Australian Prescriber
Volume 26
Number 3
2003

EDITORIAL

Withdrawal of useful drugs from the market

Bill Lyndon, Clinical Lecturer, Department of Psychological Medicine, University of Sydney, Sydney, and Chairman, Committee for Psychotropic Drugs and Other Physical Treatments, Royal Australian and New Zealand College of Psychiatrists

Index words: drug industry, Pharmaceutical Benefits Scheme.

(Aust Prescr 2003;26:50–1)

In the last few years pharmaceutical companies have announced the discontinuation of useful drugs in several areas of medicine. These withdrawals included four important psychotropic drugs. Three were antidepressants (nortriptyline, desipramine, phenelzine) and the fourth was benztropine, an anticholinergic drug widely used to control the extrapyramidal effects of antipsychotic drugs. Although the antidepressants involved are not frequently used, clinicians do not consider them to be obsolete and these drugs continue to have an important role in the management of treatment-resistant depression. Indeed, for a small but important minority of patients they are the drug of choice because of intolerance of, or failure to respond to, other antidepressants. An appreciable number of patients have been successfully maintained free of illness for many years because of long-term use of these antidepressants.

Following the announcements that the drugs would be withdrawn the Royal Australian and New Zealand College of Psychiatrists worked with the Department of Health and Ageing, the Pharmaceutical Benefits Advisory Committee (PBAC) and the companies to try and have these drugs retained for use in Australia and New Zealand. This approach was successful for three of the four drugs – desipramine was discontinued worldwide and is no longer manufactured. Unfortunately, supplies of phenelzine were rapidly and unexpectedly exhausted, forcing many patients to change to another antidepressant. Regrettably some patients experienced withdrawal symptoms or had a recurrence of depression after many years of stability, and in some cases hospitalisation was required. These adverse outcomes show that the pharmaceutical industry, government and the medical profession need to work together to deal with the issue of proposed drug withdrawals in order to ensure that important drugs are retained for use.

A company may decide to discontinue the supply of a drug for various reasons. New products coming to the market inevitably mean that some older drugs appear to become redundant. Companies may then be under economic pressure to discontinue older, less profitable drugs. The cost of supplying a subsidised drug may, over time, exceed the price set by the Pharmaceutical Benefits Scheme. Failure to reach agreement on a higher price may lead the company to withdraw the drug rather than to continue supplying it at a price which is less profitable. Some older drugs are difficult to manufacture and the cost of upgrading the process to meet increasingly stringent government standards for manufacturing may be uneconomic. Occasionally new data may reveal unexpected adverse reactions, leading to discontinuation for safety reasons. Mergers of pharmaceutical companies may also result in a decision to stop manufacturing some products.

No matter how justified a company's decision may be, the discontinuation of an important drug has major implications for patients. This is particularly so for drugs which are used long-term to prevent disease or maintain health. These drugs include antidepressants, antipsychotics, antihypertensives and drugs for diabetes. Having to change from long-term treatment to a new drug can be a long and difficult process. It involves a significant risk of losing control of the illness, withdrawal reactions, recurrences of the illness, new adverse effects, and drug interactions. Sometimes more than one alternative may need to be tried and hospitalisation may result. Pharmaceutical

In this issue...

Cutting costs is a current corporate obsession. This often results in reduced services and less choice for consumers. In extreme cases safety could be compromised. Bill Lyndon discusses how cost-cutting in the pharmaceutical industry may reduce patients' access to useful drugs.

Old drugs still have a role to play in hypertension and Suzanne Hill tells that a combination of drugs may be needed to reach a target blood pressure. Cheryn Palmer also reports that HIV is best managed with a combination of drugs. Combinations of drugs have disadvantages as well as advantages. Michael Hall and Nick Buckley say that severe cases of serotonin syndrome are often due to patients taking two or more serotonergic drugs.

Reducing meningococcal disease is the target of the new immunisation program, but Margaret Burgess and Rosemary Lester remind us that the vaccines only protect against type C infection.

companies need to advise and fully inform doctors and patients about the process of changing treatment to try and avoid inappropriate actions. Medicolegal issues relating to duty of care and responsibility are clearly relevant and no doubt will surface in time, potentially affecting the companies, individual doctors, pharmacists, specialist colleges and government bodies.

Currently, when a company decides to discontinue a drug, there is no formal process in place to prevent these problems. Nor is it usual for a company to secure the ongoing supply of an essential drug, by arranging for another company to continue its production or distribution, before announcing the decision to withdraw the product. Often the notice given is much too short for all patients to be satisfactorily transferred to an alternative drug before supplies run out, a situation compounded by the inevitable stockpiling which follows the announcement. In some instances the drug supply can continue by finding a generic supplier or through further price negotiations, but this is a lengthy process during which the drug may become temporarily unavailable.

Clearly it is in the best interest of all parties, particularly patients, to develop a co-ordinated and systematic approach to the discontinuation of important drugs. The pharmaceutical industry needs to develop guidelines to follow whenever a drug is being considered for withdrawal, including the early notification of health professionals, their colleges, and other relevant organisations. This would provide the opportunity for the profession to make a case for the retention of essential drugs. Ideally, companies should then join in the process, with government, of securing an alternative supplier. The colleges and other professional organisations need to ensure that they can respond quickly and have an established process for participating with the companies and government in trying to retain the drug. If unsuccessful, the colleges and the company need to work together to ensure that individual patients can be transferred to alternative drugs safely and effectively before supplies run out. This requires a system of rapid communication with clinicians to disseminate information and advice about potentially complex management problems. With sufficient goodwill between the parties involved and with a common focus on patient welfare, significant improvement in the management of drug discontinuations should be achievable.

E-mail: rlyndon@mail.usyd.edu.au

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.

Global drug prices

Editor, – According to Professor Ron Penny, there is an unbelievable array of effective medicines that have reduced the number of HIV/AIDS related deaths in Australia from 2790 in 1992 to 97 in 2001.

The World Health Organization (WHO) has categorically stated that access to innovative medicines and vaccines has been substantially the most important factor in achieving the dramatic decline in mortality rates throughout the twentieth century.[1]

These statements contrast starkly with the opinion of Dr Moran who hypothesised in her recent editorial ('Why are global drug prices so high… and other questions' Aust Prescr 2003;26:26–7) that the interests of the prescription medicines industry lie in 'maximising profits and growth, not in identifying and filling health needs'.

