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CONTENTS

Editorial

Signing the script

Paul Nisselle, Senior Advisor, Risk Management, Medical Defence Association of Victoria

Key words: legal issues, Pharmaceutical Benefits Scheme.

(Aust Prescr 2004;27:108–9)

It is perhaps galling to realise, after all your years of medical training and experience in practice, that your most valuable asset is not your knowledge and skill – but your signature!

Your signature does not just give patients access to the Pharmaceutical Benefits Scheme (PBS) and prescription-only drugs, it can open the door to sickness benefits, invalid pensions, workers' compensation and other benefits. The power of that signature brings with it a heavy burden of responsibility **and** the threat of dire consequences if that power is abused.

If you apply your signature negligently, you can find yourself sued. Similarly, if your signature enables a patient to obtain a benefit to which he or she is not entitled, you can face criminal charges, or at best, a demand that you repay the benefit improperly obtained by the patient.

Not once but **four** times, in my almost 20 years in general practice, I signed, and gave to the patient, a prescription for a penicillin derivative, when on the outside of their notes, in red ink, in my own handwriting, were the words 'Allergic to penicillin'. In three out of the four cases, the patient took the script to the local pharmacist, whom I knew well enough for him to be able to ring me and say, 'Listen, you idiot, you've done it again!'. The fourth time, the patient had the script filled by a pharmacist who did not know either her or me. Fortunately, she only suffered a mild rash and when she rang me, my abject apology was accepted. Clearly, that was negligent prescribing. I did not meet the standard of care to which she was entitled when I signed that script.

Most general practitioners now use computers to print prescriptions. The software will alert the prescriber if a drug to which the patient is known to be allergic is about to be prescribed or if the drug will interact with the patient's (known) usual medications. These warnings will not occur if the necessary information is missing or incorrectly entered into the database. Such systems are only as good as the data entered into them. Ultimately, if you sign a computer-printed script, you are responsible for it, not the computer!

There is a downside to computer-generated scripts. They are too easy. At the end of an already extended consultation, when a patient says, 'Oh, and seeing I am here, can I have a repeat of all my tablets?', do you carefully review the medication to see if all of it is still appropriate or do you just hit the 'print' button, grab the scripts as they emerge from the printer and sign them automatically while talking to the patient?

Apart from liabilities in negligence which can arise from signing scripts, there is also the consequence of falling foul of the law. Prescribing is governed by State law, such as those relating to prescribing of drugs of addiction, and Commonwealth law, such as those relating to the PBS.

When did you last read the Explanatory Notes section of the Schedule of Pharmaceutical Benefits? That is, the yellow pages at the front of the book. They detail both what is required of you by law and what is requested of you. For example, the Schedule requests that prescriptions contain no more than three items and be clearly legible. That might seem gratuitously insulting, but pharmacists should not have to struggle to understand your writing. Tragedies occur; for example, while the pharmacist who dispensed 'Inderal' instead of 'Intal' was roundly criticised by the Coroner (yes, the patient died), so was the doctor who compounded illegible handwriting by adding as the only instruction on the script, 'prn' (an antiquated Latin abbreviation for 'take as needed').

In this issue…

Prescriptions are such a routine part of practice that it is easy to forget that they are legal documents. Paul Nisselle therefore reminds us of some of the medicolegal issues in prescribing.

As advertising influences prescribing it also requires regulation. Craig Davies informs us what the Therapeutic Goods Administration is doing to protect Australian health professionals and consumers from inappropriate pharmaceutical advertisements.

Sometimes it is appropriate not to prescribe for a patient, but withdrawing treatment can be problematic. Christine Kilpatrick discusses the issues to consider when stopping antiepileptic drugs. In some conditions it is not possible to stop a drug which may be increasing the patient's risk of adverse effects. For example, Joe Proietto outlines the difficulties of managing patients who have schizophrenia and diabetes.

Insulin resistance also has an important role in polycystic ovary syndrome. Metformin has been studied in this condition, but Beres Joyner suggests caution before prescribing it to women with infertility.

You will come under pressure to 'bend' the law. Common examples when I was in practice included:

- 'Doc, the chemist said that if you just add "SP" to the script, I'll get the tablets much cheaper' or 'Doc, I'm told that if you ring to get a special authority…'
- 'My mother overseas can't afford to buy the tablets she needs over there. Give me a script in my name and I'll get it filled here and send them to her.'
- 'My mum's/dad's on Repat. Write the script in her/his name and I'll get the medicine cheaper.'

To agree to such requests is not compassionately 'bending' the law, it is fraud. It is criminal fraud, because it would satisfy the test of *mens rea* (literally, guilty mind). You clearly knew that you were issuing a document which would enable a Commonwealth benefit to be obtained improperly. Penalties can be heavy. Section 128B of the *Health Insurance Act 1973* [Commonwealth] states that the penalty for such offences is a fine of up to $10 000 or five years in prison, or both.

You should also be aware that section 128A of that same Act says that it is an offence even if, without intent (that is, without *mens rea*), you:

> make, or authorise the making of, a statement (whether oral or in writing) that is:
>
> (a) false or misleading in a material particular; and
>
> (b) capable of being used in connection with a claim for a benefit or payment under this Act.

The penalty for a breach of section 128A is a fine of up to $2000. That's called a 'strict liability' offence, meaning that there is no need to prove *mens rea*. In other words, if you wish to prescribe under the PBS the burden is on you to learn how the Scheme works.

A prospective study[1] has described how latent conditions interact with error-producing conditions leading to active failures and then prescribing errors:

- 'Latent conditions' – organisational sloppiness, such as the boss saying to the intern, 'Put Mr X on digoxin' without checking that the intern knew the correct dose, frequency, route of administration, and duration of treatment.
- 'Error-producing conditions' – such as overwork, poor team communication, inadequate protocols, H.A.L.T. doctors (Hungry, Angry, Late or Tired), and unhelpful patients with perhaps both complex medical problems and language or other communication difficulties.
- 'Active failures' – these can be subdivided into:
  - 'errors', such as slips (thinking of one name but when distracted writing another), lapses (such as failing to delete the previous drug from a medication chart when substituting it with another) and frank mistakes (such as co-prescribing drugs known to interact)
  - 'violations' (such as consciously ignoring clearly stated protocols, for example checking procedures).

This research points the way to avoiding treatment errors:

- When delegating treatment, always give clear, detailed (preferably written) instructions.
- Slow down and concentrate even more than usual when H.A.L.T. (Of course, it is better to HALT when H.A.L.T.!)
- Concentrate when writing prescriptions – do not try to write them while the rest of your brain is attending to another task. (How often do you attend to the list of requested repeat scripts when also returning that day's phone calls?)
- If the computer prescribing system is down, and you have come to rely on it, slow down and check, check, check.

One way or another, general practitioners probably use their signatures about 50 times a day. That means that over the average professional lifetime, you will sign your name about half a million times. It is frightening to think that any one of those signatures applied carelessly could land you in medicolegal hot water.

Reference

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Conflict of interest: none declared

Letters

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

Withdrawal of temazepam gelcaps

Editor, – I was disappointed to read certain advice and factual inaccuracies in the article regarding issues relating to the use/misuse of temazepam capsules (Aust Prescr 2004;27:58-9). The withdrawal by Sigma of its temazepam capsules from the market has not led to a complete lack of this drug in Australia and temazepam gelcap injection still continues to be a problem.

Furthermore, I am concerned about the comment, 'in this instance they have a duty of care not to prescribe benzodiazepines'. While doctors should not respond to coercion, as alluded to in the article, appropriate

management of benzodiazepine abuse/dependence might include notification to the relevant government department and an appropriate prescription for benzodiazepines (usually diazepam) in controlled amounts; such as by daily, or alternate daily, pick-up from a nominated chemist. Such an approach, conducted as part of a planned strategy to attempt to gradually wean the patient off benzodiazepines, is a more appropriate, caring and responsible response to a request for benzodiazepines than an outright refusal. It will ensure that the individual will not suffer the possibility of withdrawal seizures as well as diminishing the possibility of ever-increasing demands on other healthcare providers further down the track as the individual becomes ever more desperate in their attempt to obtain such drugs.

Martyn Lloyd-Jones
Director, Drug and Alcohol Services
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Dr H. Wilce, the author of the article, comments:

I am not sure what factual inaccuracies Dr Lloyd-Jones is referring to as nowhere in the article does it state that the removal of temazepam gelcaps has led to a complete lack of this drug in Australia. The article states that front-line services are seeing a reduction in problems since the removal of gelcaps from the market. Unfortunately we will continue to see problems with this medication until stockpiles have been depleted. Gelcaps may also continue to be available via the internet or via overseas imports. It is possible that we will continue to see the physical sequelae of past injecting misuse for years to come.

Dr Lloyd-Jones has misinterpreted the advice that 'doctors have a duty of care not to prescribe benzodiazepines'. This statement was made in the context of coercion. While the article does not attempt to discuss the vexed issue of benzodiazepine reduction regimens, there is little good evidence that such regimens are effective and in fact they may be associated with an escalation rather than reduction in use. This problem is one that is likely to continue while the ongoing supply of benzodiazepines is difficult to control. However, it is clear that these regimens have the greatest chance of success if there is an effective therapeutic relationship between the doctor and patient. This is very unlikely to be the case if the doctor is coerced into providing scripts for benzodiazepines.

Inside the isomers: the tale of chiral switches

Editor, – Reference is made to the article 'Inside the isomers: the tale of chiral switches' (Aust Prescr 2004;27:47–9). In this article it is asserted that 'in overdose, there is a concern about the potential for sudden death, possibly related to QT prolongation due to a secondary metabolite formed from (R)-citalopram. (S)-citalopram (escitalopram) was therefore developed with the aim of a better harm:benefit ratio compared to (R)-citalopram'.

Significantly, the authors of this article have not referenced any of the statements in this paragraph. I would like to advise that the statement regarding the propensity of a metabolite of the (R)-enantiomer of citalopram to cause sudden death as a result of QT prolongation is completely unfounded.

A survey has investigated the effects of citalopram, at therapeutic doses, on ECG parameters.[1] The authors concluded that citalopram has no significant effects on PQ, QRS or QTc intervals, during short- or long-term treatment. Nor were there any deaths or clinically significant arrhythmias reported among all pure citalopram intoxications (n=108 with doses up to 5.2 g) over a two-year period in Sweden.[2]

Since there is absolutely no basis to the assertion that a metabolite of (R)-citalopram is associated with sudden death as a result of QT prolongation, the reason given for the development of (S)-citalopram is also purely speculative and quite simply, untrue.

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Associate Professor Andrew Somogyi, one of the authors of the article, comments:

There is evidence that the didesmethyl metabolite of (R)-citalopram prolongs the QT interval in animals and therefore might contribute to those rare instances of cardiac arrhythmia after very high doses of citalopram in a suicidal setting.[1,2,3,4]

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4. Meuleman C, Jourdain P, Bellorini M, Sadeg N, Loiret J, Guillard N, et al. [Citalopram and torsades de pointes. A case report] [French]. Arch Mal Coeur Vaiss 2001;94:1021-4.

Pharmaceutical free trade – will it be fair?

