducing diets can achieve a 3–9% decrease in body weight and may reduce systolic and diastolic blood pressure by approximately 3 mmHg.

Weight reduction confers a range of other cardiovascular health benefits including reduced insulin resistance and hyperlipidaemia, and reduced risk of left ventricular hypertrophy and obstructive sleep apnoea.[2]

Integrating lifestyle advice into clinical management

Practical resources are now widely available to help Australian health professionals effectively promote positive lifestyle changes (see Box 2). These encourage and support health professionals to take a systematic approach, by providing a simple framework for broaching the subject with patients, negotiating goals, giving tailored advice including written information, and referring patients to more information and other medical and support services.

The '5As' approach – Ask, Assess, Advise, Assist and Arrange – is often advocated as a useful framework for primary care health professionals to provide brief interventions for lifestyle modification in the clinical setting.

Conclusion

Current Australian guidelines for the management of hypertension recommend lifestyle modification as an important and effective first-line treatment strategy. In addition to the significant lowering of blood pressure achieved through changes to eating patterns, moderating alcohol intake, weight loss and regular physical activity, lifestyle measures (including smoking cessation) confer other significant cardiovascular health benefits. Regardless of other treatments indicated, all patients who need to lower their blood pressure should be given advice and support to achieve and maintain healthy behaviours.

Box 2

Resources for promoting lifestyle management to patients

- Heart Foundation's Heart Health Information Service – for professional and consumer resources phone 1300 36 27 87.
- Lifescripts (including resources developed for Aboriginal and Torres Strait Islander people and pregnant women) http://www.agpn.com.au
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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 167)

3. There is evidence that smoking cessation reduces blood pressure in people with established hypertension.
4. A low potassium diet may help to reduce blood pressure in patients with hypertension.

Dental notes

Prepared by Dr M McCullough, Chair, Therapeutics Committee, Australian Dental Association

New guidelines for infective endocarditis prophylaxis

Therapeutic Guidelines has revised the guidelines for the use of antibiotics for prophylaxis against infective endocarditis (see www.tg.org.au/Prevention_of_endocarditis_update). The major change is that antibiotic prophylaxis is no longer indicated in patients with aortic stenosis, mitral stenosis, or symptomatic or asymptomatic mitral valve prolapse.

The justifications and reasoning behind these changes have been reviewed in the Australian Dental Journal.[1] These new guidelines take into consideration the guidelines of the American College of Cardiology/American Heart Association, as well as the British Society for Antimicrobial Chemotherapy and the UK National Institute for Health and Clinical Excellence. The most recent UK guidelines do not recommend antibiotic prophylaxis for any cardiac risk group. Prophylaxis is also not indicated in adolescents and young adults with heart valve disease, apart from indigenous Australians.

The Australian infective endocarditis prophylaxis guidelines differ from the American and UK guidelines in two specific ways:

- The consensus was that, as there is a high incidence of rheumatic heart disease among indigenous Australians and the outcomes of this disease in this population are considered to be significant, indigenous Australians with rheumatic heart disease require prophylaxis.
- Very clear guidelines are given for dental procedures that always require antibiotic prophylaxis for patients with specific cardiac conditions. Further, these guidelines clearly outline dental procedures for which, irrespective of the patient in question, prophylaxis is never required. Finally, dental procedures are outlined where antibiotic prophylaxis should be considered if multiple procedures are being undertaken or the procedure is expected to be prolonged.

Doctors and dentists need to be prepared to discuss the updated guidelines as these changes are bound to concern patients who previously received prophylaxis. The changes may be more of a slow evolution as both patients and clinicians come to appreciate the lack of evidence for a benefit of antibiotic prophylaxis.

Reference

1. A change of heart: the new infective endocarditis prophylaxis guidelines. Daly CG, Currie BJ, Jeyasingham MS, Moulds RF, Smith JA, Strathmore NF, et al. Aust Dent J 2008;53:196-200.

See also National Prescribing Service (NPS) patient information leaflet 'Preventing infections of the heart' at www.nps.org.au/health_professionals/patient_resources/patient_leaflets

Managing the cardiovascular complications of chronic kidney disease

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Summary

Patients with chronic kidney disease have risk factors for cardiovascular disease which are additional to those found in the general population. Many patients will die of cardiovascular disease before they require dialysis for their kidney disease. While lifestyle modification is essential, it is important to manage the patient's anaemia, dyslipidaemia and hypertension. Managing heart failure can be difficult because of the need to adjust the patient's fluid balance according to renal and cardiac function. If the progression of chronic kidney disease can be slowed, cardiac risk may be reduced.

Key words: anaemia, heart failure, hyperlipidaemia, hypertension.

(Aust Prescr 2008;31:154–8)

Introduction

Chronic kidney disease, defined by a glomerular filtration rate (GFR) under 60 mL/min/1.73 m^2 or evidence of kidney damage (for example, proteinuria) for at least three months, is a major public health problem. At least one in seven Australian adults has at least one marker of kidney damage or dysfunction.[1]

Chronic kidney disease is one of the most potent risk factors for cardiovascular disease. Patients with advanced chronic kidney disease have up to a 10- to 20-fold greater risk of cardiac death than age- and sex-matched controls.[2] These patients are up to 20 times more likely to die from cardiovascular disease than to survive to require dialysis.[3] However, patients with chronic kidney disease who also have cardiovascular disease are more likely to progress to renal failure than those without cardiovascular disease.[4]

The 'traditional' risk factors, listed in Table 1, are independent predictors of cardiovascular disease in chronic kidney disease, but do not account for the total increased risk. There are also many 'non-traditional' cardiovascular risk factors which play a potentially important role in chronic kidney disease. There is randomised controlled trial evidence that timely intervention can substantially reduce the progression of renal failure, and can reduce cardiovascular risk by up to 50%.[5]

Table 1

'Traditional' and 'non-traditional' cardiovascular risk factors in chronic kidney disease [2]

Traditional risk factors	Non-traditional risk factors
Older age	Albuminuria
Male	Elevated homocysteine
Hypertension	Elevated lipoprotein (a)
Dyslipidaemia (high LDL and low HDL cholesterol)	Anaemia
Diabetes	Abnormal calcium and phosphate metabolism
Smoking	Extracellular fluid volume overload
Physical inactivity	Oxidative stress
Family history of (premature onset) cardiovascular disease	Inflammation (C-reactive protein)
Left ventricular hypertrophy	Malnutrition
	Thrombogenic factors

LDL low density lipoprotein
HDL high density lipoprotein

Modifying cardiovascular risk in patients with chronic kidney disease

As chronic kidney disease accelerates cardiovascular disease, management of the risk factors should begin as soon as possible.