There are many industry driven programs that treat disease and alleviate suffering in resource poor countries. One of the most successful partnerships is the Accelerating Access Initiative program that includes UNAIDS (Joint United Nations Programme on HIV/AIDS), WHO, the World Bank and pharmaceutical companies. This currently has 27 000 people on antiretroviral therapy throughout the world.[2]

Dr Moran suggested that the medicines industry targets 'money-spinner drugs and diseases'. This ignores the critical fact that in Australia these diseases are precisely the diseases that are the focus of the seven National Health Priorities (asthma, cancer, cardiovascular health, diabetes, injury prevention, mental health and arthritis) established not by the medicines industry but by Australian Health Ministers.

Innovative cures to treat disease only come from the research-based medicines industry because governments and even venture capitalists are not prepared to invest in such a high-risk venture. Latest research estimates that it costs about $1.1 billion[3] to bring a new medicine from discovery to patient – along a 12–15 year journey.

This vitally important commitment of the medicines industry is ignored by Dr Moran.

Kieran Schneemann
Chief Executive
Medicines Australia
Canberra

REFERENCES

1. The World Health Report 1999. Geneva: World Health Organization; 1999. p. xxi.
2. Accelerating Access Initiative Progress Report June 2002. Geneva: World Health Organization; 2002.
3. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ 2003;22: 151-85.

Dr M. Moran, author of the article, comments:

I absolutely agree that the pharmaceutical industry develops useful, new drugs. My point is that they only do so when these new drugs are also likely to deliver substantial profits, thereby effectively restricting new drug development to common diseases of Western consumers.

I am not criticising industry for seeking profitable research investments nor suggesting that they stop doing so – this is unrealistic. What I am saying is that profit-seeking firms should not be in charge of setting global drug research agendas, since the vast bulk of the world lies outside their sphere of economic interest. An alternative model is needed: for instance, an international research and development convention to define research needs and establish mechanisms to fund these.

I disagree that 'innovative cures only come from the research-based medicines industry because governments are not prepared to invest in such a high risk venture'. This is not true. Half of the US$70 billion invested in drug research each year comes from the public sector, chiefly as funding for basic research, which is the **highest** risk part of the drug development pipeline.[1] Ten AIDS drugs were fully developed or supported by publicly funded research[2], and the US Government supported the clinical research for 34 of the 37 new cancer drugs marketed in the USA since 1955.[3]

The time for pointing the finger or seeking public relations wins is over. We must accept that our current system is not delivering the drugs the world needs and start working together to solve this problem.

REFERENCES

1. The 10/90 Report on Health Research 2001-2002. Global Forum for Health Research; Chap. 6, p.107. http://www.globalforumhealth.org (go to Publications)
2. Consumer Project on Technology. Additional notes on government role in the development of HIV/AIDS drugs. February 23, 2000. http://www.cptech.org/ip/health/aids/gov-role.html
3. Nader R, Love J. Federally funded pharmaceutical inventions. Testimony before the Special Committee on the Aging, of the United States Senate. February 24, 1993. http://www.cptech.org/pharm/pryor.html

The gift of the gabapentin

Editor, – Your fascinating article outlines the decision by one pharmaceutical company to employ unethical strategies to promote off-label uses for gabapentin (Aust Prescr 2003;26:3–4), a decision which could be described as corporate risk. However, the prescriber and the patient also share the risks associated with off-label prescribing. While the final paragraph highlights an 'imperative to carefully weigh the potential benefits and harms' of off-label prescribing, I believe the article stopped prematurely in developing this notion of who bears the risks.

Off-label prescribing includes using the drug for an unapproved indication, or at an unapproved dose or by an unapproved route, or disregarding the contraindications or precautions of the product information. In the gabapentin example, a belief by prescribers that off-label use was supported by clinical evidence was probably unfounded. The decision as to whether this use was appropriate will come down to standards of reasonable care. The pharmaceutical company will consider that its drug has been used in an unauthorised manner and so cannot officially sanction such prescribing.

It has been noted that 'prescribing outside the licence [approved product information] alters, and probably increases, the doctor's professional responsibility'.[1] When considering prescribing a drug, it is important to be aware of what is on the label to minimise the chances of being left 'hung out to dry'.

Craig Patterson

Pharmacist

National Prescribing Service

Sydney

REFERENCE

1. Prescribing unlicensed drugs or using drugs for unlicensed indications. Drug Ther Bull 1992;30:97–9.

Editor, – Further to the articles in *Australian Prescriber* on prescribing of gabapentin (Aust Prescr 2003;26:3–4), in addition to the issues discussed, there are legal issues for the prescriber and the manufacturer/sponsor of the product to consider.

My first observation is that prescribers who use gabapentin for a condition which is outside the marketing approval in Australia could be subjected to a compensation claim should a patient suffer a serious adverse event due to the drug. If such an event occurred it could also involve the promoter of the drug if off-label promotion was involved.

The second observation concerns prescribing gabapentin as a pharmaceutical benefit. The National Health Act provides penalties for prescribing 'restricted' and 'authority required' drugs for other than the allowable conditions determined for that drug. In instances of off-label prescribing, the prescriber has breached the legislation. The articles allude to off-label promotion of gabapentin overseas. If this occurred in Australia it follows that the manufacturer promoting the drug for an off-label condition may also be party to an offence under the National Health Act.

Brian Foster

Pharmacist

Melbourne

(Until 1996 I was Manager of the Pharmaceutical Benefits Branch of the Health Insurance Commission in Victoria. I joined the Pharmaceutical Branch of the Commonwealth Department of Health in 1969 and retired from the Health Insurance Commission in 1996.)

Sulfadiazine

Editor, – In the article 'Treatment of ocular toxoplasmosis' (Aust Prescr 2002;25:88–90) sulfadiazine is described as a *sulfur* analogue. It is, however, a *sulfa* analogue as sulfur is the element and sulfa, or sulfonamide, is the class of antimicrobial having the chemical group $-SO_2NHR$ in its structure.

Lisa Blair

Pharmacist

Cairns

Hypertension: how low to go?

Suzanne Hill, Senior Lecturer, Clinical Pharmacology, Faculty of Health, University of Newcastle, Newcastle, New South Wales

SYNOPSIS

As blood pressure rises the risk of dying of cardiovascular disease increases. Lowering blood pressure aims to reduce the risk, but it is not certain that a low target for blood pressure will improve survival. An important consideration is the presence of other risk factors such as diabetes. Reducing the diastolic blood pressure, of a patient with hypertension but no other risk factors, to below 90 mmHg may cause more harm than benefit.

Index words: blood pressure, antihypertensives, cardiovascular disease.

(Aust Prescr 2003;26:53–5)

Introduction

Epidemiological studies have established that systolic and diastolic blood pressures have a strong, continuous, graded and aetiologically significant positive association with cardiovascular disease outcomes. Treatment of hypertension reduces cardiovascular risk, and this has been a major focus of campaigns aimed at reducing cardiovascular mortality and morbidity.[1]

We now have many effective treatments for hypertension. In recent studies the questions about treatment have generally addressed the refinement and comparison of treatment regimens. The questions of which type of drug should be first-line treatment, which type of drug is best for what type of patients, and what should be the target blood pressure have all been considered.