Editor, – What has happened to your HONcode? Your editorial (Aust Prescr 2004;27:54–5) on the US Free Trade Agreement fails to meet the requirement of honest informed reliable advice that your magazine purports to hold dear. Your editorial is not only a farrago of unsubstantiated and false claims on what is a contentious political issue, it reveals an abysmal lack of knowledge of the agreement itself. It is insulting to your professional colleagues in the Department of Health whose fully-informed public statements correcting the falsehoods you have regurgitated have been ignored by you – if you ever bothered to inform yourself of them.

It is now possible for you to discover reality, and inform your readers of it, by reading the 18 recommendations in the recent report on the FTA of the Joint Standing Committee on Treaties, chaired by your professional colleague, Dr Andrew Southcott MP. All but one of these 18 were supported by the three Labor members of the committee; this report demolishes your stand.

As a former federal Shadow Minister for Health and subsequently Consul-General in New York, I have closely studied the US Free Trade Agreement. I challenge you to point to any section of the agreement that supports the thrust of your claims. You appear to have confused the terms of the agreement which are clear and self-evident with the inevitable uncertainty of the exact nature of the Australian government's measures to implement it – measures that are entirely up to an elected Australian government and subject to the democratic political process – and which could be introduced whether there was an FTA or not. The US has no power to require action otherwise than in the strict wording of the agreement and attached side letters, reflecting the same right we have at their end. In no instance does that right establish a US position that justifies your scare-mongering.

This is how your nonsensical claims fall down:

- There is nothing in the agreement that empowers the Medicines Working Group, which has a specified advisory-only role (giving us access to the world's most dynamic innovative pharmaceutical knowledge) to determine 'details of the agreement'. You are just plain wrong in claiming it 'probably' will do so; you cannot provide any evidence to support this.
- It does not 'remain to be seen' whether an Australian decision not to approve a drug or not to list it on the PBS 'could be construed as a breach' of the FTA; the agreement guarantees the basic architecture of the PBS and you cannot point to any section of it that leaves this issue otherwise than totally in the hands of the Australian government; even the nature of the independent review process for PBS listing is entirely up to the Australian government.
- There is nothing in the agreement that requires or empowers the independent review process to overturn a listing decision; the Minister remains the only instrument of approval and can only act on the recommendation of the PBAC. The FTA does nothing to change this and the government has already said it has no intention to do so.
- No trade deal can dictate how much the Australian government spends on medicines or what they cost and you cannot point to anything in the US FTA that has the capacity to do so.
- The FTA specifies that any marketing and advertising to consumers must comply with Australian laws (such as prohibiting industry advertising direct to consumers) and there is nothing in the agreement requiring the government to change them.
- The agreement reinforces Australia's existing intellectual property protection of pharmaceuticals, ensuring that generics cannot enter the market until a patent has expired. What on earth is your objection to that – or do you favour us joining the patent-pirates and getting excluded from western commerce?
- Most rational people think greater transparency of governmental agency decisions (and a formal appeal mechanism) represents a more democratic approach. Why don't you?

Your editorial demeans you and your journal. Like most quack medicines, it should be marked 'harmful if swallowed'.

Michael Baume
Mosman, NSW

The Editorial Executive Committee comments:

The controversy surrounding the editorial is ironic, as the Editorial Executive Committee's intention was to bring to readers' attention some of the issues that have been raised concerning the pharmaceutical part of the Free Trade Agreement. As pharmaceutical policy influences prescribing it was appropriate for *Australian Prescriber* to comment.

While the wording of parts of the agreement seemed ambiguous this may have been to allow flexibility in implementing the agreement.[1] Although the Editorial Executive Committee is grateful for Mr Baume's insight into the arcane language of international treaties, some questions remain. They will only be answered with the passage of time. It is therefore appropriate that the first of the 23 recommendations made by the Joint Standing Committee on Treaties was to have a review of the impact of the agreement after five years.

Reference

1. The Australia-United States Free Trade Agreement. Report 61. Canberra: Commonwealth of Australia; 2004. http://www.aph.gov.au/house/committee/jsct/usafta/report/fullreport.pdf [cited 2004 Sept 6]

New drug – teriparatide

Editor, – Your recent comment on our product Fortéo (teriparatide) (Aust Prescr 2004;27:22–3) was an informative and well-rounded review, however, I would like to address a couple of points.

Your final paragraph states: 'Until more data are available teriparatide should only be prescribed for patients who have a high risk of fractures and cannot take other treatments for osteoporosis'.

In fact, the product information approved by the Therapeutic Goods Administration for the use of teriparatide states:

> Fortéo is indicated for the treatment of osteoporosis in postmenopausal women and the treatment of primary osteoporosis in men when other agents are considered unsuitable and when there is a high risk of fractures.

While this may seem like a small change in wording, it is actually a significant consideration for those prescribing Fortéo.

A published paper helps to place the rat osteosarcoma issue in context. It concluded that: 'in adult humans … it is unlikely that the risk of bone neoplasia would be increased by daily treatment with PTH (1-34) for a relatively small fraction of the normal life span'.[1]

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Reference

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MedSafety – www.medsafety.net

Editor, – Medication errors occur regularly in Australian and overseas health systems[1,2,3,4], and their incidence may be increasing.[5] There is therefore a need to improve medication use and to educate health professionals in the rational and safe use of medicinal drugs.[3] The recent rapid development in safety and quality improvement in overseas and Australian healthcare systems has made it difficult for undergraduate courses to adapt quickly enough and incorporate appropriate content. It is also difficult for health professionals working at the coalface to keep up to date with the latest developments.

The Tasmanian Schools of Pharmacy and Medicine have produced an on-line learning resource for medication error prevention. Modules have been developed around actual clinical problems or cases involving a medication error. There are supporting electronic resources so that the modules may be used for self-directed learning, or as a basis for teacher-led discussion on medication safety issues.

There are currently six modules:

- how to disclose errors to patients
- patient communication skills
- system improvement methods
- the role of information technology in reducing error
- intravenous therapy and error
- high-risk medications.

Each module takes approximately one hour to complete. In addition there are topics covering incidence of medication error, causes, root cause analysis, the 'systems approach' to understanding error, and many case examples of medication error with suggestions for prevention. The site also features a full text search, extensive links to on-line medication safety information, quizzes and a discussion forum. A facility to report personal experiences of medication incidents is also available.

The web site should be of interest to hospitals and healthcare institutions, within and outside Australia. Flyers for doctors, nurses and pharmacists have been developed to introduce the first module. These are available on-line at www.medsafety.net

Professor Gregory Peterson
Professor of Pharmacy, Tasmanian School of Pharmacy

Mr James Reeve
PhD candidate, Tasmanian School of Pharmacy

Associate Professor Janet Vial
Associate Head, Tasmanian School of Medicine
University of Tasmania
Hobart

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5. Lesar TS, Lomaestro BM, Pohl H. Medication-prescribing errors in a teaching hospital. A 9-year experience. Arch Intern Med 1997;157:1569-76.

Glucosamine for osteoarthritis of the knee

Editor, –The article on glucosamine (Aust Prescr 2004;27:61–3) understated a couple of points. Firstly, that 'both trials were sponsored by the Rotta Research Laboratorium and used that company's formulation of glucosamine sulphate'. Surely this implies some considerable bias. Secondly, because no glucosamine product in Australia has an AUST R rating by the Therapeutic Goods Administration, does this not also imply that the products in Australia may be subject to qualitative and quantitative variations to the product studied and therefore may not produce the same or any therapeutic effect? This point is implied by the author who states 'this formulation may differ from those available in Australia'.

While glucosamine may have a unique mechanism of action, is this not thrown into doubt by the 'poor correlation between structural and symptomatic responses'? Regardless, where are the well-designed comparative trials necessary to show that glucosamine is better than standard therapy? Previous comparative trials were poorly designed, of short duration and involved small numbers.

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Associate Professor G. McColl, the author of the article, comments:

Both of the major randomised controlled studies were sponsored by the Rotta Research Laboratorium and this may have introduced bias into the studies. This notion, of course, would also have to apply to the majority of medications available on the Pharmaceutical Benefits Scheme, as the studies supporting their listing would also have been supported by their manufacturers.

The issue of 'qualitative and quantitative' variation in glucosamine products available in Australia is a significant one. In the purest view of evidence-based medicine we should only use the preparation that was tested in the study. As the Rotta glucosamine product is difficult to access in Australia this creates a problem. In practical terms, however, it is reasonable to extrapolate the data from these studies to 'reputable' glucosamine products in Australia, particularly if a therapeutic trial of three months is recommended.

No high quality trial has compared routine therapies such as paracetamol or non-steroidal anti-inflammatory drugs to glucosamine. I agree that this is a deficiency and will hopefully be addressed by a current study sponsored by the National Institutes of Health in the USA.

Book review

Australian Medicines Handbook 2004

Adelaide: Australian Medicines Handbook; 2004.

788 pages. Price $152; students $99; plus postage

Tracy Soh, General practitioner, Canberra

The Australian Medicines Handbook was developed jointly by the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, the Pharmaceutical Society of Australia and the Royal Australian College of General Practitioners. It was designed as a national formulary that would provide concise, up-to-date, independent drug information to facilitate better prescribing and dispensing practice. The contributors to the handbook represent all disciplines and all parts of Australia.

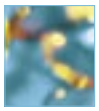
The latest edition is a well presented and simple to use, practical formulary of most of the drugs currently marketed in Australia. As with previous editions, the information is well researched and reflects current and reliable sources. The new edition provides several new sections including HIV, hepatitis B, hepatitis C, tinnitus, macular degeneration, functional dyspepsia and prostatitis.

The handbook is organised broadly according to organ systems and clinical presentations. Each section provides an overview of the clinical problem and the general considerations involved in treatment, including a brief summary of the available classes of medication. It subsequently presents a monograph of each class of medication which includes comparative information between medications within that class and specific practice points. The handbook then details the key features particular to each of the drugs within that class including specific indications and dosage.

The presentation of the information makes the handbook a useful tool for quick reference during clinical practice. The logic and consistency of the format of each section makes the relevant information easy to find and quick to read.

The Preface suggests that the handbook may be used as a learning tool for students – the clinical approach would provide a good structure for students to base their learning upon. However, the information has been well summarised and medical students are likely to need more detailed references.

I found this book to be a useful and practical addition to the available information resources for general practice. Its compact size makes it portable enough to carry to home visits and on the ward. It is a well designed tool to support the practice of evidence-based medicine.



Withdrawal of antiepileptic drugs in seizure-free adults

Christine J. Kilpatrick, Associate Professor, Departments of Neurology and Medicine, Royal Melbourne Hospital, University of Melbourne, Melbourne

Summary

Whether or not antiepileptic drugs should be withdrawn after a patient has been seizure-free for several years is a complex issue. Some studies suggest the overall risk of seizure recurrence is approximately 30% if treatment is withdrawn. Clinical factors associated with a greater chance of successful withdrawal include childhood onset epilepsy, a normal electroencephalogram prior to drug withdrawal, being seizure-free for more than two years, monotherapy, normal neuroimaging and normal intellect. If antiepileptic drugs are withdrawn, they should be withdrawn slowly, ideally over several months.