Lifestyle modification

Lifestyle modification underpins all other therapeutic approaches and must continue to be practised throughout the treatment of chronic kidney disease.[6] Particular attention should be paid to smoking, nutrition, alcohol and physical activity (Table 2).[7] Successful modification of the patient's lifestyle can reduce blood pressure.

All guidelines recommend a reduction of dietary sodium for patients with hypertension and chronic kidney disease. A meta-analysis of 20 randomised trials involving patients with hypertension found that halving salt intake (from approximately 10 g per day to 5 g per day) for four or more weeks had a modest but important effect on lowering blood pressure (–5.06 mmHg (95% CI* –5.81 to –4.31) for systolic and –2.70 mmHg (95% CI –3.16 to –2.24) for diastolic blood pressure).[8] In addition to direct

* CI confidence interval

Table 2

Treatment targets for patients with chronic kidney disease [15]

Parameter	Target
Smoking	Cease smoking
Weight	BMI 18–25 kg/m^2 Waist circumference ≤94 cm (male), ≤80 cm (female)
Nutrition	Dietary salt intake 40–100 mmol/day
Alcohol	<2 standard glasses alcohol/day (men) <1 standard glass alcohol/day (women)
Physical activity	>30 mins physical activity/day
Blood pressure	<130/80 mmHg <125/75 mmHg if proteinuria >1 g/day
Proteinuria	>50% reduction of baseline value
Cholesterol	Total <4.0 mmol/L LDL <2.5 mmol/L
Blood glucose (for people with diabetes)	Pre-prandial blood glucose 4.4–6.7 mmol/L HbA1c <7.0%

BMI body mass index
LDL low density lipoprotein

effects on blood pressure, lowering the extracellular volume by limiting sodium intake significantly enhances the response to most antihypertensive drugs, especially angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists.

The consensus on dietary protein intake in Australia for people with chronic kidney disease is to advise a normal intake (0.75–1.0 g/kg body weight/day).[5] Reduced protein intake is of inconsistent benefit and may accentuate the chance of malnutrition.

Hypertension

In patients with chronic kidney disease, hypertension is the most powerful risk factor for the progression of kidney dysfunction and the development of cardiovascular disease. The most important goal for reducing cardiovascular risk in patients with chronic kidney disease is to lower blood pressure to a target (<130/80 mmHg if proteinuria less than 1 g/day or <125/75 mmHg if proteinuria more than 1 g/day).[5,6] In order to reach these targets, multiple (often 3–4) antihypertensive drugs are often needed, particularly in more advanced chronic kidney disease.[5]

The activity of the renin-angiotensin-aldosterone system is increased so ACE inhibitors are the first-line therapy for patients with chronic kidney disease, although angiotensin receptor antagonists may provide comparable renoprotection (preservation of renal function) and therefore cardioprotection. The degree of renoprotection appears to be greater in patients with more severe kidney failure and in those who experience a greater initial increase in serum creatinine concentration when treatment begins.[5] It is therefore important not to withdraw ACE inhibitors or angiotensin receptor antagonists in patients with chronic kidney disease who experience an acute rise in plasma creatinine concentration of less than 30% which stabilises within the first two months of treatment. These individuals are the ones who are most likely to derive the greatest renoprotective benefit.[5,6] However, if the rise in creatinine is more than 30% above the baseline value, stop the drugs and consider investigating the possibility of bilateral renal artery stenosis.[6]

ACE inhibitors and angiotensin receptor antagonists should also be withdrawn if the serum potassium concentration exceeds 6 mmol/L, despite dose reduction, dietary potassium restriction and concomitant diuretic therapy. However, the frequency of this complication in patients with chronic kidney disease is less than 2%, with the average rise in serum potassium being of the order of 0.5 mmol/L.

Other antihypertensive drugs have a role, as optimal blood pressure control often requires combination therapy. Diuretics, beta blockers and calcium channel blockers are commonly used. When a diuretic is given to treat hypertension or oedema in a patient with chronic kidney disease, a loop diuretic is generally preferred, because thiazide diuretics become less effective as monotherapy when the GFR falls below 50 mL/min/1.73 m^2.[6] However, thiazides still produce additive effects when co-administered with a loop diuretic.

Dyslipidaemia

Chronic kidney disease is associated with hyperlipidaemia. A meta-analysis of 50 randomised trials involving over 30 000 patients found that statin use significantly reduced fatal cardiovascular events by 19% and non-fatal cardiovascular events by 22%, irrespective of the stage of chronic kidney disease.[9] Although there have been concerns about an increased incidence of rhabdomyolysis with statins in chronic kidney disease, their adverse effect profile in this large group of patients was similar to that of placebo. Current guidelines therefore recommend that statins be used to reduce cardiovascular risk in patients with chronic kidney disease. Aim for a serum total cholesterol below 4 mmol/L and a low density lipoprotein cholesterol below 2.5 mmol/L.

Glycaemic control in patients with diabetes mellitus

Diabetes is a common cause of renal failure. Intensive blood glucose control significantly reduces the risk of developing chronic kidney disease and reduces cardiovascular risk. Current guidelines recommend aiming for a glycated haemoglobin (HbA1c) of less than 7%.

Metformin is the first-line drug and can be used in patients with chronic kidney disease with a GFR above 60 mL/min/1.73 m^2. In patients with a GFR of 30–60 mL/min/1.73 m^2, the maximum recommended dose should be halved. Avoid metformin if the GFR is under 30 mL/min/1.73 m^2. All patients should be warned

to cease metformin for up to a few days during intercurrent illness or around the time of receiving radiographic contrast media. Dose reduction is often required for oral hypoglycaemic drugs (and insulin) as kidney function declines.

Caution should be exercised with thiazolidinediones in chronic kidney disease, particularly as there is the possibility of significant fluid retention.