A number of international guidelines (WHO/ISH, JNC-VI) suggest that blood pressure should be reduced at least to below 160/90 mmHg to normalise cardiovascular risk in patients with hypertension. In patients at higher baseline risk of cardiovascular disease, for example those with diabetes[2], the recommendations in JNC-VI are that the target blood pressure should be substantially lower: 130/85 mmHg. This recommendation is based on the view that the absolute risk of a cardiovascular event in these patients is much greater, and therefore the absolute benefit of treatment is larger. The question is, how good is the evidence for these recommendations?

Research evidence

Several randomised controlled trials published in the last 3–4 years are used to support proposals for lower target blood pressures in hypertension.[3,4] In addition, there are two cohort studies that provide important information about the likely risk of heart disease in patients with blood pressures that are lower than those previously considered to be a problem.[5,6]

One analysis examined the outcomes for participants in the Framingham study according to their baseline blood pressure.[6] It had a particular focus on the group who started the study with a 'high-normal' blood pressure (defined as systolic pressures of 130–139 mmHg and/or diastolic pressures of 85–89 mmHg). This group did not have cardiovascular disease at the outset of the study, but they were older, had a higher body mass index and higher cholesterol concentrations than completely normotensive participants. After 10 years, the cumulative age-adjusted incidence of cardiovascular disease in people with 'high-normal' blood pressure was 4.4% (95% CI* 3.2–5.5%) in women and 10.1% (95% CI 8.1–12.1%) in men, compared with 1.9% (95% CI 1.1–2.7%) and 5.8% (95% CI 4.2–7.4%) in the participants with optimal blood pressure. The 'high-normal' blood pressure appeared to be associated with an increased risk of cardiovascular disease, even after adjustment for other coexisting risk factors.

An analysis of blood pressure in six different populations (USA, northern Europe, Mediterranean southern Europe, inland southern Europe, Serbia and Japan) examined the relationship between deaths from coronary heart disease and blood pressure.[5] After 25 years of follow-up, for an increase of 5 mmHg in diastolic blood pressure the **relative** risk of mortality ranged from 1.06 (in inland southern Europe) to 1.19 (in Mediterranean southern Europe). The differences in these risks between populations for a given level of change in blood pressure were not statistically significant – that is, the relative risk of death remained constant. The **absolute** risk of death, however, was clearly different among the six populations, varying from 44 per 10 000 person years (Japan) to 153 per 10 000 person years (northern Europe).

These two cohort studies suggest that elevated blood pressure – according to whatever definition – alone does not predict risk of the final event (death) and that not all populations are equal. Although the risk goes up with increasing blood pressure very consistently, the studies do not tell us if the risk comes down with decreasing blood pressure.

HOT study

Only one intervention study has examined the effect of lowering blood pressure to different targets in patients with or without the other major cardiovascular risk factor of diabetes. The Hypertension Optimal Treatment (HOT) study randomised 18 790 patients aged 50–80 years from 26 countries to one of three groups, each defined by a target diastolic blood pressure. The targets were ≤ 90 mmHg, ≤ 85 mmHg and ≤ 80 mmHg.

* CI confidence interval

These targets were to be achieved by treatment with a series of drugs starting with long-acting felodipine 5 mg per day, followed if necessary by stepwise addition of ACE inhibitors or beta blockers, increasing doses of felodipine, and then finally addition of a diuretic. All patients were also randomised to receive low-dose aspirin (75 mg per day) or placebo. Follow-up was for up to five years (mean actual follow-up 3.8 years), and the main end-points were cardiovascular events, cardiovascular mortality and total mortality.

The patients in each group were similar in terms of the presence of other risk factors. At the start of the study 8% of patients had diabetes, and approximately 15% were smokers. By the end of the study, approximately 80% of the patients were still taking felodipine, usually with an ACE inhibitor (41%) or a beta blocker (28%). The reason why 20% had stopped felodipine by the end of the study is not stated in the main report of the study.[4]

The key results of the study are summarised in Table 1. The majority of patients achieved their target blood pressure and the authors concluded that the intensive lowering of blood pressure in patients with hypertension was associated with a low rate of cardiovascular events and that the study showed the benefits of lowering the diastolic blood pressure down to 82.6 mmHg. The implication was therefore that targets for the treatment of hypertension should be lower, than the previously accepted 90 mmHg, to maximise the reduction in cardiovascular risk. This was the recommendation in much of the correspondence which followed the publication of the study, but is this recommendation reasonable?

Questions about the HOT study

In the lengthy correspondence about the HOT study, it was pointed out that:

- using an intention to treat analysis, there was no difference in results between treatment groups[7]
- the method of blood pressure measurement was not optimal[8]
- the data, excluding patients with diabetes, suggested an **increase** in mortality with lower blood pressures[9]
- the results did not take into account the potential increase in adverse effects and costs of medications that might be required to achieve lower blood pressures.[10]

This list of problems is not comprehensive. There was also debate about the potential influence of the pharmaceutical company sponsoring the trial and the promotion of calcium channel blockers as first-line treatment.

On reviewing the data in the original publication, the argument that there is no significant difference in the results for mortality or cardiovascular events between treatment groups (arguably the primary analysis for the primary outcomes) appears to be correct. The confidence intervals for the relative risks for the comparisons between groups all include 1.00 (see the last column in Table 1). The data for cardiovascular event rates actually appear to show an increase in mortality with lower blood pressure, although given the relatively small total number of deaths (approximately 600 out of nearly 19 000 patients), the increase is not statistically significant.

There have been several subsequent analyses of the data from the HOT study.[11,12] The most comprehensive analysis examined the data set using a 'risk stratification' approach. Patients were grouped according to the presence or absence of other cardiovascular risk factors, and the frequency of events in each risk group was considered. The analysis suggested that the higher the risk group, the more likely the chance of cardiovascular events. Unfortunately, the analysis did not compare the outcomes in the risk strata according to the blood pressure target – hence it is not helpful in assessing the value of intensive treatment. A second analysis examined the impact of the presence of other risk factors on the outcomes and concluded that blood pressure alone did not predict the risk of cardiovascular events.