Key word: epilepsy.

(Aust Prescr 2004;27:114–7)

Introduction

Longitudinal and community-based studies suggest that antiepileptic drugs will result in approximately 70% of adults diagnosed with epilepsy becoming seizure-free.[1] Whether or not antiepileptic drugs should be withdrawn after a patient has been seizure-free for several years is a complex issue. Discontinuing antiepileptic drugs implies the seizure tendency is no longer present. A number of clinical factors can help to predict the risk of seizure recurrence. This can assist when making a decision as to whether or not to discontinue antiepileptic drug treatment. The decision must include weighing up the harms and benefits of continuing and discontinuing therapy, and the risk and consequences of seizure recurrence.

Importance of remaining seizure-free

For many adults a recurrence of their seizures would have significant implications. Seizures impact on the ability to drive, possibly the ability to work. For many patients there is a significant negative impact on their psychological state and well-being. Seizures may also be associated with injury, and sudden unexpected death may occur as a direct result of seizures, particularly tonic-clonic seizures. Although the risk of seizure recurrence may be low, some patients choose to remain on treatment as they feel more secure taking an antiepileptic drug.

Reasons for discontinuing antiepileptic drugs

Patients may want to stop their treatment because antiepileptic drugs are commonly associated with mild adverse effects and have the potential for serious adverse effects. The risk of teratogenicity in women of childbearing years may prompt drug withdrawal earlier than might otherwise occur, but the risk of seizures recurring in pregnancy needs to be balanced against the possible harm of continuing treatment. Other problems include interactions with other drugs, for example the interaction between carbamazepine (liver enzyme inducer) and the oral contraceptive pill. For some patients, taking daily medication is a constant reminder of their chronic condition and has a negative impact on their well-being.

Relapse following withdrawal of antiepileptic drugs

A meta-analysis of 25 studies estimated the overall rate of seizure relapse following the withdrawal of antiepileptic drugs.[2] After discontinuing therapy 25% of patients relapsed within one year and 29% by two years. A randomised study of continued treatment versus slow withdrawal in 1013 patients who had been seizure-free for at least two years, reported that 78% of patients who continued treatment and 59% of those who stopped treatment were still seizure-free two years later.[3] These figures are overall estimates only and several factors need to be considered in individual patients when determining risk of relapse.

Factors influencing relapse

A number of studies have assessed clinical factors which might predict seizure recurrence following antiepileptic drug withdrawal (see Table 1).

Age of onset of epilepsy

The risk of seizure recurrence following drug withdrawal is higher in adolescents than children.[2,3] This probably reflects the prognosis of age-related syndromes. Childhood absence epilepsy and benign rolandic epilepsy have a good prognosis for antiepileptic drug withdrawal while juvenile myoclonic epilepsy is more likely to recur.

Seizure type and epilepsy syndrome

Epilepsy is not one disease, but comprises a number of syndromes each with a different prognosis (see Box 1). Juvenile myoclonic epilepsy, probably the commonest type of primary

Table 1

Factors predicting seizure recurrence following antiepileptic drug withdrawal

Associated with increased risk	Associated with reduced risk
Juvenile myoclonic epilepsy	Childhood absence epilepsy
Partial seizures with secondary generalisation	Benign rolandic epilepsy
Abnormal electroencephalogram	Normal electroencephalogram
Epileptogenic lesion on neuroimaging	Normal neuroimaging
	Onset in childhood
	No seizures for more than two years prior to antiepileptic drug withdrawal
	Monotherapy
	No seizures following introduction of antiepileptic drug
	Normal intellect

Box 1

Features of common epilepsy syndromes

Childhood absence epilepsy

This is a form of primary generalised epilepsy which has a genetic predisposition and begins in childhood. It is characterised by frequent absence seizures, however it is estimated that 50% of patients will have a generalised tonic-clonic seizure. Seizures usually respond well to treatment and the condition often remits in adult life.

Juvenile myoclonic epilepsy

This is a common form of primary generalised epilepsy which usually begins in adolescence. It is characterised by tonic-clonic seizures and myoclonic jerks. Seizures may be precipitated by sleep deprivation and excess alcohol. The condition responds well to valproate, but there is a high chance of recurrence after drug withdrawal.

Benign rolandic epilepsy

This is a common form of idiopathic partial epilepsy which occurs in otherwise normal children and usually remits in adolescence. The seizures are often sleep-related and characterised by orofacial or oropharyngeal involvement which frequently evolve into secondarily generalised tonic-clonic seizures. The interictal EEG demonstrates a spike focus in the centrotemporal region. Seizures usually respond to carbamazepine.

Partial epilepsy (focal epilepsy)

The most common form is temporal lobe epilepsy characterised by frequent complex partial seizures and occasional secondarily generalised tonic-clonic seizures. Partial epilepsy is often resistant to antiepileptic drug treatment.

generalised epilepsy in adults, has a high risk of seizure recurrence on drug withdrawal.

Studies assessing seizure type report myoclonic seizures, tonic-clonic seizures and partial seizures as associated with an increased risk of seizure recurrence following antiepileptic drug withdrawal.[3] One study reported 63% of patients with partial seizures relapsed on drug withdrawal.[4] Remote symptomatic seizures (defined as seizures occurring in patients with a prior neurologic insult such as head injury, stroke or history of intellectual disability) are associated with a high risk of seizure relapse following discontinuation of therapy.[2]

Seizure frequency, timing and antiepileptic drug usage

The UK Medical Research Council (MRC) trial found that an increased risk of seizure recurrence was associated with:

- a shorter duration of seizure-free period prior to study entry
- seizures after starting antiepileptic drug treatment
- patients taking multiple antiepileptic drugs at the time of study entry.[3]

Electroencephalogram

There is limited evidence to support the assumption that an interictal electroencephalogram (EEG) is predictive of seizure recurrence following antiepileptic drug withdrawal. The MRC study found that patients with only tonic-clonic seizures and generalised spike wave on EEG had a higher recurrence rate. Patients with tonic-clonic seizures and focal features or normal EEG had no increased risk of recurrence.[3]

The meta-analysis of 25 studies noted that an abnormal EEG was associated with an increased risk of recurrence, but there was considerable variability in the results and in most studies the epileptiform activity was not differentiated.[2] In some studies patients with an abnormal EEG, particularly the presence of epileptiform activity, were excluded, biasing the results.

Another study assessed the role of the EEG in predicting seizure recurrence in partial epilepsies. It found that although the interictal EEG at time of antiepileptic drug withdrawal did not predict recurrence, a worsening of the EEG after withdrawal was predictive of seizure recurrence.[4]

Role of video-EEG monitoring

The value of video-EEG monitoring in assessing the chance of remaining seizure-free following antiepileptic drug withdrawal has not been systematically studied. However, it is not uncommon for patients with generalised epilepsy to report no seizures and yet continuous monitoring reveals frequent sub-clinical seizure activity.

Neuroimaging

Although studies are lacking, it seems likely that patients with an epileptogenic lesion on computed tomography or magnetic resonance imaging of the brain are more likely to have recurrences on drug withdrawal. This is consistent with the data on recurrences in a population of patients presenting with their first seizure – patients with an epileptogenic lesion on neuroimaging have a higher risk of seizure recurrence.[5]

Patients need to be advised there is no guarantee they will remain seizure-free

Provoked seizure

It is likely that provoked seizures (such as seizures occurring with excess alcohol, sleep deprivation or induced by drugs) are less likely to recur if these factors are avoided.

Certainty of diagnosis

Occasionally patients are commenced on an antiepileptic drug and in retrospect there is some doubt about the diagnosis of epilepsy. In these patients drug withdrawal is a reasonable option.

Withdrawal after surgery for temporal lobe epilepsy

A reduction in antiepileptic drug therapy following successful surgery on the temporal lobe should be considered. However, the timing of withdrawal and whether or not all medications should be withdrawn is controversial. Many experts would agree that treatment should continue for two years. If the patient is then seizure-free and on several drugs, a reduction in medication could be commenced, but at least one antiepileptic drug should be continued for the long term.[6]

When to start antiepileptic drug withdrawal

No randomised-controlled trials have studied how long patients should be seizure-free before withdrawing their treatment can be considered. Studies in children suggest two years, but the MRC study of adults suggests a longer period of at least three years is desirable.[3]

Precautions during and after antiepileptic drug withdrawal

Patients need to be advised there is no guarantee they will remain seizure-free. The risk of relapse is greatest during the first 12 months.

'Assessing fitness to drive', produced by Austroads and the National Road Transport Commission, advises that the patient 'should not drive for the full period of withdrawal and for three months thereafter' unless withdrawal is advised by an experienced consultant on the basis that the risk of seizure recurrence is low.[7] Safety advice such as not swimming alone, avoiding heights and having a shower rather than a bath, should be reinforced.

How to withdraw antiepileptic drugs

Withdrawal should be gradual and take place over approximately six months. Rapid withdrawal, particularly of barbiturates and benzodiazepines, can precipitate seizures. The withdrawal protocol for adults in the MRC study decreased doses every four weeks (see Box 2).[3] This approach may need to be modified in patients on low doses of antiepileptic drugs. For patients taking multiple drugs, the withdrawal should be sequential.[3]

Box 2

Suggested protocol for antiepileptic drug withdrawal

The following decrements are recommended every four weeks:

phenobarbitone	30 mg
phenytoin	50 mg
carbamazepine	100 mg
valproate	200 mg
primidone	125 mg

Management of seizure recurrence

If seizures recur the previous medication that controlled seizures should be restarted.

Conclusion

For adults who are seizure-free, there are limited data to help them make an informed decision regarding drug withdrawal. The decision is an individual one and in general should be patient driven, as it is very important that the patient supports the decision, is aware that seizures may recur and understands the associated risks.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 133)

1. Seizures which began after a head injury rarely recur after antiepileptic drugs are stopped.
2. Patients with epilepsy who stop their medication should not drive for three months after their treatment is withdrawn.

Book review

Medicines out of control? Antidepressants and the conspiracy of goodwill. Medawar C, Hardon A.

Amsterdam: Aksant Academic Press; 2004.

258 pages. Price approx $64*

Professor Robert Moulds, Professor of Medicine, Fiji School of Medicine, Suva, Fiji, and Chairman, Australian Prescriber Editorial Executive Committee

This book is not for the faint-hearted. It is in small type, heavily referenced (30 pages of references), and has extensive footnotes (on some pages the footnotes occupy more space than the text). However, as a chronicle of the complexity of the development and use of drugs in modern medicine it makes fascinating reading.

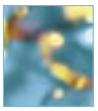
The authors use the example of the selective serotonin reuptake inhibitors (SSRIs) and the slow percolation of knowledge about their adverse effects to develop the overall thesis that we are all part of a 'conspiracy of goodwill' regarding new drugs. They contend that this conspiracy is fostered by the pharmaceutical industry for its own financial purposes. The book also contends that the industry is aided by academia and the medical profession, not only by their endless pursuit of panaceas and naïve faith that new drugs must be better than old ones, but also by their reluctance to tackle the conflicts of interest that arise in acting as intermediaries between the industry and patients.