Anaemia

Anaemia is a common complication of chronic kidney disease and is associated with the development of left ventricular hypertrophy and increased cardiovascular risk. This complication starts when the GFR is below 60 mL/min/1.73 m^2 and its prevalence increases with decreasing GFR. Treatment of anaemia in chronic kidney disease can be accomplished with iron supplementation and erythropoiesis stimulating drugs (such as epoietin alfa, epoietin beta, darbepoietin alfa). Erythropoiesis stimulating drugs have substantial health benefits for patients with chronic kidney disease, including improved quality of life, reduced blood transfusion requirements, decreased left ventricular mass, diminished sleep disturbance and enhanced exercise capacity. The vast majority of patients treated with erythropoiesis stimulating drugs require concomitant iron supplementation, either as oral iron or as a periodic intravenous dose.

There is currently no evidence that normalising haemoglobin concentrations in patients with chronic kidney disease improves clinical outcomes. Two large randomised controlled trials and a meta-analysis[10] have shown increased morbidity and mortality with higher haemoglobin targets. Current practice guidelines therefore recommend a haemoglobin target of 11–12 g/dL for all patients with chronic kidney disease.

Calcium and phosphate metabolism

Hyperphosphataemia and hyperparathyroidism in chronic kidney disease have been associated with increased vascular calcification, cardiovascular risk and death. This often manifests when the GFR falls below 60 mL/min/1.73 m^2. It becomes more prevalent as kidney function declines and is present in most patients having dialysis. Although there is no definitive evidence yet that correcting calcium-phosphate balance or secondary hyperparathyroidism improves cardiovascular outcomes, current clinical practice guidelines recommend treatment. This includes varying combinations of dietary phosphate restriction (preferably with the assistance of a renal dietitian), phosphate binder administration with meals (e.g. calcium carbonate, aluminium hydroxide, sevelamer, lanthanum carbonate, magnesium trisilicate), vitamin D supplementation (calcitriol or a vitamin D analogue such as paricalcitol) or calcimimetic therapy (cinacalcet). Recommended targets for treatment include a serum phosphate below 1.65 mmol/L, a serum calcium within the normal range and serum parathyroid hormone approximately 2–3 times the upper reference limit.

Aspirin and other treatments

Low-dose aspirin should be considered in patients with chronic kidney disease, especially in those with established cardiovascular disease. The only published controlled trial in patients with chronic kidney disease found that aspirin reduced the risk of myocardial infarction, but did not reduce the overall risk of cardiovascular death.[11] The potential benefit must be weighed against the risk of gastrointestinal bleeding, which is increased in patients with chronic kidney disease.

There is currently no convincing evidence to recommend routine prescription of folic acid, antioxidants (such as vitamin E or N-acetylcysteine) or fibrates to reduce cardiovascular risk in chronic kidney disease.

Managing cardiovascular disease in chronic kidney disease

Those with chronic kidney disease are more likely to be hospitalised for cardiovascular disease than those without.[12] Controlling the progression of renal disease may help to limit these complications.

Cardiac failure

Cardiac and renal failure often coexist because dysfunction of one organ frequently causes dysfunction of the other or because common systemic diseases, such as diabetes mellitus and extensive atherosclerosis, often cause both cardiac and renal dysfunction. Cardiac failure is present in up to 40% of patients with chronic kidney disease.[12] Hospitalisations for cardiac failure are five times more common in patients with chronic kidney disease than in other patients. The incidence is further increased by 30% in patients having dialysis.[12] Cardiac failure in renal disease should be managed as usual.

Diuretics are frequently required for symptomatic management and to control fluid retention in chronic kidney disease. The combined effects of renal failure (impaired delivery to site of action) and cardiac failure (impaired response) mean that patients with cardiorenal failure require frequent administration of large doses of loop diuretics (e.g. frusemide 120 mg twice a day) to achieve an adequate diuretic response.[7] This attempt to remove fluid must be balanced against the need to avoid dehydration and further deterioration of kidney function. Clinical signs of excessive fluid removal include postural hypotension (postural drop in systolic blood pressure of more than 10 mmHg) and postural tachycardia (postural rise in pulse rate of more than 10 beats/min). Daily weighing and fluid balance records may assist with optimisation of fluid balance.

Blockade of the renin-angiotensin-aldosterone system (ACE inhibitors and angiotensin receptor antagonists) and beta

blockade (bisoprolol, carvedilol or long-acting metoprolol) improves prognosis. ACE inhibitors and angiotensin receptor antagonists are underused in patients who have heart failure with chronic kidney disease, possibly due to fears about the effects on renal function.[13] However, prescription of these drugs is associated with a significant reduction in deaths (adjusted one-year mortality) in these patients.[13] Adding the angiotensin receptor antagonist telmisartan to an ACE inhibitor in a randomised controlled trial in 303 haemodialysis patients with symptomatic heart failure significantly reduced both all-cause mortality (20% risk reduction) and hospitalisations due to congestive heart failure. If patients cannot tolerate ACE inhibitor or angiotensin receptor antagonist therapy, consider giving them a combination of hydralazine and nitrate therapy to improve their prognosis.

Carvedilol significantly improved all-cause mortality (49% risk reduction), cardiovascular death (68% risk reduction) and hospitalisations (56% risk reduction) in a randomised, placebo-controlled trial of 114 patients with heart failure having dialysis.[14] Spironolactone and eplerenone should not be given to patients with a creatinine clearance of less than 30 mL/min/1.73 m^2. Caution should still be exercised when giving these drugs to patients with milder degrees of renal impairment, especially if they are taking an ACE inhibitor or angiotensin receptor antagonist. There is a significant potential for hyperkalaemia, as well as deterioration in renal function.

Ischaemic heart disease

Ischaemic heart disease is very common in patients with chronic kidney disease. It progresses at a more rapid rate than in people without chronic kidney disease and is often undertreated.[12] A study of patients with ischaemic heart disease and chronic kidney disease managed in primary health care showed that their risk factors for coronary heart disease were not as well controlled as those of patients with normal GFR.[15] Even though patients with chronic kidney disease had a higher prevalence of diabetes mellitus and hypertension, the rate of prescription of evidence-based cardiovascular therapies (aspirin, beta blockers, ACE inhibitors, statins) was lower than for those with normal renal function. This situation is undesirable, but may be caused in part by the perception of a higher number of complications, fear of adverse effects, and less evidence from controlled trials in this population.