Table 1

Summary of key outcomes from HOT study[4]

Event	*Target blood pressure*	*Total number of events*	*Events per 1000 patient years*	*Comparison between target groups **	*Relative risk (95% confidence interval)*
Major cardiovascular events					
	≤ 90 mmHg	232	9.9	90 vs 85	0.99% (0.83–1.19%)
	≤ 85 mmHg	234	10.0	85 vs 80	1.08% (0.89–1.29%)
	≤ 80 mmHg	217	9.3	90 vs 80	1.07% (0.89–1.28%)
Cardiovascular mortality					
	≤ 90 mmHg	87	3.7	90 vs 85	0.97% (0.72–1.30%)
	≤ 85 mmHg	90	3.8	85 vs 80	0.93% (0.70–1.24%)
	≤ 80 mmHg	96	4.1	90 vs 80	0.90% (0.68–1.21%)
Total mortality					
	≤ 90 mmHg	188	7.9	90 vs 85	0.97% (0.79–1.19%)
	≤ 85 mmHg	194	8.2	85 vs 80	0.93% (0.77–1.14%)
	≤ 80 mmHg	207	8.8	90 vs 80	0.91% (0.74–1.10%)

Adapted from Table 4, reference 4

* This represents the comparison between the groups of target blood pressures (mmHg)

Conclusion

The HOT study does not provide sufficient evidence of the benefits of intensive treatment of blood pressure (that is, reducing diastolic pressures below 90 mmHg) in patients with hypertension. However, in the original sub-group analysis of the HOT study, which looked at the results in patients with diabetes, there **are** differences in the outcomes between treatment groups. Patients with diabetes in the lowest target blood pressure group had significantly lower rates of cardiovascular events. Total mortality was also decreased.

This difference in the results, depending on the presence of other risk factors, highlights the need to consider hypertension in the context of the other risk factors that an individual patient possesses. It is not sufficient to assess and manage blood pressure alone and indeed, we may be doing our patients a disservice if we do so. As with all treatment decisions, the question of overall benefits and harms (including the cost of medication and medical care, and the impact of taking the treatment on quality of life) need to be discussed with the patient. Just lowering blood pressure to an arbitrary target – particularly in a low-risk patient – may not provide benefits and may cause harm.

In patients with multiple risk factors for cardiovascular disease, for example diabetes, we need to be more aggressive in our approach. Trials in high-risk patients support the argument for more aggressive interventions to reduce the risk of adverse cardiovascular outcomes.[3] One size rarely fits all – and a single target blood pressure for the treatment of hypertension across all patient groups is clearly not justified.

E-mail: hillsu@mail.newcastle.edu.au

REFERENCES

1. MacMahon S. Antihypertensive drug treatment: the potential, expected and observed effects on vascular disease. J Hypertens 1990;8 (Suppl 7):S239-44.
2. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group [published erratum appears in Br Med J 1999;318:29]. Br Med J 1998;317:703-13.
3. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033-41.
4. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755-62.
5. Van den Hoogen PC, Feskens EJ, Nagelkerke NJ, Menotti A, Nissinen A, Kromhout D. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. N Engl J Med 2000;342:1-8.
6. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001;345:1291-7.
7. Avanzini F, Marchioli R, Alli C, Tognoni G. Hypertension Optimal Treatment (HOT) trial [letter]. Lancet 1998;352:571-2.
8. Simon A, Levenson J. Hypertension Optimal Treatment (HOT) trial [letter]. Lancet 1998;352:571.
9. Grossman E, Goldbourt U. Hypertension Optimal Treatment (HOT) trial [letter]. Lancet 1998;352:572.
10. Gueyffier F, Boissel JP. Hypertension Optimal Treatment (HOT) trial [letter]. Lancet 1998;352:572-3.
11. Zanchetti A, Hansson L, Menard J, Leonetti G, Rahn KH, Warnold I, et al. Risk assessment and treatment benefit in intensively treated hypertensive patients of the Hypertension Optimal Treatment (HOT) study. J Hypertens 2001;19:819-25.
12. Zanchetti A, Hansson L, Dahlof B, Elmfeldt D, Kjeldsen S, Kolloch R, et al. Effects of individual risk factors on the incidence of cardiovascular events in the treated hypertensive patients of the Hypertension Optimal Treatment Study. J Hypertens 2001;19:1149-59.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 71)

1. The target blood pressure for patients with hypertension and diabetes is 130/85 mmHg.
2. To reduce the morbidity and mortality of hypertension, the target diastolic blood pressure should be less than 80 mmHg.

New drug comments on www.australianprescriber.com

Reviews of new drugs with a marketing date between editions of *Australian Prescriber* are posted on the *Australian Prescriber* web site, under Latest News. These reviews are then published in the New Drugs section of the next bimonthly issue.

Australian Medicines Handbook 2003

The Australian Medicines Handbook 2003 is available from the AMH.

Phone: (08) 8303 6977
Web site: www.amh.net.au
E-mail: amh@amh.net.au

Prices (excluding postage) $152, students $99; CD-Rom $152; book and CD-Rom $202.

Meningococcal vaccines

Margaret A. Burgess, Director, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, University of Sydney and The Children's Hospital at Westmead, Sydney; and Rosemary Lester, Manager, Prevention and Perinatal Health, Department of Human Services, Victoria

SYNOPSIS

In Australia, most cases of invasive meningococcal disease are caused by *Neisseria meningitidis* serogroup B for which there is currently no vaccine. Serogroup C infection comprises about one third of cases, but its incidence varies between the states and between age groups. Serogroup A rarely occurs in Australia. Polysaccharide vaccines which give short-term protection against serogroups A, C, W135 and Y have been available for many years. These vaccines are mainly used for travellers to regions where serogroup A and W135 infections are prevalent, but they can also be used in outbreak control. The new conjugated serotype C vaccines are highly effective, have a low rate of adverse events and induce immunologic memory. They will be used in mass vaccination programs in Australia from 2003, but they only protect against serotype C infection.

Index words: meningitis, immunisation.

(Aust Prescr 2003;26:56–8)

Introduction

Each year in Australia, meningococcal infections cause 700–800 hospitalisations and 35–40 deaths (10 in children aged 0–4 years). Invasive disease usually presents as meningitis or septicaemia. The mortality is high and those who survive may have severe sequelae.[1,2]

Epidemiology

The causative organism (*Neisseria meningitidis*) is carried asymptomatically by about 20% of the population.[1,2] It is spread by the respiratory route. In Australia in 2001 the incidence of meningococcal disease was about 3.5 cases per 100 000 population, but the rate in indigenous people is nearly six times higher. People with inherited defects of properdin or complement, or functional or anatomic asplenia, are at increased risk of meningococcal infection. The highest attack rate is in children aged 0–4 years and young adults 15–24 years. In Australia, there is a distinct seasonality with peak incidence in winter and spring.[1,2] The course of the illness is often rapid and dramatic.

Microbiology

Neisseria meningitidis has 13 serogroups.[2] Within a serogroup there are often many serotypes and subtypes identifiable by differences in outer membrane proteins. The serogroups currently responsible for most invasive disease internationally are A, B, C, W135 and Y.