Despite its focus on the SSRIs, the book is wide ranging in its scope – and criticism. It puts the SSRIs into a historical perspective, arguing that it was naïve to think that the SSRIs would prove fundamentally different from their antecedents – alcohol, opioids, bromides, barbiturates and benzodiazepines. Along the way, the book strays into discussion of other aspects of modern drug use. These include the disease creation and awareness industry, the dangers of direct-to-consumer advertising and the power of changing terminology (for example, withdrawal syndromes becoming discontinuation syndromes).

The book is particularly critical of the reliance of regulatory systems on voluntary reporting of adverse drug reactions. It contends that for years it was clear in the voluntary reports that there were extensive problems of withdrawal reactions to SSRIs. These reactions went unrecognised because of the rigid classification system used by the regulators and their reluctance to revisit their initial evaluation that the drugs had few adverse effects. They (and others, including academia) fell for the 'NERO' argument – no evidence of risk equals evidence of no risk.

There are some strong streaks of 'wisdom of hindsight', and even paranoia, in this book, but it is powerful and well argued. It should be read by everyone interested in the sociology of the use of pharmaceuticals in modern medicine.

* ISBN 9052601348. Available from DA Information Services (03) 9210 7717 or e-mail service@dadirect.com



Diabetes and antipsychotic drugs

Joseph Proietto, Sir Edward Dunlop Medical Research Foundation Professor of Medicine, University of Melbourne and Department of Medicine, Heidelberg Repatriation Hospital, Austin Health, Melbourne

Summary

There is an increased risk of diabetes in patients with schizophrenia and this risk is elevated by some antipsychotic medications. The risk is greater with the atypical drugs clozapine and olanzapine and the low potency conventional antipsychotics than with risperidone or high potency conventional drugs. While weight gain may be a mechanism for the development of diabetes, a direct effect of these drugs on insulin action in muscle may also be an important contributor. Patients with major psychosis should be managed in the same way as other patients with diabetes, but difficulties in complying with diet, exercise and taking medication should be kept in mind. Treating cardiovascular risk factors is important.

Key words: schizophrenia, obesity, insulin resistance.

(Aust Prescr 2004;27:118–9)

Introduction

An impaired action of insulin (insulin resistance) in patients with schizophrenia was reported over 55 years ago and later confirmed in Australia.[1] The prevalence of diabetes in patients with schizophrenia was found to be higher than in the general population even before the widespread use of antipsychotic medication. The mechanisms underlying the relationship between schizophrenia and diabetes remain unknown.

Antipsychotic drugs and diabetes

It is now clear that some antipsychotic medications increase the risk of diabetes in patients with schizophrenia. Rarely, this may present as diabetic ketoacidosis. The atypical medications (Table 1) have become widely used because of their lower rate of extrapyramidal adverse effects compared to older classes of medication such as the phenothiazines and the butyrophenones. However, while some of the atypical drugs are better tolerated, they also increase the incidence of diabetes. In patients younger than 40 years of age, the odds ratio for developing diabetes is 1.63 if they are taking an atypical antipsychotic.[2]

Table 1

Classification of antipsychotic medications available in Australia

Atypical	Low potency* conventional	High potency conventional
amisulpride	chlorpromazine	droperidol
aripiprazole	pericyazine	flupenthixol
clozapine	thioridazine	fluphenazine
olanzapine		haloperidol
quetiapine		trifluoperazine
risperidone		

Not all antipsychotics increase the risk of diabetes to the same extent.[3] In a survey of two large US health plans, the risk of developing diabetes over a year was found to be higher with olanzapine and 'low potency'* conventional antipsychotics, but not with risperidone or 'high potency' conventional drugs (Table 2).[4] In one prospective study 36.6% of patients treated with clozapine developed diabetes over a five-year period.[5]

Mechanism of antipsychotic-induced diabetes

The mechanisms responsible for the elevated risk of diabetes associated with some antipsychotics are not fully understood. It is known that the atypical antipsychotics and some of the low potency conventional antipsychotics cause weight gain[6] and that, at least for olanzapine and clozapine, the magnitude of this weight gain correlates with the magnitude of the therapeutic response.[7] The weight gain in response to antipsychotic medication is also variable. Clozapine and olanzapine cause the greatest gain, risperidone and quetiapine moderate gain, and aripiprazole and amisulpride the least gain.[8] However, at present insufficient information is available about some of the newer drugs to know what their weight gain and diabetogenic potential will prove to be with more widespread use.

Obesity can precipitate diabetes in susceptible people so weight gain is one mechanism for the increased incidence in diabetes. However, the fact that hyperglycaemia improves quickly after stopping the antipsychotic medication and that diabetes can appear in some patients who do not put on weight, suggests that other mechanisms must be involved. A prospective study of 82 patients treated with clozapine also found that the risk of developing diabetes was independent of weight gain.[5]

* Low potency is defined as 'equivalent or less potent than chlorpromazine'.[10]

Table 2

Risk of developing diabetes with antipsychotic medication [4]

Drug	Number of patients	12-month odds ratio (95% CI)
Untreated	2644	1.0
Low potency* conventional	302	4.972 (CI 1.967–12.612)†
High potency conventional	785	1.945 (CI 0.794–4.786)
Olanzapine	656	4.289 (CI 2.102–8.827)†
Risperidone	849	1.024 (CI 0.351–3.015)

CI confidence interval

† significant ($p < 0.05$) compared to untreated patients

Diabetes related to antipsychotic medication is associated with high insulin concentrations, so it seems that these drugs may aggravate the insulin resistance that already exists in patients with schizophrenia. While some of this is no doubt related to weight gain, it has also been shown that antipsychotics inhibit glucose transport into muscle. There is a strong correlation between the ability of these drugs to inhibit glucose transport *in vitro* and their capacity to induce hyperglycaemia *in vivo*.[9]

Management of diabetes in patients with schizophrenia

What needs to be taken into account when treating someone coping with the dual problems of schizophrenia and diabetes?

- Be alert to the increased risk of diabetes in patients with schizophrenia and the fact that some antipsychotic medications increase the risk. Check the patients' fasting blood glucose and monitor their weight.
- Monitor blood glucose more frequently in patients with known diabetes who commence antipsychotic medication.
- Advise about diet and exercise, but keep in mind that compliance may be particularly difficult for patients with schizophrenia.
- When prescribing hypoglycaemic drugs, try to use once-daily medication so that treatment can be more easily supervised. While metformin (the preferred first-line therapy) should be given twice daily there are now two sulfonylureas that are available as once daily medication (modified-release gliclazide and glimepiride).
- There is an increase in cardiovascular mortality in patients with schizophrenia so remember to regularly assess and vigorously treat cardiovascular risk factors such as dyslipidaemia and hypertension.
- In psychotic patients who have a family history of diabetes or in those who are from an ethnic group with a high prevalence of diabetes (all non-Europeans), try to use an antipsychotic that has less potential for precipitating diabetes, such as risperidone or one of the high potency conventional drugs (Table 2).

The management of diabetes in patients with a major psychiatric illness is problematic. Weight loss or prevention of weight gain should always be attempted because of the known benefits to other comorbidities associated with obesity. However, even if successful, this approach alone may not reduce the risk of developing or worsening diabetes.

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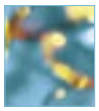
Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 133)

3. Patients with schizophrenia have an increased risk of cardiovascular disease.
4. Atypical antipsychotic drugs such as clozapine do not increase the risk of diabetes in patients with schizophrenia.



Early management of acute stroke

Richard I. Lindley, Moran Foundation for Older Australians Professor of Geriatric Medicine, Western Clinical School, University of Sydney; and Peter B. Landau, Senior Staff Specialist, Director, Stroke Unit, Department of Geriatric Medicine, Westmead Hospital, Westmead, New South Wales

Summary

Most patients with a stroke or a transient ischaemic attack require urgent imaging to determine the cause of their symptoms and to guide treatment. Stroke unit care, where available, can facilitate effective use of acute treatments (aspirin and thrombolytic therapy), good multidisciplinary care and early secondary prevention. Implementation of these strategies will have a significant public health impact.

Key words: aspirin, thrombolytic therapy, transient ischaemic attack.

(Aust Prescr 2004;27:120–3)

Introduction

In Australia nearly 50 000 people have a stroke each year. A third will die within a year, and a third are left with significant disability. The cost is considerable, whether measured in dollars (5% of the total health budget), social care or by the impact on the families and carers. In the past decade there has been a major change in how stroke is perceived and managed, especially in the acute phase.

Is it a stroke or TIA?

There is now an interesting problem with the nomenclature of stroke and transient ischaemic attack (TIA). By definition (see box) a stroke either leads to death or is still symptomatic 24 hours later, while a TIA resolves to leave no symptoms at 24 hours. These definitions have been essential for epidemiological studies and they are useful to remind clinicians of the differential diagnoses (Table 1).

Stroke

A clinical syndrome characterised by rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and those with subarachnoid haemorrhage), loss of cerebral function, with symptoms lasting more than 24 hours, or leading to death, with no apparent cause other than that of vascular origin.[1]

Transient ischaemic attack

A clinical syndrome characterised by an acute loss of focal cerebral or monocular function with symptoms lasting less than 24 hours and which is thought to be due to inadequate cerebral or ocular blood supply as a result of low blood flow, arterial thrombosis or embolism associated with diseases of the arteries, heart or blood.[2]