Current recommendations are that patients with chronic kidney disease with ischaemic heart disease should be prescribed aspirin, beta blockers, ACE inhibitors and statins to achieve similar targets to those currently suggested for patients without chronic kidney disease. International best practice clinical guidelines also recommend that percutaneous coronary intervention and coronary artery bypass grafting are appropriate revascularisation techniques for patients with chronic kidney disease who have obstructive lesions in their coronary arteries.

When angiography is to be performed, some strategies to decrease the risk of contrast nephropathy might include:

- minimising contrast load
- temporary cessation of drugs such as ACE inhibitors, angiotensin receptor antagonists, diuretics (if practical) and metformin around the time of contrast exposure (typically for 24–48 hours before and 24–48 hours after the procedure)
- gentle pre-hydration, for example 1 L of saline infused over 12 hours before the procedure.

Conclusion

Chronic kidney disease is a common, under-recognised and eminently treatable condition that affects one in seven Australians. It is also a major risk factor for cardiovascular disease. Patients with chronic kidney disease are far more likely to die of ischaemic heart disease or congestive cardiac failure than to end up on dialysis. Cardiovascular risk factor modification is an important part of the management of chronic kidney disease. There is considerable overlap between the management of chronic kidney disease, diabetes and cardiovascular risk reduction. Additional risk factor reduction strategies in patients with chronic kidney disease include treatment of anaemia and calcium and phosphate disorders. Management of cardiac failure and ischaemic heart disease in patients with chronic kidney disease is not dissimilar to that in patients without chronic kidney disease, except that more intensive diuresis is often necessary in cardiorenal failure.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 167)

5. Treating hypertension can reduce the decline of the glomerular filtration rate in patients with chronic kidney disease.
6. Diuretics are contraindicated for the treatment of heart failure in patients with chronic kidney disease.

Book review

Therapeutic Guidelines: Cardiovascular. Version 5.

Melbourne: Therapeutic Guidelines Limited; 2008. 241 pages. Price $39, students $30, plus postage

Catherine Liu, Academic General Practice Registrar, Department of General Practice, Westmead Hospital, The University of Sydney

This book provides recommendations for assessment and management of common clinical problems as well as expert advice on 'evidence-poor' areas. A notable difference from the previous Cardiovascular edition is the inclusion of an opening chapter explaining how the guidelines were produced, including the role of the expert group and the process of formulating and revising the recommendations. This explanation is important for the reader's understanding of the basis of the guidelines and represents a useful addition to the text.

Other differences between the revised version and its predecessor are the absence of the cardiovascular drug interactions chapter and the management of cerebral arterial disease (it still discusses peripheral arterial disease), and the logical transfer of the section on treatment of endocarditis to Therapeutic Guidelines: Antibiotics. This edition also has a focus on cardiovascular disease risk reduction as well as including the updated indications for statin therapy that are consistent with current Pharmaceutical Benefits Schedule guidelines.

The layout of this edition is familiar and navigable. However, overall I have found using the electronic form of Therapeutic Guidelines (eTG) easier to use in general practice as the search function is very user-friendly and information from the entire series can be accessed without needing to refer to individual books.

Modern management of thyroid replacement therapy

Peter Davoren, Clinical Director, Diabetes and Endocrinology, Gold Coast Hospital, and Senior Lecturer, Griffith University, Queensland

Summary

Hypothyroidism is a common and chronic condition. Finding a high concentration of thyroid stimulating hormone in a symptomatic patient confirms the diagnosis and a cause is usually readily found. Lifelong thyroxine therapy relieves symptoms and restores 'normal' thyroid function. Commencing thyroxine can aggravate cardiac disease but is relatively free of adverse effects. The concentration of thyroid stimulating hormone is used to monitor therapy.

Key words: hypothyroidism, pregnancy, thyroid stimulating hormone, thyroxine.

(Aust Prescr 2008;31:159–61)

Introduction

Hypothyroidism is a common condition with an annual incidence of 3.5/1000 in women and 0.6/1000 in men.[1] The prevalence increases with age. In areas without iodine deficiency the common causes of chronic hypothyroidism are autoimmune thyroid disease, thyroidectomy, radiotherapy (both radioiodine therapy and external beam radiotherapy), congenital disorders and disorders of thyroid hormone metabolism. Secondary hypothyroidism occurs with some pituitary and hypothalamic diseases.

Diagnosis

Patients may not present with the typical clinical features of hypothyroidism. They may have vague symptoms such as tiredness. The diagnosis can be made by finding a persistently elevated serum concentration of thyroid stimulating hormone (TSH). The serum free thyroxine (fT4) concentration will be low. Measuring triiodothyronine (fT3) adds little to the diagnosis or monitoring of hypothyroidism.

In secondary hypothyroidism the pituitary fails to produce TSH appropriately so measurement of TSH is unhelpful. The diagnosis is suggested by a low fT4 and features of pituitary disorder.

In subclinical hypothyroidism the TSH is elevated (usually to 5–10 mIU/L) but the fT4 is normal. The typical symptoms of hypothyroidism are often absent.

The cause of primary hypothyroidism in an adult will usually be determined from a history of thyroidectomy or radiotherapy or finding high titres of antithyroid antibodies (thyroid peroxidase, antimicrosomal or antithyroglobulin antibodies). The use of lithium and iodine-containing preparations (such as amiodarone) can cause a drug-induced hypothyroidism.

Providing patients with a copy of the laboratory results which confirm their need for thyroxine often proves helpful for the patient and future treating doctors.

Treatment

Primary hypothyroidism is treated by giving the patient replacement thyroxine, usually for life. Liothyronine rarely needs to be used unless there is life-threatening hypothyroidism. Alternative sources of thyroid hormones such as thyroid extracts should be avoided.

Thyroxine dose

Thyroxine has a half-life of 7–10 days but a much longer biological effect. Once-daily dosing is appropriate.

The dose is dependent on body weight and age. Children require larger doses of thyroxine per kg body weight than adults who require approximately 1.6 microgram/kg/day.[2] Most adults will maintain euthyroidism with a dose of thyroxine of 100–200 microgram/day. There may be a decline in thyroxine requirements in the elderly.

Both brands of thyroxine currently available in Australia come from the same supplier and are identical. Concerns regarding the bioavailability of different preparations are not relevant in Australia.