In Australia serogroup B causes most infections and serogroup C about one third of cases (Fig. 1). However, an increase in the rate of serogroup C infections has been noted over the past seven years. There are marked differences in serogroup C rates from state to state, with New South Wales and Victoria experiencing the largest recent increases.[3] The number of notifications of serogroup C disease exceeded the number of notifications of serogroup B disease in Victoria in 2000 and 2001 (Fig. 2).[4] Increasing rates of serogroup C infection have also been seen in the UK and North America.

Serogroup A disease has rarely been seen in Australia since a small outbreak in the early 1990s, but occurs regularly in Africa and Asia. Serogroup W135 has recently been seen in Africa and in pilgrims to the Hajj. New Zealand has been experiencing an outbreak of serogroup B disease since 1991 with rates of type B disease nearly 10 times higher than those reported in Australia.[5]

Vaccines

There are two quite different types of meningococcal vaccines. The multivalent polysaccharide vaccine (containing polysaccharides from serogroups A, C, W135, Y) has been available for many years. It is frequently used in adults and older children travelling to endemic areas of Africa and Asia. The new conjugated serogroup C vaccine is effective in young children.

Fig. 1

Meningococcal cases per year – Australian estimates
(estimates for 1997–2001)

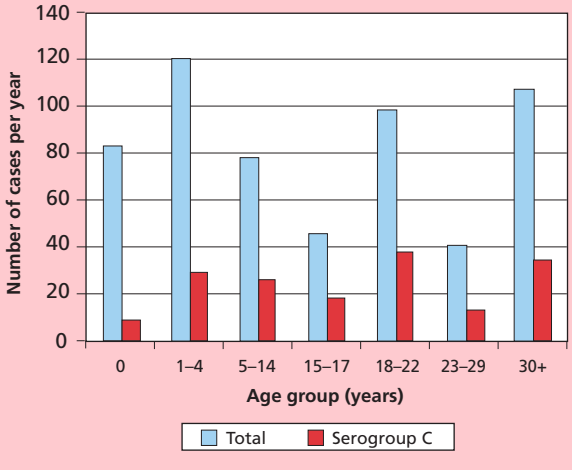
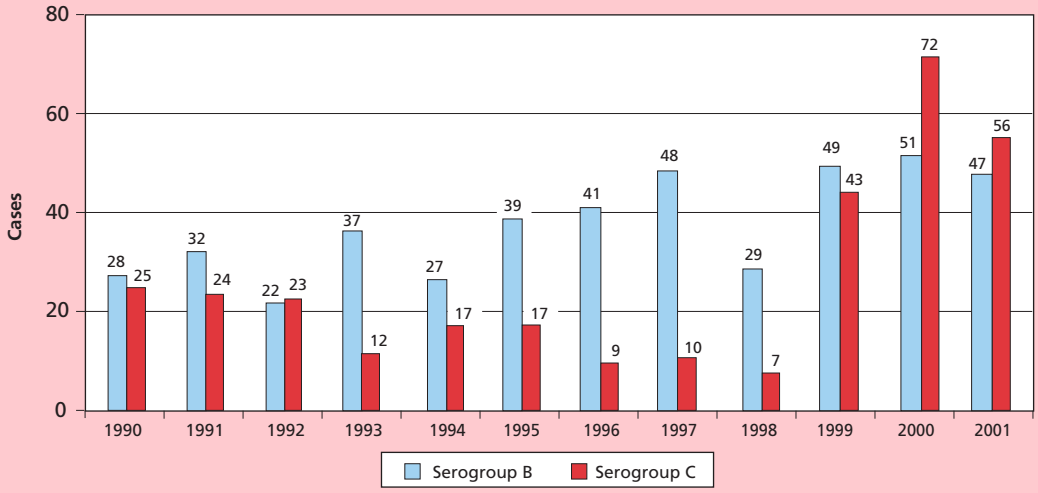


Fig. 2

Serogroup B & C meningococcal infection in Victoria, 1990–2001



There is no vaccine for serogroup B. A prototype vaccine especially developed for the subtype (B:4:P1.7b,4) prevalent in New Zealand is currently being studied in Auckland.[5]

Meningococcal tetravalent polysaccharide vaccine

There are two products available (Mencevax ACWY – containing phenol 0.25% as a preservative, and Menomune – containing thiomersal 0.01% as a preservative). Each protects against serogroups A, C, W135 and Y. These vaccines are provided in a monodose vial with 0.5 mL saline diluent.[2] They do not contain infectious material.

These tetravalent polysaccharide vaccines can be used for travellers and in outbreak control although the conjugated vaccine would be preferred for control of serogroup C outbreaks. Polysaccharide vaccines are not suitable for mass vaccination programs because:

- children under the age of 10 years have a diminished immunologic response and the vaccines are not approved for use in children under the age of two years
- immunity persists for only 3–5 years depending on the age of the recipient
- hyporesponsiveness occurs following subsequent doses
- effectiveness against serogroup C disease varies according to age and length of follow-up (one study showed 65% effectiveness for two years in people aged six months–20 years).

Adverse events such as injection site reactions and fever, which occur in 2% of children, are usually mild. Contraindications are hypersensitivity to any of the vaccine components or anaphylactic reaction following a previous dose.[2]

Meningococcal serogroup C conjugate vaccine

There are three products available:

- Meningitec – the 0.5 mL dose contains group C oligosaccharide conjugated to 15 microgram of non-toxic *Corynebacterium diphtheriae* CRM_{197} protein + aluminium phosphate adjuvant
- Menjugate – the 0.5 mL dose contains group C polysaccharide conjugated to 12.5–25 microgram of a non-toxic *Corynebacterium diphtheriae* CRM_{197} protein + aluminium hydroxide adjuvant
- NeisVac-C – the 0.5 mL dose contains group C polysaccharide conjugated to 10–20 microgram of tetanus toxoid + aluminium hydroxide adjuvant.

These vaccines contain no infectious material and have some important features:

- they can be given to all age groups including infants from the age of six weeks
- only a single dose is required for people over one year old (babies under the age of four months require three doses at least one month apart; those aged over four months but less than 12 months old require two doses*)
- the effectiveness is about 90% in the short term[6,7]
- they may have a long duration of protection – possibly 15 or more years.

Adverse event rates vary with the age of the child. Children under the age of two years can develop local redness (2%), irritability (20–50%) and fever more than 38°C (2–5%). Older children more frequently develop local redness (30%) and headaches (10–14%), but have a slightly lower rate of fever (1–2%).[3,6]

The vaccines are contraindicated in people with a hypersensitivity to any of the components or an anaphylactic reaction to a previous dose. They are not recommended in pregnancy (Category 2B) due to lack of data.