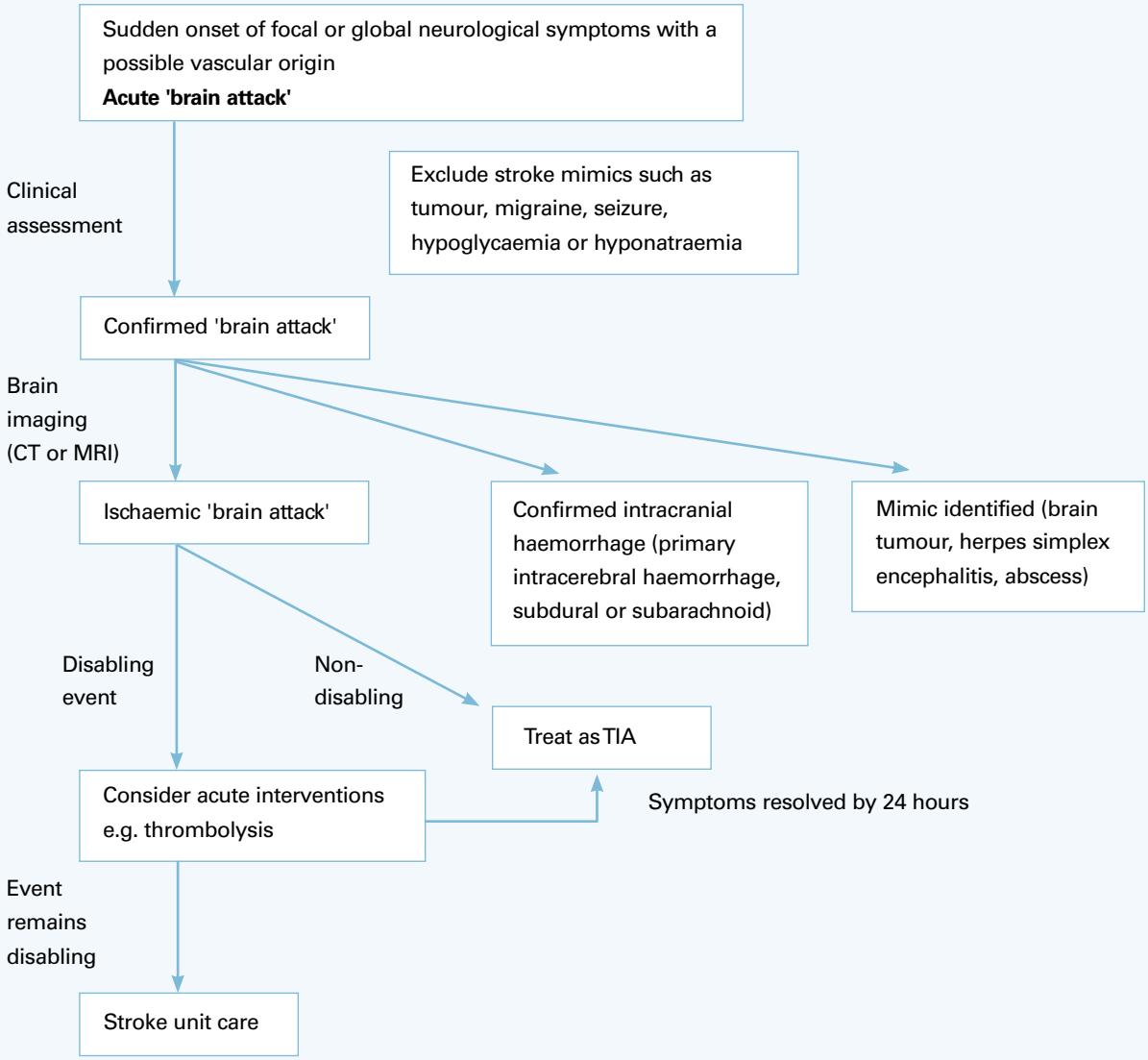
Table 1

Important or common mimics of 'brain attack'

Mimics of transient ischaemic attacks (shorter attacks)	Mimics of stroke (longer attacks)
Migraine	Brain tumour and other space-occupying lesions
Partial seizures	Todd's paresis
Hypoglycaemia	Previous stroke and new non-stroke illness
Brain tumour and other space-occupying lesions	Bell's palsy or other mononeuropathy
Benign paroxysmal positional vertigo	Multiple sclerosis
Hyperventilation	Vestibular neuronitis
Panic attacks	Delirium
Transient global amnesia	Hepatic encephalopathy
Medically unexplained (e.g. somatisation)	Hyponatraemia
	Head injury
	Medically unexplained (e.g. somatisation)

Fig. 1

A flow diagram for the assessment of patients with suspected stroke or transient ischaemic attack



The definitions obscure the fact that TIA and ischaemic stroke are actually the same disease. New interventions for some strokes will change the natural history, resulting in a TIA (that is, symptoms resolved by 24 hours). In order to increase the priority given to patients with a suspected stroke it has been suggested that all TIAs and strokes should be called 'acute brain attacks' in the first 24 hours. The final diagnosis of stroke or TIA can be made when the situation is clearer 24 hours later (Fig. 1).[3]

No matter what we call the attack, the immediate medical priority is to distinguish attacks that are vascular from the numerous non-vascular causes. The commonest mimics of stroke are seizure (and the resulting Todd's paresis), migraine (the presence of positive symptoms is often a clue) and brain tumour. A variety of miscellaneous neurological and other conditions can also be misdiagnosed as strokes. Diagnostic uncertainty is common, for example, about a third of patients referred to a TIA/stroke clinic have non-vascular disease.[4]

What is the cause of the 'brain attack'?

When clinicians ask the right question, a logical process of investigations should follow. A young man presenting with a stroke while swimming needs cardiac imaging to exclude a right-to-left shunt (was this a paradoxical embolism from a patent foramen ovale?) and carotid imaging (was this a carotid dissection?). An 80-year-old with extensive vascular disease may require an ECG, carotid duplex scan and transthoracic echocardiogram in addition to computed tomography (CT) and the usual blood tests. A patient with a fever needs blood cultures to exclude bacterial endocarditis.

Imaging and pathology of the 'brain attack'

Computed tomography is the most reliable way to identify intracranial haemorrhage as the cause of the 'brain attack'. Blood shows up immediately as a high attenuation lesion on CT and remains visible for the next four to seven days. After this time

CT can be unreliable as the blood becomes isodense and then the lesion appears as a low attenuation lesion mimicking an ischaemic area.

Magnetic resonance imaging (MRI) can be used if patients present late, as haemosiderin from a haemorrhagic stroke can be identified by special MRI sequences (such as gradient echo T2 or Flash 2D sequences). However, old blood due to early haemorrhagic transformation of a cerebral infarction will also be identified by this technology.

The key point is that a CT scan is needed as soon as possible to identify the pathology. This is also the most cost-effective strategy. Early pathological diagnosis helps determine the investigations required, for example a carotid duplex scan is not required for a stroke due to primary intracerebral haemorrhage.

A CT scan for a straightforward single TIA is not always required. If the 'brain attack' has completely resolved within hours, it is a definite TIA; a haemorrhage is very unlikely (less than 1% chance) so the event can be considered ischaemic. While some TIAs are caused by space-occupying lesions, the patients generally have unusual symptoms or multiple attacks.

Who to admit?

Admission to hospital depends on numerous factors:

- the need for CT or other investigations
- comorbidity and the need for assistance with personal care
- the presence of new disability
- the suspicion of a serious underlying problem such as bacterial endocarditis.

Most experts recommend admission to a stroke unit but there may be circumstances when this would not be in the patient's best interest. For example, a demented patient with a history of a recent gastrointestinal bleed, living in a nursing home, may be better off staying in the nursing home, rather than having the unsettling experience of hospital admission. The patient is ineligible for any antithrombotic treatment so a CT scan would be of little help.

General management

There is now overwhelming evidence that care in a stroke unit gives the patient the greatest chance of independent survival. For every 100 patients treated there will be 40 independent survivors with general non-specialist care and 46 independent survivors in a stroke unit. This gain (six more independent survivors) is two to three times the treatment effect of thrombolysis for acute myocardial infarction.[5]

The benefit is due to the cumulative effect of numerous small interventions performed by an interested specialised multi-disciplinary team of nurses, allied health staff and doctors, who are enthusiastic, well trained and participate in continuing professional development. These interventions include appropriate hydration, very early mobilisation, thorough investigation of the cause of stroke, rehabilitation, attention to swallowing and oral diet and prevention of deep venous thrombosis.

Stroke unit care is standard in many countries (for example Norway), has been mandated in others (for example England and Wales) but has been slow to be developed in Australia. In the absence of a local stroke unit, a rehabilitation unit would be a suitable alternative, once the patient is medically stable.

Medical treatment

Drug treatments include aspirin, thrombolytics and antihypertensives. Anticoagulation, neuroprotection, steroids, mannitol and glycerol have been shown to be ineffective or harmful.

Aspirin

An immediate dose of aspirin for patients with ischaemic stroke is definitely effective, but the effect is modest with only one extra independent survivor per 100 patients treated.[6] However, across Australia, this treatment will prevent 400–500 people from dying or becoming dependent each year. Putting it another way, the benefit of aspirin given for two weeks following an ischaemic stroke is the same as the benefit seen in the subsequent 50 weeks, for routine secondary prevention. This is due to the clustering of recurrent ischaemic stroke in the first few weeks after a stroke or TIA.

Thrombolysis

Recombinant tissue plasminogen activator (rt-PA) has a treatment effect of about 10–15 extra independent survivors per 100 patients treated, despite an additional eight patients with symptomatic intracranial haemorrhage.[7] There is an uncertain effect on overall deaths and treatment is not easy to deliver. In Australia, rt-PA was approved by the Therapeutic Goods Administration in 2003, but only for patients who can be assessed, scanned and treated by experienced stroke teams within three hours of onset. As it can be difficult to meet this deadline, trials are underway to broaden the indications and to evaluate whether treatment given within six hours is safe and effective. The current use of thrombolytic drugs in stroke management is unlikely to have a public health impact, but may help some patients.

Reducing blood pressure

The effect of lowering blood pressure in the acute phase of stroke is uncertain. Some experts prefer to treat patients with sustained very high blood pressure (greater than 180/120), particularly patients with primary intracerebral haemorrhage, but there is no reliable evidence behind this recommendation. Trials are needed to test this potentially widely generalisable treatment. If treatment is considered necessary, oral therapy with usual antihypertensives can be given. For dysphagic patients, oral treatment can be given by nasogastric tube or parenterally.

Reversal of antithrombotic treatment

Antiplatelet therapy should be stopped, probably indefinitely, if the stroke is due to primary intracerebral haemorrhage. If anticoagulated patients have a primary intracerebral haemorrhage they need urgent assessment, and haematological advice should be sought to reverse the anticoagulation. It is probably wise not to re-anticoagulate unless the patient has a major ongoing risk of thromboembolism (such as metal prosthetic heart valves).

Surgical treatment

Occasionally surgery is necessary to relieve acute hydrocephalus caused by a posterior fossa stroke. Hemicraniectomy (removal of a large skull flap) can occasionally save life by reducing intracranial pressure secondary to massive hemispheric swelling and is now the subject of a randomised controlled trial. The results of a trial of early evacuation of the haematoma for those with primary intracerebral haemorrhage (the STICH trial) did not show any benefit of surgical intervention and full publication is awaited.

Support for patients and carers

Stroke can be a devastating problem for patients and carers and they need support and information during this critical time. Assessment of stroke severity and subtypes can help give estimates of prognosis. For example, patients presenting with a hemiparesis, hemianopia and aphasia have a 90–95% chance of being dead or dependent at six months, a prognosis worse than most cancers. Patients with a lacunar syndrome (for example, pure motor stroke) have a low case fatality, but a 30% chance of longer-term disability. Some matters, such as advice about driving, have important medicolegal implications.

Terminal care

About 10% of patients with ischaemic stroke and 50% of those with primary intracerebral haemorrhage die within a month. Appropriate terminal care is therefore an important part of acute management.

Secondary prevention

The best opportunity to commence secondary prevention is in the acute phase. Stopping smoking should halve the future risk of vascular events. Antithrombotic therapy together with cholesterol and blood pressure lowering are effective for patients with ischaemic stroke.[8,9,10] This evidence-based polypharmacy may be a problem for some patients. Secondary prevention for primary intracerebral haemorrhage depends on effective blood pressure lowering.[8]

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Professor Lindley

The University of Sydney has received donations from several pharmaceutical companies in lieu of payment for lectures and attendance at an advisory committee by Professor Lindley (Servier, Bristol Myers Squibb). He has accepted sponsorship to attend scientific symposia in 2004 (Bristol Myers Squibb, Sanofi). He holds no shares or interests in any company.

He is the co-principal investigator of an academic trial evaluating recombinant tissue plasminogen activator for acute ischaemic stroke.