Thyroxine tablets should be kept dry and cool and in their original container.[3] Recent advice to refrigerate thyroxine tablets increases the likelihood of moisture causing deterioration in the medication. A month's supply can be kept at room temperature.[4]

Starting thyroxine

The rate of introduction of thyroxine should be determined by the duration of the hypothyroidism and the presence (or risk) of coronary disease or heart failure. Otherwise healthy patients who have recently undergone thyroidectomy or radioiodine treatment for thyrotoxicosis can immediately start at or just below their predicted daily replacement dose of thyroxine 100–200 microgram.

Elderly patients and those with known heart disease should start with a daily dose of thyroxine 25 microgram for 3–4 weeks with a reassessment of their condition before further increments of 25 microgram every 3–4 weeks until the predicted dose is reached. Worsening symptoms of coronary disease or heart failure should be controlled before increasing the dose of thyroxine and a dose reduction may be necessary while cardiac disease is stabilised.

For patients between these two extremes, a starting dose of 50 microgram/day is reasonable. This is increased at intervals of 3–4 weeks until the predicted dose is reached.

Patients should feel some symptomatic improvement within two weeks of starting thyroxine. It may take 3–4 months for the full benefit of the drug to become apparent and for the TSH to normalise.

Monitoring and dose adjustment

In primary hypothyroidism the TSH alone can be used to monitor therapy. The aim should be to maintain the TSH at the lower end of the normal range (0.4–5 mIU/L). Symptoms may be best relieved when the TSH is at the lower end of this range. It takes at least four weeks for the TSH to stabilise after a change in thyroxine dose and so any testing of TSH should be done at least 4–6 weeks after the change. At the start of treatment a patient does not need measurement of their TSH until they have been on their predicted dose of thyroxine for 4–6 weeks (unless symptoms of thyrotoxicosis dictate otherwise). Repeat testing every six weeks is appropriate until the dose is stabilised, however if the patient is approaching euthyroidism and is feeling well this interval can be increased. After the dose is stabilised an annual TSH measurement is usually adequate monitoring unless a problem arises.

> Patients should feel some symptomatic improvement within two weeks of starting thyroxine

When the thyroxine dose is in the range of 100–200 microgram/day, variable daily dosing may be necessary to achieve euthyroidism. Considering the total weekly dose is helpful when changing the dose. For example, 100 microgram/day (700 microgram/week) may be inadequate to control the TSH but 125 microgram/day (875 microgram/week) may be too much. A dose of 800 microgram/week can be taken as 100 microgram/day five days a week and 150 microgram/day two days a week. Variable daily dosing removes the need for patients to cut thyroxine tablets.

Problems

If taken correctly, thyroxine should enable patients to lead a normal life. However, there are some common problems which can affect management.

Persistently elevated TSH

Poor adherence is the most likely explanation of TSH remaining above the normal range. I advise patients to decant a week's supply of thyroxine into a separately labelled bottle and refill the bottle on the same day each week. If the patient discovers they have missed one (or more) doses they can take the missed doses in conjunction with their usual dose over the next few days.

The absorption of thyroxine may be reduced by cholestyramine, colestipol, aluminium hydroxide, ferrous sulfate and possibly fibre. Two hours should elapse between use of thyroxine and these drugs.

Symptoms do not respond to thyroxine

Hypothyroidism is often discovered on biochemical testing after patients present with non-specific complaints. While it is likely that symptoms such as muscle aches and pains, dry skin and dry hair and menstrual irregularity may respond to thyroxine, other symptoms such as lethargy, tiredness and fatigue, weight gain and depressive symptoms may have other causes. It is helpful to consider if the patient's symptoms are likely to be due to hypothyroidism before prescribing thyroxine and to tell them if you suspect that some of their symptoms are unlikely to respond. There is no proven benefit in adding liothyronine to the treatment of patients who have persistent symptoms despite taking thyroxine.

Secondary hypothyroidism

If there is pituitary or hypothalamic disease, TSH is unreliable for diagnosing and monitoring thyroid function and fT4 should be used instead. A low fT4 will be found in secondary hypothyroidism and treatment should aim to maintain fT4 within the reference range.

Most patients with secondary hypothyroidism will be hypogonadal and many will also be cortisol deficient. It is extremely important to consider cortisol deficiency before starting treatment with thyroxine in patients with pituitary and hypothalamic disease as its use will speed the metabolism of cortisol and can induce an adrenal crisis.

When commencing thyroxine in secondary hypothyroidism it is therefore safest to also treat the patient with a corticosteroid (for example prednisone 5 mg daily). Subsequently, cortisol reserve can be assessed with an early morning cortisol measurement. A morning cortisol less than 100 nmol/L always indicates the need for ongoing steroid replacement. Results greater than 500 nmol/L indicate adequate reserve and values in between may require provocation tests.[5]

Drug-induced hypothyroidism

Lithium and iodine are the common causes of drug-induced hypothyroidism. Amiodarone, iodine-containing contrast media and kelp tablets are common sources of large doses of iodine.

All forms of drug-induced hypothyroidism will usually resolve on withdrawal of the drug. Thyroxine can be used to control symptoms if required while recovery occurs. Lithium- and amiodarone-induced hypothyroidism are managed with thyroxine. The ongoing need for the lithium or amiodarone should be considered, but they can be continued if necessary.

Pregnancy and lactation

Thyroxine requirements increase by 25–30% during pregnancy with increased requirements seen as early as the fifth week of pregnancy.[6] Children born to women whose hypothyroidism was inadequately treated in pregnancy are at increased risk of neuropsychological impairment.[7]

I advise women taking thyroxine who are planning to conceive to increase their dose of thyroxine by 30% at the confirmation of the pregnancy. TSH should be monitored every 8–10 weeks during pregnancy with further dose adjustments as necessary. The thyroxine dose returns to the pre-pregnancy dose after delivery whether the mother is breastfeeding or not.

Transient hypothyroidism

Some patients have transient hypothyroidism so it is appropriate to consider withdrawing the drug. For example, women who develop hypothyroidism in the postpartum period (postpartum thyroiditis) may not require long-term thyroxine replacement. In some patients a clear cause of hypothyroidism is not established, but the cause will often have been the hypothyroid phase of subacute (de Quervain's) thyroiditis or possibly iodine-induced hypothyroidism. Other patients may ask if they can stop thyroxine therapy.