The vaccines may be administered simultaneously with other vaccines in the Australian Standard Vaccination Schedule. They should not be mixed in the same syringe with other vaccines.

* The National Health and Medical Research Council (NHMRC) recommends two doses, but this conflicts with the product information which recommends three doses in this age group. The NHMRC recommendations should be followed.

Meningococcal serogroup C vaccination programs

A mass vaccination program using conjugated meningococcal C vaccines began in the UK in November 1999.[6] The program offered vaccine progressively to everyone aged less than 18 years and there has been a very high uptake (80%). The UK program has resulted in a reduction of at least 75% in serotype C disease in the vaccinated age groups. While there is evidence of herd immunity in these age groups, there has been no evidence of herd immunity in other age groups.[6,7]

The Australian Government has announced approval for a meningococcal C vaccination program to commence in 2003. The conjugated vaccine has been included in the Australian Standard Vaccination Schedule for all children reaching the age of one year. In 2003 the vaccine will also be offered in a catch-up program to children aged one to five years by general practitioners and to senior high school children in a school-based program. In 2004–05 the remaining school-age children will have the opportunity to receive the vaccine in school-based programs. The rapidity of implementation of school-based programs will vary between jurisdictions. In view of the excellent response to the Measles Control Campaign, these school-based programs are likely to be popular.

The community must understand that this program will only prevent serogroup C disease. It will take several years to make a significant impact on group C disease and the 200 cases and 18 deaths which group C infection causes nationally each year (Fig. 1).

E-mail: margarb1@chw.edu.au

REFERENCES

1. McIntyre P, Gidding H, Gilmour R, Lawrence G, Hull B, Horby P, et al. Vaccine preventable diseases and vaccination coverage in Australia, 1999 to 2000. Commun Dis Intell 2002;Suppl:1-111. http://www.health.gov.au/pubhlth/cdi/pubs/pdf/vpd99_00.pdf
2. Australian Technical Advisory Group on Immunisation. The Australian Immunisation Handbook. 7th ed. Canberra: National Health and Medical Research Council; 2000. http://immunise.health.gov.au/handbook_7.pdf
3. Australian Technical Advisory Group on Immunisation. Recommendations on the use of meningococcal C conjugate vaccine in the Australian population. Canberra: Department of Health and Ageing. In press 2003.
4. Lester R, Pitcher H, Pellissier S, Robinson P. Vaccination against serogroup C meningococcal disease. Vic Infect Dis Bull 2002;5:26-8.
5. Baker MG, Martin DR, Kieft CE, Lennon D. A 10-year serogroup B meningococcal disease epidemic in New Zealand: descriptive epidemiology, 1991-2000. J Paediatr Child Health 2001;37:S13-S19.
6. Miller E, Salisbury D, Ramsay M. Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. Vaccine 2001; 20 Suppl 1:S58-67.
7. Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. Lancet 2001;357:195-6.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 71)

3. The currently available conjugate meningococcal vaccines do not protect against serogroup B infection.
4. Most cases of meningitis in Australia are caused by *Neisseria meningitidis* serogroup C.

Book review

Therapeutic Guidelines: Gastrointestinal. Version 3.
Melbourne: Therapeutic Guidelines Limited: 2002. 208 pages.
Price (including GST and postage): $38.75, students $31.05, RACGP members $35.45.

Mark de Souza, General Practitioner, Adamstown, NSW

Firstly, the format in a small soft cover book is useful. It doesn't fit into any pocket that I have, but is easy to toss into a briefcase or the back of the car. It is the sort of book that one might refer to at the time of a difficult problem, but it is also useful to read when one can snatch a few minutes.

The book begins in a similar format to other guidelines with a chapter devoted to 'Getting to know your gastrointestinal drugs'. This is often a good starting place and worth a read. It serves as a good summary for points to remember when prescribing these medications.

The most useful aspects for general practice seem to be the topics on the more nebulous aspects of medicine. I found it useful to peruse the chapters on 'Oral disorders', 'Common disorders of vitamin and mineral metabolism', 'Constipation', 'Diarrhoea', 'Irritable bowel syndrome' and 'Perianal disorders'.

There are several good tables such as Table 12 which shows the recommended daily intakes for various vitamins. You can compare these recommendations with the contents of the common vitamin preparations listed in the table.

Other tables of interest included the comparison table for commonly used laxatives, lactose content of infant formulae and milk products as well as a comparison table for infant rehydration formula.

At the end of the book, there is a section about gastrointestinal drugs in pregnancy and breastfeeding. While I suspect that many of my colleagues would now find this information on a computer, it is useful to know that it can be found here too. There is also a handy list of support groups for the case manager in us; very useful when accreditation comes around.

The other chapters read more like a textbook, but give comprehensive coverage of gastrointestinal issues. These include topics like oesophageal disorders, peptic ulcers, pancreatic disorders, hepatitis, liver disorders, small bowel disorders and inflammatory bowel disease. There is a good summary on how to manage enteral nutrition and stomas, although I find it rare if the patient or their carer does not know more about the problem than I do.

HIV treatments and highly active antiretroviral therapy

Cheryn Palmer, Sexual Health Physician, Infectious Diseases Unit, Nambour Hospital, Sunshine Coast, Queensland

SYNOPSIS

The treatment of HIV and AIDS has changed considerably over the last 20 years as knowledge and treatment options have increased. Highly active antiretroviral therapy is the prescription of a variety of antiretroviral medications used in combination. Potent combined regimens offer the greatest likelihood of reducing the replication of HIV, facilitating CD4 T cell expansion and delaying progression to AIDS. However, these treatments are not without complications and have substantial adverse effects.

Index words: AIDS, antiviral drugs.

(Aust Prescr 2003;26:59–61)

The early years of HIV

A great deal has happened since HIV/AIDS first came to the attention of the medical community in the early 1980s. The first reports were made to the Centers for Disease Control in the USA in 1981 when five young, homosexual men were diagnosed with the rare *Pneumocystis carinii* pneumonia. The risk groups for this new syndrome of immunosuppression soon extended from homosexual men to include injecting drug users, Haitians, transfusion recipients, female sexual contacts and Africans.[1] In 1982, the term 'acquired immune deficiency syndrome' (AIDS) was first used, replacing the previous acronym 'gay related immune deficiency'. The virus responsible for HIV was isolated in 1983 and serological tests to detect HIV antibodies were commercially available from March 1985.

Early treatments

In 1987, zidovudine was the first drug approved for the treatment of HIV. Zidovudine was the first of a class of antiretroviral drugs called nucleoside analogue reverse transcriptase inhibitors. Members of this drug class are nucleoside analogues and when they are phosphorylated in the cell they inhibit the HIV enzyme, reverse transcriptase. This results in premature termination of the HIV proviral DNA copy of the viral RNA chain and disrupted viral replication.