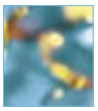
Dr Landau

Dr Landau is the co-principal investigator in several pharmaceutical company sponsored clinical trials. He holds no shares or interests in any pharmaceutical companies.

Self-test questions

The following statements are either true or false (answers on page 133)

5. If 100 patients with acute strokes are given aspirin there will only be one additional survivor.
6. Most patients with a suspected acute stroke should have urgent computed tomography of the brain.



Keeping advertisers honest – an overview of the regulation of the advertising of medicines and medical devices in Australia

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Summary

Australia has long-standing co-regulatory systems governing the advertising of therapeutic goods to consumers and healthcare professionals. These systems include representatives of all key stakeholder groups and are underpinned in law by the Commonwealth *Therapeutic Goods Act 1989* and associated Regulations. The co-regulatory systems also include processes for handling complaints. These processes differ depending on the product involved and how it is advertised. Most complaints are made by rival companies rather than by consumers or health professionals. This lack of diversity in the source of complaints is seen by some as a weakness in the complaints system.

Key words: drug industry, consumers, Therapeutic Goods Administration.

(Aust Prescr 2004;27:124–7)

Introduction

In Australia, the Therapeutic Goods Administration (TGA) is responsible for administering the *Therapeutic Goods Act 1989* (the Act) and the accompanying Therapeutic Goods Regulations (the Regulations). The object of the legislation is to establish and maintain a national system of controls for the quality, safety, efficacy and timely availability of 'therapeutic goods' that are used in or exported from Australia.

Generally, therapeutic goods are required to be entered on the Australian Register of Therapeutic Goods (the Register) before they may be lawfully manufactured, supplied, imported or exported for use by humans. Additionally, the legislation prescribes requirements for 'advertisements' which, in relation to therapeutic goods, 'includes any statement, pictorial representation or design, however made, that is intended, whether directly or indirectly, to promote the use or supply of the goods'.

Advertising controls – a co-regulatory approach

Co-regulatory systems control the advertising of therapeutic goods to consumers and healthcare professionals. These systems include representatives of the regulated industry sectors, consumers, healthcare professionals, media, advertisers and government.

Advertising to consumers

The co-regulatory system governing advertising to consumers is legally underpinned by the Act and Regulations, which adopt the Therapeutic Goods Advertising Code (TGAC). This Code specifies detailed requirements for advertisements and aims to ensure that the marketing and advertising of therapeutic goods to consumers is conducted in a socially responsible manner that promotes the quality use of therapeutic goods and does not mislead or deceive the consumer. A copy of the TGAC may be downloaded from www.tgacc.com.au/codeList.cfm

The TGAC is administered by the Therapeutic Goods Advertising Code Council. This includes representatives from stakeholder groups and is established under the Therapeutic Goods Regulations. The role of the Council includes:

- considering the advertising requirements for therapeutic goods
- considering amendments to the TGAC
- making recommendations to the Commonwealth Minister for Health and Ageing.

Mandatory pre-approval of consumer advertisements

Advertisements to consumers which are broadcast, published or inserted in the mainstream media (such as television, radio, newspapers and magazines) are subject to mandatory pre-approval before publication or broadcast. This pre-approval is carried out, under delegated authority from the Commonwealth Department of Health and Ageing, by the Australian Self-Medication Industry (ASMI) and the Complementary Healthcare Council of Australia (CHC). These industry associations represent the sponsors and manufacturers of non-prescription (over-the-counter **and** complementary) medicines.

Prescription medicines

Prescription medicines are not subject to the provisions of the TGAC as it is unlawful to advertise these medicines to consumers.

Advertising prescription medicines to healthcare professionals

Advertisements for prescription medicines are subject to the provisions of the *Trade Practices Act 1974*, section 22(5) of the Therapeutic Goods Act (which establishes an offence where therapeutic goods are advertised with indications other than those that have been accepted in the Register), and any other conditions which may be assigned to the marketing approval of the product.

Advertisements for prescription-only medicines (which may be published in professional journals) are not subject to mandatory pre-approval.

Complaints resolution including industry self-regulation

Included in the self-regulatory components of Australia's system for advertising controls are voluntary codes of practice with 'built-in' complaints handling mechanisms. These voluntary codes are administered by the industry associations – Medicines Australia (for prescription medicines) and ASMI and CHC (for non-prescription medicines).

The complaints committees of these industry associations consist of industry representatives and independent, external representatives (including healthcare professionals, consumer groups and the TGA). These self-regulatory complaints committees primarily consider complaints about 'non-mainstream' advertisements for therapeutic goods such as:

- leaflets, catalogues and brochures distributed via letterbox drop
- point-of-sale material, for example flyers and 'shelf-talkers'
- advertisements directed to healthcare professionals.

While requiring compliance with the legislative provisions, the industry codes of practice include additional, 'ethical/industry' requirements which are not necessarily prescribed by law. The complaints committees can impose commercial sanctions and government agencies such as the TGA and the Australian Competition and Consumer Commission (ACCC) expect industry participants to comply with the findings of these committees, whether or not the company in question is a member of the particular industry association.

In the few cases where the complaints committees are unable to achieve a satisfactory outcome, the matter is then referred to the TGA and/or ACCC for consideration of appropriate action under the Therapeutic Goods Act or the *Trade Practices Act 1974*.

Advertising to consumers

The Complaints Resolution Panel is established under the Regulations to consider complaints relating to consumer advertisements for therapeutic goods appearing in the mainstream print media and broadcast media. The Panel is representative of the relevant stakeholder groups.

Complaints about these advertisements may be submitted to the Complaints Resolution Panel (see Box 1). A copy of the complaints form, procedure and related information may be obtained from the Therapeutic Goods Advertising Code Council web site.

Over-the-counter and complementary medicines

Generally, advertisements for non-prescription medicines may be directed at consumers or healthcare professionals. However, the Regulations prohibit the advertising to consumers of certain medicines included in Schedule 3 of the Standard for the Uniform Scheduling of Drugs and Poisons ('pharmacist-only' medicines).

Box 1

Contact details for complaints

Advertising to consumers (including advertisements for medical devices) in mainstream print and broadcast media

The Secretariat
Complaints Resolution Panel
PO Box 764
NORTH SYDNEY NSW 2059

Over-the-counter (pharmaceutical) medicines (advertising to consumers in other than mainstream media, and to health professionals)

The Executive Director
Australian Self-Medication Industry
PO Box 764
NORTH SYDNEY NSW 2059

Complementary medicines (advertising to consumers in other than mainstream media, and to health professionals)

The Executive Director
Complementary Healthcare Council of Australia
PO Box 104
DEAKIN WEST ACT 2600

Advertising of prescription-only medicines advertised to health professionals

Secretary, Code of Conduct Committee
Medicines Australia
Level 1
16 Napier Close
DEAKIN ACT 2600

Medical devices (advertising to consumers in other than mainstream media, and to health professionals)

Advertising and Export Section
Non-Prescription Medicines Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Advertisements for non-prescription medicines are subject to the Act, Regulations (including the provisions of the TGAC) **and** the industry codes of practice administered by the ASMI and CHC. Complaints about advertisements in the mainstream media are considered by the Complaints Resolution Panel, while complaints about 'non-mainstream' advertisements are considered by the ASMI or CHC self-regulatory complaints committees.

Complaints about advertisements for over-the-counter (pharmaceutical) medicines may be submitted to the ASMI (see Box 1).

Complaints about advertisements for complementary (for example herbal, vitamin) medicines may be submitted to the CHC (see Box 1).

Prescription-only medicines

It is an offence under the Act to advertise prescription-only medicines to consumers. These medicines can only be advertised to healthcare professionals. The TGA's letter of marketing approval requires advertisements to comply with the requirements of the Medicines Australia Code of Conduct, irrespective of whether a company is an association member or not.

Complaints about advertisements for prescription medicines directed to healthcare professionals may be submitted to Medicines Australia (see Box 1). Copies of the Code of Conduct are available from the Medicines Australia web site.

Medical devices

Medical devices may be advertised directly to consumers. The regulatory requirements are similar to those which apply to the advertising of non-prescription medicines. However, there is currently no requirement for pre-approval of advertisements.

The Complaints Resolution Panel considers complaints about advertisements for medical devices appearing in the mainstream media. In the absence of a self-regulatory complaints committee, all other complaints about medical device advertisements may be submitted to the Non-Prescription Medicines Branch of the TGA (see Box 1).

Weakness in the co-regulatory system

A continued weakness in the system is the lack of diversity in sources of complaint. The majority of complaints are generated from competitors within the regulated industry sectors. The active involvement of consumers and health professionals in particular should be encouraged.

The question about how to encourage such groups to lodge complaints continues to be asked. There have been, and continue to be, initiatives in this area. For example, during the mid-1990s the TGA, the ASMI and Medicines Australia published joint advertisements in medical and pharmacy journals advising health professionals of the mechanisms which exist to enable them to lodge complaints concerning the inappropriate promotion of therapeutic goods.

Education seminars for stakeholder groups are now held on a regular basis. For the past few years information about the various complaints handling processes has also been available on the internet.

The role of the TGA

The TGA is the primary government stakeholder and regulator within the co-regulatory system of advertising for therapeutic goods. It is one member of the Therapeutic Goods Advertising Code Council and regularly participates in the complaints committees of the industry associations.

In the majority of cases, the TGA will support the consideration of advertising complaints by these committees, as opposed to initiating its own independent action at the outset. However, when deemed necessary, the TGA will proceed with administrative and/or legal action in order to enforce the findings of complaints committees and, more broadly, to underpin the Australian system of advertising controls in the interests of public health and safety (see Box 2).

Approximately 5–10 times a year the TGA has to enforce the findings of the complaints system (see Box 2). This represents less than 3% of the complaints considered by the committees.

Recent developments

The Therapeutic Goods Amendment Act was passed in 2003. This transferred the offence provisions for advertising from the

Box 2

The TGA in action

Last year, the Complaints Resolution Panel upheld a complaint against an advertisement published in a mainstream media magazine for a complementary medicine indicated for weight loss or weight management.

The breaches were considered to be serious enough to warrant the publication of a corrective advertisement and the Panel requested the sponsor to do this. The sponsor refused to comply with the request and the Panel subsequently made a recommendation to 'the Secretary' (TGA) to make an Order under the Regulations to enforce the earlier request.

The TGA agreed with the Panel's findings and recommendation, and proceeded to order the sponsor to publish the corrective advertisement. The sponsor ignored the TGA's Order and the TGA then proceeded to cancel the product from the Register on the grounds of nonconformity with the legislative advertising requirements. (Once cancelled from the Register, all further supply becomes unlawful.)

Regulations to the Act, with a significant increase in penalties. The mandatory requirements for the pre-approval of broadcast advertisements have also been transferred to the Therapeutic Goods Act.

Future directions

The Australian and New Zealand Governments have agreed to harmonise the regulatory requirements for therapeutic goods. Throughout 2002 a review of the advertising of therapeutic goods in Australia and New Zealand was undertaken as part of the proposal to establish a trans-Tasman regulatory agency for therapeutic goods. The review aimed to develop an advertising scheme, including approval and complaints handling processes, that could be implemented as part of a joint agency.