If treatment is stopped it usually takes four weeks for the TSH to rise, but it can be tested earlier if symptoms occur. The onset of symptoms and a rising TSH show an ongoing need for thyroxine and patients can immediately recommence their previous dose.

Subclinical hypothyroidism

Some patients have an elevated TSH, but a normal concentration of fT4. The need for treatment is debatable. I consider treating patients who have had an elevated TSH for over six months with persistent symptoms which may be due to hypothyroidism, and also patients who have antibodies suggesting autoimmune thyroid disease. After a 3–6 month trial I continue treatment if there has been a substantial symptomatic improvement, or stop and reassess symptoms and TSH after 4–6 weeks to determine if there is an absolute need for ongoing thyroxine replacement. Patients with a modestly elevated TSH and positive thyroid antibodies have a 5% per year chance of developing overt hypothyroidism.[1] Pregnant women and those considering pregnancy should be treated.

Addison's disease

Addison's disease and autoimmune hypothyroidism occasionally occur together. This is a rare but dangerous association. Increased pigmentation, postural hypotension and possibly weight loss may suggest the additional diagnosis. As in secondary hypothyroidism, give steroid replacement before introducing thyroxine to avoid inducing an adrenal crisis.

Thyroid cancer

Some patients with differentiated thyroid cancer are given thyroxine at a higher dose to suppress TSH (to less than 0.1 mIU/L) with minimum elevation of fT4. This helps prevent recurrence of the cancer.

Conclusion

Treatment of hypothyroidism is usually a lifelong necessity. Determining the cause will detect those patients who need only transient treatment. Except for those patients with or at risk of known cardiac disease, the elderly and those with long-standing symptoms, thyroxine can usually be commenced at or near a full replacement dose. The dose is adjusted to keep the concentration of TSH within the normal range.

> The need for treatment of subclinical hypothyroidism is debatable

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Further reading

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Conflict of interest: none declared

Medicine Update

Medicine Update is an online publication from the National Prescribing Service, designed for patients who may have been prescribed medicines recently listed on the Pharmaceutical Benefits Scheme.

Medicine Update is available at www.nps.org.au/consumers/publications/medicine_update and can be read in conjunction with the Consumer Medicine Information (CMI) leaflet.

The December issues cover:

- tramadol and its new extended-release formulation
- zoledronic acid, a once-yearly intravenous bisphosphonate for osteoporosis.

Both medicines are also reviewed for health professionals in the December issue of NPS RADAR at www.npsradar.org.au

Medicines Australia Code of Conduct: breaches

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

This year's report[2] differs from previous reports because of increased scrutiny of educational events. The Australian Competition and Consumer Commission now requires Medicines Australia to report details of the educational events held or sponsored by member companies. This information is available on the Medicines Australia website (at www.medicinesaustralia.com.au).

Medicines Australia appointed an independent auditor to check that the educational events contained in the reports complied with the Code of Conduct. This resulted in the Medicines Australia Monitoring Committee referring 52 events to the Code of Conduct Committee. As there were only 83 new complaints in 2007–08, educational events account for most of the total.

Table 1 shows 37 cases where at least one breach of the Code of Conduct was found. The majority of cases involved educational events where the hospitality was deemed to be out of proportion to the educational content of the event. The Code of Conduct still applies even if the event is held overseas. These transgressions resulted in a range of fines. A dinner for four specialists in Adelaide attracted a fine of $10 000 while dinner for nine specialists at the Hotel de Paris in Monaco attracted a fine of $50 000. Inappropriately luxurious and extravagant hospitality resulted in one company being fined $175 000.

While most of the promotional activity was directed at prescribers, nurses and pharmacists also attended events which breached the Code of Conduct.

Detailed information about the complaints can be found in the annual report of the Code of Conduct Committee.[2]

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Table 1

Breaches of the Code of Conduct July 2007 – June 2008

Company	Product or activity	Sanction imposed by Code of Conduct Committee
Abbott	Reductil (sibutramine)	Withdraw promotional material $10 000 fine
Allergan	Extravagant hospitality	$175 000 fine
Amgen	Extravagant hospitality Extravagant hospitality	$10 000 fine $50 000 fine
AstraZeneca	Crestor (rosuvastatin) Extravagant hospitality	Withdraw promotional material (previously found in breach of the Code) $80 000 fine $10 000 fine
Baxter	Extravagant hospitality	$35 000 fine

Continued over

Biogen	Extravagant hospitality	$10 000 fine
Boehringer Ingelheim	Micardis (telmisartan)	Withdraw promotional material $25 000 fine
CSL	Extravagant hospitality Extravagant hospitality	$50 000 fine $40 000 fine
Device Technologies	Penthrox (methoxyflurane)	Withdraw material from website Corrective letter
Eli Lilly	Actos (pioglitazone)	Corrective letter (already sent)
GlaxoSmithKline	Seretide (fluticasone/salmeterol)	Withdraw detailing aid Corrective letter $50 000 fine
	Seretide (fluticasone/salmeterol)	Withdraw promotional material $50 000 fine
	Extravagant hospitality	$20 000 fine
	Extravagant hospitality	$100 000 fine
	Extravagant hospitality	$90 000 fine
Hospira	Eligard (leuprorelin)	Withdraw promotional material Corrective letter $50 000 fine
Ipsen	Extravagant hospitality	$30 000 fine
Nycomed	Extravagant hospitality Extravagant hospitality	$70 000 fine reduced to $35 000 on appeal $60 000 fine
Octapharma	Octagam (immunoglobulin)	Withdraw promotional material Corrective letter $50 000 fine
Pfizer	Lipitor (atorvastatin)	Withdraw promotional material $50 000 fine
	Crestor (rosuvastatin)	Corrective letter Company staff to comply with the Code $200 000 fine
	Extravagant hospitality	$20 000 fine
Pharmion	Extravagant hospitality	$25 000 fine
Roche	Media releases	Remove media releases from website $60 000 fine reduced to $40 000 on appeal $40 000 fine $20 000 fine increased to $30 000 on appeal
Sanofi-aventis	Actonel (risedronate)	Withdraw detailing aid Corrective letter $100 000 fine reduced to $80 000 on appeal
Schering-Plough	Olmetec (olmesartan)	Withdraw promotional material Corrective letter Corrective advertisement Amend minimum product information
	Olmetec (olmesartan)	Corrective advertisement $50 000 fine
Servier	Extravagant hospitality	$20 000 fine
	Extravagant hospitality	$60 000 fine
	Extravagant hospitality	$50 000 fine
Solvay	Extravagant hospitality	$20 000 fine
	Extravagant hospitality	$80 000 fine
Wyeth	Extravagant hospitality	$35 000 fine

Top 10 drugs

These tables show the top 10 subsidised drugs in 2007–08. The tables do not include private prescriptions.