Initial excitement about zidovudine was tempered when the drug did not provide longer-term benefits and was accompanied by unwanted adverse effects, such as nausea, headaches, myopathy and anaemia. Following the approval of zidovudine, progress regarding HIV treatment was slow. Additional nucleoside analogue reverse transcriptase inhibitors were developed and were increasingly prescribed as 'dual therapy'. These drugs included didanosine (ddI), lamivudine (3TC), stavudine (d4T) and zalcitabine (ddC). Trials, such as Delta and ACTG (AIDS Clinical Trials Group) 175, compared the relative efficacy of monotherapy and dual therapy. The findings from these studies established the superiority of dual therapy over monotherapy. At the same time significant advances were made in the prophylaxis of opportunistic infections, especially *Pneumocystis carinii* pneumonia and *Mycobacterium avium* complex.

Treatment and monitoring advances

During 1995-97, several sequential developments dramatically changed HIV care. Firstly, there was a greater understanding of the dynamics and pathophysiology of HIV. It was found that throughout most of the disease HIV replicated at an astonishing rate, producing around 10 billion virions daily. The new virions infected available CD4 T cells and other immune targets, causing depletion of CD4 T cells and driving the immune system to increase T cell replication.

Following these revelations, HIV viral load testing was introduced as a new means of assessing the prognosis and response to therapy. (Previously treatment was monitored using the CD4 T cell count and other surrogate markers.) Viral load testing quantified the number of copies of HIV RNA/mL of blood. This test is currently the most accurate and reliable predictor of the rate and likelihood of HIV disease progression.[2]

The third significant development was the introduction of new and more potent antiretroviral drugs. Two new classes of antiretroviral drugs emerged—the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors.

Protease inhibitors are designed to inhibit the HIV protease enzyme which is essential for the production and cleavage of mature infective virions. The first trial of these new drugs (ACTG 229) investigated saquinavir, in combination with zidovudine and zalcitabine. The success of the triple combination arm of this trial led to the accelerated approval of saquinavir.

The non-nucleoside reverse transcriptase inhibitors have a similar mode of action to the nucleoside analogue reverse transcriptase inhibitor class, but prevent HIV replication by directly binding to the reverse transcriptase enzyme. Inhibiting this enzyme prevents the synthesis of a DNA copy of the RNA strand.

HAART

From 1996, the management of HIV underwent substantial change. Drugs from three different classes could now be combined to form more effective treatment regimens. Highly active antiretroviral therapy (HAART) became the new

standard of care for controlling the HIV epidemic in the Western world. There was initial hope that HAART taken continuously for a number of years might lead to the eventual eradication of HIV from the body.

The effectiveness of this new style of treatment was rapidly apparent. Impressive results were obtained from trials of the protease inhibitors. With the use of potent combinations of medication, typically containing one protease inhibitor and at least two other drugs from one or more different classes, there were sharp and sustained declines in the incidence of AIDS defining illnesses, hospitalisations and deaths.[1] The estimated number of AIDS-related deaths in the USA fell nearly 70% from 1995 to 1999 (Fig.1). Hospitalisations and AIDS defining diagnoses fell by 60–80% during this period and the time to diagnosis of AIDS was also extended.[2] Studies in 1999 confirmed that immune reconstitution resulting from HAART was nearly complete and researchers showed that it was safe to discontinue prophylaxis for opportunistic infection when sufficient CD4 T cells had been re-established. The new combined regimens were expensive, but savings from inpatient care and quality life years regained offset treatment costs.

HAART failure

Treatment success did not come without a price and unpleasant adverse effects were relatively common with the new classes of medications. The protease inhibitors often cause gastrointestinal adverse effects such as significant nausea and diarrhoea. Drug interactions between protease inhibitors and other medications were frequent and problematic. The non-nucleoside reverse transcriptase inhibitors had the potential to cause rashes, hepatotoxicity and occasionally Stevens-Johnson syndrome. Treatment regimens with HAART were more complex than monotherapy or dual therapy and typically required numerous tablets to be taken multiple times a day with rigid dosing intervals and restrictions around food. Adherence to these schedules was difficult and needed to be sustained for treatment to be effective.

Fig. 1

This graph shows that when HAART became available in 1996, the outlook for patients with HIV improved dramatically. The number of HIV-related deaths fell as HAART usage rose from zero to almost 80% of patient days (on average, patients with HIV received HAART therapy 80% of days).

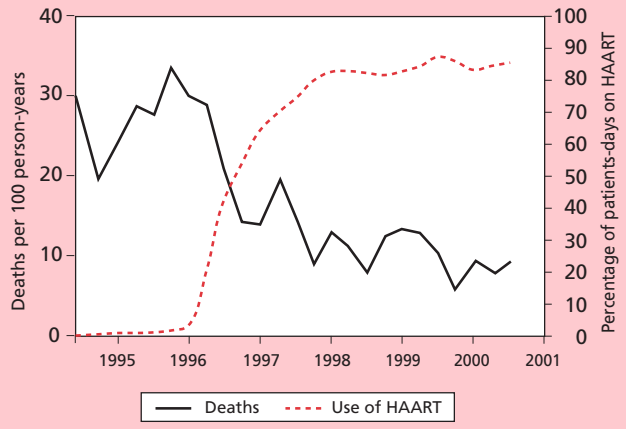


Figure reproduced from AIDS 2002;16:1617-22 with permission from Lippincott Williams & Wilkins.

Within a short period of time less favourable reports emerged that in clinical practice around half of the patients were 'failing' HAART. Treatment failure was shown by the re-emergence of virus, detectable by viral load testing, in the blood of patients who had received HAART for a year or more.[2] Failure rates were highest in those with advanced disease, those who received antiretroviral treatments before HAART was instituted, and those with less than optimal compliance with treatment.

Drug resistance developed to the new classes of antiretroviral drugs, as had already been seen with zidovudine and other nucleoside analogue reverse transcriptase inhibitors. The result of drug resistance was a loss of viral suppression leading to a rise in viral load and fall in T cell numbers, with the resultant risk of disease progression.

Treatment complications

Significant toxicity and adverse effects are associated with antiretroviral therapy. These include:

- lipodystrophy and insulin resistance
- mitochondrial toxicity, lactic acidosis and hepatic steatosis
- osteopenia
- peripheral neuropathy
- myopathy
- nephrolithiasis.