A final report was issued in 2003 and is available from the TGA web site. The recommendations are now being considered and further developed in consultation with stakeholders. To facilitate this, the Interim Advertising Council has been established. Its recommendations for a trans-Tasman advertising model will be considered by the Australian and New Zealand Governments as part of the overall arrangements for establishing the new, joint regulatory agency.

A topic of interest to prescribers is whether direct-to-consumer advertising of prescription medicines will be permitted in Australia under the terms of the trans-Tasman agreement. Such advertising is currently legal in New Zealand, but it is unlikely that there will be a change to the current Australian policy.

Further information

Information about advertising therapeutic goods is available from several sources:

Therapeutic Goods Administration
www.tga.gov.au

Therapeutic Goods Administration related legislation
www.tga.gov.au/legis/index.htm

TGA Information Officer
1800 020 653 (telephone)

Therapeutic Goods Advertising Code Council
www.tgacc.com.au

Industry associations

- Medicines Australia
  www.medicinesaustralia.com.au
- Australian Self-Medication Industry
  www.asmi.com.au
- Complementary Healthcare Council of Australia
  www.chc.org.au
- Medical Industry Association of Australia
  www.miaa.org.au

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 133)

7. Medical devices cannot be advertised directly to the public.
8. Advertisements for prescription medicines directed to health professionals require pre-approval by the Therapeutic Goods Administration.

The story of one complaint

In November 2002 a member of the Editorial Executive Committee of *Australian Prescriber* noticed an advertisement from Sanofi-Synthelabo in the Qantas in-flight magazine. Although this advertisement could be read by members of the public, it contained the brand names of prescription-only drugs.

As this advertisement was a promotion directed at consumers a complaint was made to the Complaints Resolution Panel. However, the Complaints Resolution Panel did not deal with the complaint. It said that the advertisement was outside its jurisdiction, because direct-to-consumer advertisements for prescription medicines are illegal. The complaint was therefore redirected to the Therapeutic Goods Administration (TGA).

When nothing further was heard, the TGA was asked about the outcome of the complaint. The TGA advised that the matter had 'been addressed and the advertisement in question has been withdrawn'.

Although subsequent correspondence revealed why the TGA did not take any further action, a separate complaint about the same advertisement by another academic to Medicines Australia produced a different sanction. The Code of Conduct Committee of Medicines Australia ruled that the advertisement was 'a serious breach of the Code of Conduct as it promoted the use of a prescription-only product to members of the general public'. In contrast to the TGA, Medicines Australia published its assessment and imposed the maximum fine of $50 000.[1]

Reference

1. Medicines Australia. Code of Conduct Annual Report 2003. Canberra: Medicines Australia; 2003.

NPS RADAR
Rational Assessment of Drugs and Research

The National Prescribing Service (NPS) produces RADAR (Rational Assessment of Drugs and Research) to inform people about changes to the Pharmaceutical Benefits Scheme. This is an abridged version of a RADAR comment. For the full comment on this drug, go to http://www.npsradar.org.au

Ezetimibe (Ezetrol) for dyslipidaemia

Pharmaceutical Benefits Scheme (PBS) listing

Ezetimibe inhibits the intestinal absorption of cholesterol and related phytosterols.[1] It is listed as an authority item for:

- combination therapy with a 'statin' for people who have coronary heart disease or diabetes and whose cholesterol levels are inadequately controlled by a statin
- monotherapy for people who are unable to take statins due to contraindications or clinically important adverse effects
- people with homozygous sitosterolaemia or homozygous familial hypercholesterolaemia.

Reason for listing on the PBS

Economic analyses submitted in support of the PBS listing of ezetimibe were based on short-term changes in lipid parameters. The effect of ezetimibe on clinical outcomes is unknown.

Patients with coronary heart disease or diabetes whose cholesterol levels are inadequately controlled by a statin

Ezetimibe was recommended for listing as its cost-effectiveness was acceptable compared to a statin alone. The additional cost of adding ezetimibe to a statin was justified by the expected benefit in terms of coronary heart disease events prevented by lowering cholesterol.[2]

Patients who are unable to take statins

Ezetimibe was considered no worse than cholestyramine and was recommended for listing on the basis of similar efficacy and cost.

Patients with homozygous familial hypercholesterolaemia or homozygous sitosterolaemia

Ezetimibe was recommended for listing because the benefits of treatment outweigh the risks and costs of long-term use in these patients who are at high risk of coronary heart disease.[3]

Place in therapy

Statins remain the drugs of choice for low-density lipoprotein (LDL) cholesterol because they are effective and have recognised cardiovascular benefits.

Ezetimibe is an alternative to other non-statin drugs, such as bile acid resins (cholestyramine and colestipol), fibrates (gemfibrozil and fenofibrate) and nicotinic acid for:

- combination therapy for people with diabetes or coronary heart disease whose cholesterol is inadequately controlled by a statin. Check compliance with lifestyle changes and statin therapy before starting combination treatment.
- monotherapy for people unable to take a statin due to contraindications or clinically important statin-related adverse effects.

Ezetimibe can be used to treat the rare inherited disorders of homozygous familial hypercholesterolaemia and homozygous sitosterolaemia.

Safety issues

Ezetimibe is the first member of a new class of drugs and has been used in only a limited number of patients.

Dosing issues

The recommended dose of ezetimibe in adults and children 10 years and over is 10 mg once daily. Doses above 10 mg provide no additional benefit.

References

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2. Department of Health and Ageing. December 2003 PBAC outcomes – positive recommendations. www.health.gov.au/pbs/general/listing/pbacrec/dec03/positive.htm#ezetimibe [cited 2004 Sept 6]
3. Department of Health and Ageing. June 2003 PBAC outcomes – positive recommendations. www.health.gov.au/pbs/general/listing/pbacrec/jun03/positive.htm#ezeti [cited 2004 Sept 6]

See the full NPS RADAR review of ezetimibe at www.npsradar.org.au for a discussion of:

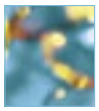
- the evidence for ezetimibe's efficacy and safety
- how to identify and manage statin-related adverse effects
- when to cease a statin because of adverse effects
- lipid-modifying options for people with insufficient response to a statin.

Also in the latest issue of RADAR:

Fenofibrate (Lipidil) for dyslipidaemia

Carvedilol (Dilatrend) titration pack for heart failure

Ethacrynic acid (Edecrin) tablets



Drug treatments in polycystic ovary syndrome

Beres Joyner, General Practitioner, Senior Lecturer, Rural Clinical Division, School of Medicine, University of Queensland, Rockhampton, Queensland

Summary

The recognition that insulin resistance has a central role in polycystic ovary syndrome has led to new approaches to treatment. While clinical presentations may still be managed symptomatically, there is increasing interest in insulin sensitisers including metformin. Drug treatments do not displace the management of behavioural risk factors to achieve weight loss in women who are overweight or obese. Weight loss leads to improvement in symptoms, and other long-term health benefits.

Key words: metformin, ethinyloestradiol, cyproterone, spironolactone.

(Aust Prescr 2004;27:129–31)

Introduction

Polycystic ovary syndrome is a heterogeneous condition characterised by hyperandrogenism and anovulation. It presents during a woman's reproductive years as menstrual disturbance, infertility, hirsutism, or acne. Insulin resistance is very common in women with polycystic ovary syndrome. It is also common in women who have a body mass index greater than 30 kg/m^2. In polycystic ovary syndrome obesity therefore adds to insulin resistance. These women have an increased prevalence of cardiovascular risk factors and many have the metabolic syndrome. Follow-up studies have shown an earlier onset of type 2 diabetes mellitus. These women are not oestrogen deficient and they may develop endometrial hyperplasia which confers an increased risk of endometrial cancer.

Polycystic ovary syndrome can be diagnosed clinically. However, it should be considered a diagnosis of exclusion and other endocrine disorders should be considered. These include congenital adrenal hyperplasia, androgen secreting tumours of the ovaries or adrenal glands, Cushing's syndrome, hyperprolactinaemia, thyroid disease and use of exogenous androgens.

Lifestyle interventions aimed at reducing body mass index and improving insulin sensitivity are central to the initial and ongoing management of women with polycystic ovary syndrome. The women need advice about reducing the calories in their diet as well as advice and support in increasing physical activity. Modest weight loss of about 5% of the initial body weight can improve the menstrual cycle and studies confirm improvements in ovulation rates and fertility. Women with polycystic ovary syndrome also need advice on long-term behavioural change to manage their increased risk of cardiovascular disease. Those who smoke should be offered assistance to help them quit. When drug therapies are required, the choice of medication is influenced by whether the patient's main complaint is menstrual irregularity, infertility, acne or hirsutism.

Menstrual problems

In women presenting with menstrual problems, it is important to clarify the diagnosis (including the exclusion of pregnancy) and ask if they need contraception or are planning pregnancy. For those with oligomenorrhoea who are not planning pregnancy, the combined oral contraceptive pill may be appropriate. However, which combined oral contraceptive pill is best for women with polycystic ovary syndrome is unknown.

Combined contraceptive pill

The combined oral contraceptive pill controls the menstrual problems by establishing regular withdrawal bleeds and reducing menstrual flow. It also reduces hyperandrogenism and long-term use reduces the risk of endometrial cancer.

The combined oral contraceptive pill does not address the pathophysiology of polycystic ovary syndrome or improve the insulin resistance that usually underlies the hyperandrogenism. It has been reported to aggravate insulin resistance in women with polycystic ovary syndrome as well as those without this phenotype. However, in the general population the combined oral contraceptive pill has not been associated with an increased risk of type 2 diabetes mellitus. There is also no convincing evidence of an increased risk of diabetes when the combined oral contraceptive pill is used in women with polycystic ovary syndrome.

Of concern is the long-term risk of cardiovascular disease in women with polycystic ovary syndrome. At present, there is no evidence to suggest that they experience more cardiovascular events while taking the combined oral contraceptive pill. However, women over the age of 35 who smoke should not be prescribed the combined oral contraceptive pill because of the substantially increased risk of myocardial infarction. This risk is also increased in women with hypertension, and it is not known if control of hypertension reduces the risk.

Progestogens

The effect of progestogens on metabolic risk factors varies and is not well understood. Although there are no studies regarding the use of the progestogen-only levonorgestrel intrauterine system in women with polycystic ovary syndrome, it may be useful in affording endometrial protection in women who also require contraception. Erratic bleeding is a problem especially in the first three months, and 50% of women have infrequent bleeding at six to nine months.

Depot medroxyprogesterone acetate also results in amenorrhoea in 50% of women at 12 months, but it may produce erratic bleeding as well as metabolic disturbances affecting lipids and glucose tolerance. As depot medroxyprogesterone acetate is associated with a delayed return to fertility, other contraceptive methods should be considered in women with polycystic ovary syndrome who are planning pregnancy.

In women who present with menstrual disturbance and who are not planning a pregnancy, and who do not require contraception, cyclic progestogens can be used to regulate the endometrium and control irregular bleeding. Medroxyprogesterone 10–20 mg daily for 14 days each month, or norethisterone 5 mg daily for 14 days each month may be used. However, the optimal regimen for protection against endometrial cancer in women with polycystic ovary syndrome is not known.