Table 1

Top 10 drugs by DDD/1000 pop/day *†

Drug	PBS/RPBS ‡
1. atorvastatin	136.215
2. simvastatin	52.996
3. ramipril	29.266
4. perindopril	23.142
5. esomeprazole	19.445
6. aspirin	18.155
7. frusemide	17.877
8. irbesartan	17.272
9. omeprazole	16.678
10. salbutamol	16.624

Table 2

Top 10 drugs by prescription counts †

Drug	PBS/RPBS ‡
1. atorvastatin	10 542 015
2. simvastatin	5 773 055
3. esomeprazole	5 221 504
4. perindopril	3 836 043
5. omeprazole	3 702 832
6. paracetamol	3 666 627
7. atenolol	3 245 793
8. pantoprazole	3 150 985
9. irbesartan	3 085 338
10. metformin hydrochloride	2 961 175

Table 3

Top 10 drugs by cost to Government †

Drug	Cost to Government ($A)	DDD/1000 pop/day * PBS/RPBS ‡	Prescriptions PBS/RPBS ‡
1. atorvastatin	585 491 600	136.215	10 542 015
2. simvastatin	237 274 763	52.996	5 773 055
3. clopidogrel	196 649 817	9.776	2 636 907
4. esomeprazole	184 420 078	19.445	5 221 504
5. salmeterol and fluticasone	160 894 401	– §	2 874 427
6. olanzapine	158 220 450	3.051	864 937
7. omeprazole	108 931 730	16.678	3 702 832
8. rosuvastatin	104 846 840	9.248	1 674 364
9. venlafaxine	104 082 531	13.196	2 644 753
10. tiotropium bromide	100 464 420	5.662	1 437 217

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

† Based on date of supply

‡ PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

§ Combination drugs do not have a DDD allocated

Source: Drug Utilisation Sub-Committee (DUSC) Drug Utilisation Database, as at 30 October 2008. © Commonwealth of Australia.

Book review

Therapeutic Guidelines: Toxicology & Wilderness. Version 1.

Melbourne: Therapeutic Guidelines Limited; 2008. 311 pages. Price $39, students $30, plus postage

Edi Albert, Senior Medical Educator and Co-ordinator, Expedition Medicine Program, General Practice Training Tasmania, and Medical Officer, Polar Medicine Unit, Australian Antarctic Division, and Medical Officer, Department of Emergency Medicine, Hobart Private Hospital, Hobart

Most sections of this book are of an excellent standard while others are inadequate and disappointing. I think this may reflect some uncertainty about the purpose of the book, which to my mind has not had enough thought put into who will use it, why and how.

The bulk of the book covers important topics in toxicology and toxinology. These sections are well prepared and will undoubtedly be very useful for practising clinicians like me, who rarely deal with such cases.

The book starts with an excellent section on resuscitation which underpins most of the other emergency medicine topics. However, given the book includes 'wilderness topics', it would

have been helpful to include the role of cardiopulmonary resuscitation (CPR) and how it differs in hypothermia, near drowning and electrical injury compared to the standard cardiac arrest situations.

While the chapter on burns is excellent, anaphylaxis is probably too detailed and makes the book look unbalanced given the inadequate coverage of some of the other environmental topics.

The section on altitude illness is so short as to be almost useless. It does not correctly describe the diagnostic criteria for acute mountain sickness, and confusingly, and perhaps dangerously, lumps this common and benign condition together with two less common and deadly ones. The section on prevention is overly brief and contains recommendations for ascent rates that do not comply with internationally accepted standards.

The information on diving medicine and heat-related illness are so short they could only be interpreted by clinicians who understand the topic.

The chapter on hypothermia is again so short that it lacks clarity and accuracy. It misses out critical management issues such as clinical assessment, gentle handling of patients and the role of CPR. The treatment algorithm is too simplified.

This book should cover common wilderness topics such as motion sickness, carbon monoxide poisoning, evacuation and long-term patient care, non-freezing cold injury, frostbite and avalanche rescue medicine. The focus should be as much on prevention as it is on treatment in the emergency situation.

My recommendation for the prospective purchaser is to read the book for its excellent toxicology and toxinology sections. If you want something to cover 'wilderness' topics, I suggest Auerbach's Field Guide to Wilderness Medicine, or the new Oxford Handbook of Expedition Medicine.

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.

Maraviroc

Celsentri (Pfizer)

150 mg and 300 mg film-coated tablets

Approved indication: HIV infection

Australian Medicines Handbook section 5.4

Highly active antiretroviral therapy has improved survival for patients infected by HIV, but long-term toxicity and the development of viral resistance are problematic. There is still a need to develop new drugs to treat people with clinically advanced disease which is resistant to several classes of antiretroviral drugs. The entry of HIV into a patient's cells is one target of research and has led to the development of fusion inhibitors such as enfuvirtide (see 'HIV fusion inhibitors: a review', Aust Prescr 2008;31:66–9).

Maraviroc blocks the entry of HIV into cells, but it is not a fusion inhibitor. It acts on human chemokine co-receptor 5 (CCR5) which is found on the cell membrane. Some strains of HIV (CCR5-tropic HIV-1) enter the cell after interacting with this receptor. By selectively binding to the receptor, maraviroc prevents HIV from penetrating the cell surface. This ultimately results in reduced viral replication.

The approval of maraviroc was based on the interim results of two clinical trials involving a total of 635 patients. These patients were infected with CCR5-tropic HIV-1 and had more than 5000 copies of viral RNA/mL despite previous treatment with at least one drug from at least three different classes of antiretroviral drug. A group of 209 patients were randomised to take a regimen of three to six antiretroviral drugs, while 426 added maraviroc 300 mg twice daily to this regimen. After 24 weeks the viral RNA in 23% of the patients taking the 'optimised background regimen' was less than 50 copies/mL. In the group which added maraviroc 45% had less than 50 copies/mL. The increase in the concentration of CD4 lymphocytes was 57 cells/mm^3 with the regimen alone and 106 cells/mm^3 when maraviroc was added.