Infertility

When women with polycystic ovary syndrome present to their general practitioners because of difficulty conceiving, history, physical examination and laboratory investigations for infertility, including analysis of their partners' semen, should be performed. If lifestyle measures such as weight loss are unsuccessful, metformin therapy can be considered.

Metformin is an oral biguanide insulin sensitiser. It is inexpensive and safe, but should not be prescribed if there is significant renal impairment or other contraindications. Renal function should be checked before treatment. As metformin does not promote insulin secretion, hypoglycaemia does not occur (except very rarely if taken with alcohol and no food). Prominent adverse effects include diarrhoea, nausea and vomiting.

In clinical trials, metformin has been used in doses of 500 mg two to three times a day, or 850 mg twice daily. Metformin improves menstrual patterns and ovulation rates and this effect, if it occurs, is seen within two to three months.[1] Trials in primary care are lacking and specialist societies do not recommend initiation of metformin therapy by general practitioners.[2] 'Off-label' prescribing of metformin for polycystic ovary syndrome should be discussed with the patient and documented.

General practitioners who do prescribe metformin to restore ovulation need to plan how they will monitor their patient to determine when pregnancy has occurred. Prompt discussion with the woman's obstetrician regarding management of the metformin therapy in pregnancy is necessary. There are a limited number of non-randomised studies describing a reduction in spontaneous miscarriages in women with polycystic ovary syndrome who continue metformin.

Specialist referral is appropriate if metformin and lifestyle measures have not been effective in restoring fertility in six months. Clomiphene or additional fertility treatments may be required.

When managing women with type 2 diabetes during their reproductive years, it is prudent to ask about menstrual history, contraception and fertility before treatment with metformin as one may inadvertently treat concomitant polycystic ovary syndrome and then need to manage a pregnant patient with diabetes.

Acne and hirsutism

Treatment of acne or hirsutism that cannot be cosmetically controlled involves reducing androgen concentrations, or blocking the actions of androgens (antiandrogens), or inhibiting the action of 5α reductase. Antiandrogens are teratogenic and male fetuses may potentially be feminised. When these treatments are prescribed for women, effective contraception is essential.

The combined oral contraceptive pill is effective in managing acne, and preparations containing ethinyloestradiol and cyproterone (antiandrogen) are frequently prescribed. Oestrogens stimulate the hepatic production of sex hormone binding globulin, resulting in increased binding of testosterone and thus reducing the level of active free testosterone. Gonadotrophin suppression leads to suppression of ovarian androgen synthesis. The reduction in free androgen levels improves acne over three to six months. However, the combined oral contraceptive pill is less effective in the management of hirsutism.

When hirsutism is managed medically, treatment for three to six months is needed before the effect is apparent. Local cosmetic treatments are necessary during this time. Drug therapies are not curative. Options are:

- a combined oral contraceptive pill containing ethinyloestradiol and cyproterone acetate
- a different combined oral contraceptive pill plus cyproterone acetate 25–100 mg per day in a reversed sequential regimen for 10 days per month
- spironolactone (antiandrogen) 50–100 mg per day.[3,4]

Liver function tests should be checked prior to the prescription of cyproterone acetate, and at six-monthly intervals. Spironolactone should not be used in patients with renal impairment, and renal and potassium status should be checked before therapy and after three months.

Flutamide, a potent antiandrogen, and finasteride, a 5α reductase inhibitor, have been used overseas to treat women with

hirsutism. However, they are not in general use in Australia. Flutamide may cause hepatotoxicity, while finasteride is teratogenic.

Management of long-term risks

Insulin resistance is important in the development of the metabolic syndrome and is associated with an increased risk of cardiovascular disease. There are no long-term clinical studies to assess the benefit of metformin in reducing adverse cardiovascular outcomes in women with polycystic ovary syndrome.[5] However, the findings of the Diabetes Prevention Program Research Group (which found lifestyle changes were more effective than metformin in reducing the incidence of type 2 diabetes in people at high risk) suggest that clinicians should persist in working with their patients to achieve lifestyle changes that will reduce body mass and improve insulin sensitivity.[6]

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6. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 133)

9. In polycystic ovary syndrome, the combined oral contraceptive pill has more effect on acne than on hirsutism.
10. Metformin is the drug of choice in the treatment of polycystic ovary syndrome if there are no contraindications to its use.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been 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.

Agalsidase beta

Fabrazyme (Genzyme)

5 mL vials containing 5 mg powder for reconstitution

20 mL vials containing 35 mg powder for reconstitution

Approved indication: Fabry's disease

Australian Medicines Handbook section 10.6

Lysosomal storage diseases are caused by inborn errors of metabolism. The lack of a specific enzyme results in the substrate accumulating inside lysosomes. Fabry's disease results from an X-linked recessive genetic defect which causes a deficiency of α-galactosidase A. This deficiency leads to the accumulation of globotriaosylceramide in the lysosomes in blood vessel walls. Patients usually die of cerebrovascular disease, myocardial infarction, heart failure or renal failure.

Agalsidase beta is a recombinant form of α-galactosidase A produced by genetically engineered Chinese hamster ovary cells. To replace the deficient enzyme requires an intravenous infusion, for at least two hours, every two weeks.

The infused agalsidase is taken up by endothelial lysosomes and has an elimination half-life of 45–100 minutes. As agalsidase is broken down by peptide hydrolysis, impaired liver or renal function may have little effect on clearance.

As the incidence of Fabry's disease is less than 1 in 100 000 births, clinical trials involve only a few patients. In a placebo-controlled trial 29 adult patients were treated with agalsidase beta for 20 weeks. After 11 infusions, 69% of this group had no microvascular endothelial deposits of globotriaosylceramide in more than 50% of the capillaries seen on renal biopsy. Deposits were also significantly reduced in the skin and the heart. There was also a significant reduction in the amount of globotriaosylceramide in the urine.[1]

Agalsidase is a protein so infusion reactions are common. Approximately half the patients will have an adverse reaction on the day of the infusion. They may develop headache, fever, muscle pain and altered sensation. Oedema, hypertension, nausea and vomiting are also very common.

More than 80% of patients will develop IgG antibodies to agalsidase. The long-term consequences of the seroconversion are unknown, but no evidence of immune-complex glomerulonephritis was seen in the clinical trials. Although agalsidase improves the pathological appearance of tissue samples, its clinical benefits are unknown. Agalsidase did not reduce the pain experienced by patients with Fabry's disease significantly more than placebo.[1] Longer-term follow-up shows some improvement in pain and quality of life, but there were no statistically significant changes. The effect of agalsidase in children is unknown.

Agalsidase is likely to be expensive, but other companies are genetically engineering α-galactosidase A so competition may help to control costs. In the absence of clinical outcomes calculating cost-effectiveness could be a problem.

Reference †

1. International Collaborative Fabry Disease Study Group. Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. N Engl J Med 2001;345:9-16.

Agalsidase alfa

Replagal (Orphan)

vials containing 3.5 mL concentrate

Approved indication: Fabry's disease

Australian Medicines Handbook section 10.6

Agalsidase alfa is a recombinant form of α-galactosidase A approved in Australia for Fabry's disease. It is produced using human cell lines, but the process should ensure viral safety. Like agalsidase beta, agalsidase alfa is given by infusion every two weeks, however a shorter infusion time (40 minutes) is recommended.

In a six-month trial 14 men with Fabry's disease were randomised to receive agalsidase alfa and 12 were given placebo infusions. At the end of the trial renal biopsies showed a 21% increase in the proportion of normal glomeruli in patients given agalsidase and a 27% decrease in the placebo group. Renal function, assessed by creatinine clearance, decreased in the placebo group, but not in the active treatment group. Agalsidase also significantly reduced the urinary concentration of globotriaosylceramide (the glycosphingolipid which accumulates in Fabry's disease).[1]

Unlike the main trial of agalsidase beta[2], the effect of enzyme replacement on neuropathic pain was a major focus of the trial of agalsidase alfa. Patients given agalsidase had small but statistically significant changes in the severity of their pain and four were able to stop taking analgesics.[1]

Infusion reactions are the most common adverse effects of agalsidase alfa. These reactions may not develop until patients have had a few months of treatment. More than half the patients develop antibodies to the enzyme.

There are differences between the alfa and beta forms of agalsidase, but it is difficult to compare their effectiveness as the trials[1,2] had different designs.[3] The US Food and Drug Administration has approved agalsidase beta, but not agalsidase alfa. Further research is needed to determine the best use of these expensive products. For example, will they change the outcomes for patients if they are started early in the course of the disease?

References †

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Iobenguane sulfate

MIBGen (ANSTO Radiopharmaceuticals)

vials containing 90–110 MBq/mL

Approved indication: tumour localisation

Iobenguane is meta-iodobenzylguanidine, an analogue of noradrenaline. Radiolabelling the iodine (I^{123}) in the molecule therefore enables investigation of the sympathetic nervous system. Iobenguane localises in the adrenal medulla so it can be used in diagnostic scintigraphy of phaeochromocytomas. It can also be used to locate ganglioneuroblastomas, ganglioneuromas and paragangliomas, and to detect end stage neuroblastomas.

Patients are given a slow intravenous injection. The radioactivity spreads around the body with a high uptake in hyperplastic adrenal glands. Most of the dose is excreted in the urine within four days.

In a trial involving 120 patients, radiolabelled iobenguane showed intense uptake in 21 of 24 phaeochromocytomas confined to the adrenals. The uptake was partly increased in the other three tumours, however partial uptake also occurred in 30% of the normal adrenal glands.[1]

In a preoperative study involving 16 patients with neuroblastoma, radiolabelled iobenguane showed the primary tumour in 15 cases.[2]

Although radiolabelled iobenguane is a sensitive technique its advantages over other imaging techniques and its role in diagnostic algorithms will need clarification.

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2. Hadj-Djilani NL, Lebtahi N-E, Delaloye AB, Laurini R, Beck D. Diagnosis and follow-up of neuroblastoma by means of iodine-123 metaiodobenzylguanidine scintigraphy and bone scan, and the influence of histology. Eur J Nucl Med 1995;22:322-9.

† At the time the comment was prepared, a scientific discussion about this drug was available on the web site of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int).

NEW FORMULATIONS

Glatiramer acetate

Copaxone (Aventis Pharma)

20 mg solution in pre-filled syringes

Sodium cromoglycate

Intal CFC-free (Aventis Pharma)

1 mg/actuation metered dose aerosol

NEW STRENGTH

Levobupivacaine hydrochloride

Chirocaine (Abbott)

0.625 mg/mL and 1.25 mg/mL in 100 mL and 200 mL infusion bags

NEW BRANDS

Cefaclor monohydrate

Karlor CD (Aspen Pharmacare)

375 mg tablets

Cephalexin

Ialex (Aspen Pharmacare)

125 mg/5 mL and 250 mg/5 mL oral suspension

Gabapentin

Nupentin (Alphapharm)

100 mg, 300 mg and 400 mg capsules

Answers to self-test questions

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

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