When these trials were published they reported on outcomes at 48 weeks, having randomised 1075 patients. Viral RNA had fallen to less than 50 copies/mL in 17% of the patients taking the optimised regimen. The same outcome had been reached by 46% of the patients taking maraviroc twice daily and by 43% of patients using a once-daily regimen. CD_4 lymphocytes increased by 61 cells/mm^3 in the control group, by 124 cells/mm^3 with twice-daily maraviroc and by 116 cells/mm^3 with once-daily maraviroc.[1,2]

Adding maraviroc to the treatment of patients taking multiple other drugs does not greatly affect the number of adverse reactions. Nausea, diarrhoea and headache are common. Adverse events which occurred more frequently when maraviroc was added to treatment include paraesthesia, muscle

aches, cough, fever, infections and rashes. Liver enzymes were more likely to increase in patients taking maraviroc and in the USA the drug has a black box warning about hepatotoxicity. There is little information about the safety of the drug in patients with liver disease, especially those who are infected with hepatitis B or C. It is uncertain if the cardiovascular events reported in patients taking maraviroc were related to the drug.

The absorption of maraviroc is variable, possibly because of saturation of the P-glycoprotein transporter. Although absorption can be reduced by a high fat meal, there are no restrictions on taking maraviroc with food. As maraviroc is mainly metabolised by cytochrome P450 3A4, there are many potential drug interactions. A lower dose of maraviroc is recommended if the patient is prescribed an inhibitor of this enzyme such as clarithromycin, itraconazole and the protease inhibitors (except tipranavir/ritonavir and fosamprenavir/ritonavir). A higher dose is recommended if the patient is taking an enzyme inducer such as rifampicin, efavirenz and carbamazepine. Patients should not take St John's wort as it is likely to decrease concentrations of maraviroc. The usual twice-daily dose has a half-life of 16 hours with most of the metabolites being excreted in the faeces.

Maraviroc is being studied in previously untreated patients, but its role in therapy depends on whether the patient is infected with CCR5-tropic HIV-1. CCR5-tropic HIV-1 predominates early in the infection, but viral forms emerge which can use another co-receptor to enter the cell. The use of maraviroc is therefore limited to patients only infected with CCR5-tropic virus. It can take several weeks to test for CCR5-tropic HIV-1, so testing may be a barrier to treatment. The effectiveness of maraviroc will also be reduced if the virus develops a reduced sensitivity to the drug. Like other antiretroviral drugs approved on surrogate end points, maraviroc will require more research to determine its optimal use in combination regimens.

T T T manufacturer provided clinical evaluation

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Romiplostim

Nplate (Amgen)

vials containing 375 microgram and 625 microgram for reconstitution

Approved indication: idiopathic thrombocytopenic purpura

Australian Medicines Handbook Appendix A

One of the causes of thrombocytopenia is idiopathic thrombocytopenic purpura. As the platelets are destroyed by antiplatelet autoantibodies the condition is also known as chronic immune thrombocytopenic purpura. Other causes of thrombocytopenia should be excluded before making the diagnosis.

If the platelet count is low enough to require treatment, corticosteroids are usually prescribed first. Patients who do not respond may be given immunoglobulins. Severe thrombocytopenia can be an indication for splenectomy.

A new approach to managing idiopathic thrombocytopenic purpura is to boost platelet production rather than trying to limit platelet destruction. Romiplostim is a genetically engineered protein which binds to the thrombopoietin receptor even though its structure differs from that of human thrombopoietin. Activation of the receptor increases platelet production.

Romiplostim is given by subcutaneous injection. As the volume is small, a syringe with 0.01 mL gradations should be used. The serum concentration peaks after a median of 14 hours and the median half-life is 3.5 days.

A dose-ranging study gave romiplostim to 24 patients with previously treated immune thrombocytopenic purpura. Depending on the platelet count a second injection was given after at least 14 days. In four of the 12 patients given 3, 6 or 10 microgram/kg of romiplostim the platelet count rose to at least twice the baseline count. Lower doses were not effective.[1] In another phase of this trial 21 patients were given romiplostim (1, 3 or 6 microgram/kg) or a placebo injection containing the excipients of the formulation every week for six weeks. Seven of the eight patients given 1 microgram/kg and three of the eight given 3 microgram/kg achieved the target concentration for platelets. (The 6 microgram/kg dose was dropped from the trial due to an exaggerated increase in platelets.) Adverse events which were more frequent with romiplostim than its excipients were headache and blistering of the oral mucosa.[1]

Using the information from the dose-ranging studies, two parallel trials were designed. Starting with 1 microgram/kg weekly the dose of romiplostim was adjusted to achieve a target platelet count of 50–200 x 10^9/L. One trial enrolled 62 patients and the other enrolled 63 patients following splenectomy. Both trials were placebo-controlled and lasted for six months. Within three weeks half the patients given romiplostim had reached the target. During at least six of the last eight weeks of treatment, 49% of the patients given romiplostim, but only 2% of the placebo group, were in the target range. This durable response was seen in 61% of the non-splenectomised patients and 38% of the splenectomised patients. On average, in patients given romiplostim, the platelet count was above the target for 15.2 weeks in the non-splenectomised group and 12.3 weeks in the splenectomised group. They needed less rescue therapy than patients in the placebo group who only achieved the target for a mean of 0.8 weeks.[2]

Adverse events which were more frequent with romiplostim

than with placebo included headache, epistaxis, arthralgia, myalgia, dizziness, insomnia and abdominal pain.[2] As platelet counts rise there could be an increased risk of thrombosis. An increase in the amount of reticulin in the bone marrow can cause morphological changes in blood cells. Peripheral blood films, as well as platelet counts, should be checked during treatment.

Romiplostim is not a cure for immune thrombocytopenic purpura, the platelet count will fall again after treatment is discontinued. As patients are therefore likely to require repeated treatments, establishing the long-term efficacy and safety will be important. The data are limited, but neutralising antibodies have not yet emerged as a major problem. At present the use of romiplostim will be limited to patients who have had an inadequate response to splenectomy, and those who have not had a splenectomy but cannot tolerate or have not responded to corticosteroids and immunoglobulins.

T T T manufacturer provided clinical evaluation

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

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

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

Answers to self-test questions

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

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