Lipodystrophy, a syndrome of fat redistribution and serum lipid/glucose abnormalities, was first reported in 1998. High concentrations of triglyceride, cholesterol and glucose are found, typically in combination with body fat changes including fat wasting in the limbs, truncal obesity and loss of facial fat. This syndrome occurred most frequently in patients taking protease inhibitors and certain nucleoside analogue reverse transcriptase inhibitors (such as stavudine). Some of the physical manifestations of the condition were obvious and stigmatising, particularly the formation of a 'buffalo fat hump' on the upper back and marked facial wasting. Concerns about the long-term impact of these changes and the potential for an elevated risk of cardiovascular disease and diabetes, further complicated decisions about treatment options.

The current state of play

HIV continues to have enormous global impact, particularly in the developing world. Around 40 million people are infected worldwide and new infections occur at a rate of 14 000 per day. Currently in Australia, approximately 22 100 people are HIV positive and to October 2002, 6184 deaths had occurred due to AIDS.[3] Eradication of HIV by continuous therapy is highly unlikely, due to the very long half-life and latency of some immune cells infected with HIV. No cure is in sight and a preventive vaccination will not be available in the near future.

New drugs within the existing classes of antiretrovirals and further classes of drugs (such as vaccines, fusion inhibitors

Table 1

Risk of developing AIDS in 6 years (%)

HIV viral load (copies/mL)	*CD4 T lymphocyte count (cells/microlitre)*		
	CD4 < 350	*CD4 350-500*	*CD4 > 500*
> 55 000	93	79	67
20–55 000	73	57	50
7–20 000	42	40	26
< 7000	19	22	15

Treatment is recommended when the risk of developing AIDS is greater than 50%.

and co-receptor antagonists) have been developed. These are variously available through trials and special access schemes. Modifications to existing drugs have sought to improve dosing schedules, with once-daily treatments and the combination of up to three drugs in a single tablet. Attention has been focused on the need to improve and maintain compliance to maximise the impact and duration of whatever treatment regimen is adopted. Consequently, there is a need to tailor treatment to suit each individual and the lifestyle they lead.

From the late 1990s to the present time, HIV treatments have come under increasing scrutiny. Long-term treatment with HAART is clearly not straightforward or without consequences. Developing alternative regimens for those in whom treatment has failed, simplifying regimens to improve compliance and managing the wide range of adverse effects is a challenge.

HIV treatment has become increasingly complex and clinicians must confront numerous issues and dilemmas, without a clear consensus on the best treatment strategy to adopt.

Awareness of the complications and adverse effects related to antiretroviral therapy has made many clinicians more cautious about advocating early treatment, in contrast to the 'hit hard and early' approach initially adopted with HAART. The current Australian, American and British guidelines for starting antiretroviral therapy are much more conservative than those released in 1997. Protease inhibitors are now used less frequently in early treatment regimens than they were when HAART first came into vogue and nearly every drug combination included at least one protease inhibitor.

Treatment of symptomatic HIV infection or AIDS extends life and most clinicians would offer therapy in these situations. However, in asymptomatic patients, current recommendations suggest that treatment does not start until the CD4 T cell count falls below 350/microlitre or the HIV load exceeds 50 000 copies/mL. These recommendations are based on the risk of developing AIDS within six years without treatment (Table 1).[4]

In just over 20 years AIDS has grown from a cluster of cases into a substantial global health problem. In the Western world, the disease has changed from being predictably fatal to a chronic manageable condition, for those in whom the drugs work well. In the world's poorest nations, however, little has changed and effective therapy is almost completely unattainable. The epidemic continues to rage out of control and the main concerns are more basic; prevention, diagnosis, access to health care and palliation.

REFERENCES

1. Sepkowitz KA. AIDS – the first 20 years. N Eng J Med 2001;344:1764-72.
2. Bartlett JG. The Johns Hopkins Hospital 2002 guide to medical care of patients with HIV infection. 10th ed. Baltimore: Lippincott Williams & Wilkins; 2002.
3. National Centre in HIV Epidemiology and Clinical Research. Australian HIV Surveillance Report 2002;18:9,10. Sydney: Communicable Diseases Surveillance Unit, Communicable Diseases Branch, NSW Health; 2002.
4. Kelly M. The state of play: HIV treatment. HIV Australia 2002;1:13-5.

FURTHER READING

AIDSinfo: HIV/AIDS Medical Practice Guidelines. US Department of Health and Human Services.
http://www.aidsinfo.nih.gov/guidelines

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 71)

5. The best combination of drugs for the treatment of HIV infection is unknown.
6. HIV has not developed a resistance to protease inhibitors.

Patient support organisations

National Association of People living With HIV/AIDS (NAPWA)

and

State and Territory AIDS Councils (see page 67)

The National Association of People living With HIV/AIDS (NAPWA) is Australia's peak non-government advocacy organisation representing people living with HIV/AIDS community-based groups from each of Australia's states and territories.

Contacts

National Association of People living With HIV/AIDS (NAPWA)

Level 1, 222 King Street
Newtown NSW 2042
Phone: (02) 9557 8825
Web site: www.napwa.org.au
E-mail: admin@napwa.org.au

continued on page 67

Serotonin syndrome

Michael Hall, Clinical Pharmacology/Toxicology Registrar, and Nick Buckley, Associate Professor, Department of Clinical Pharmacology and Toxicology, The Canberra Hospital, Canberra

SYNOPSIS

Serotonin syndrome is a toxic state caused mainly by excess serotonin within the central nervous system. It results in a variety of mental, autonomic and neuromuscular changes, which can range in severity from mild to life-threatening. Most cases are self-limiting. Severe serotonin syndrome is nearly always caused by a drug interaction involving two or more 'serotonergic' drugs, at least one of which is usually a selective serotonin reuptake inhibitor or monoamine oxidase inhibitor. Management involves withdrawal of the offending drugs, aggressive supportive care and occasionally serotonin antagonists such as cyproheptadine. Treatment of the condition for which the serotonergic drugs were prescribed should be reviewed.

Index words: selective serotonin reuptake inhibitors, drug interactions, cyproheptadine.

(Aust Prescr 2003;26:62–3)

Introduction

The treatment of depression in Australia has evolved greatly over the last two decades. Tricyclic antidepressant use is decreasing, while the use of selective serotonin reuptake inhibitors (SSRIs) is increasing. In 2001, prescriptions for SSRIs outnumbered those for tricyclics by two to one.[1] Other new antidepressants with serotonergic properties are also being introduced. Although SSRIs and the other 'atypical' antidepressants are generally regarded as having lower toxicity than tricyclics, minor toxic effects are common, and serious toxicity can occur.

Serotonin syndrome refers to a drug-induced syndrome that is characterised by mental, autonomic and neuromuscular changes. It is not an idiosyncratic adverse reaction, but a dose-related range of toxic symptoms that are largely attributable to increasing serotonin concentrations in the central nervous system. Serotonin syndrome was first described in 1955, but during the 1990s reports became increasingly common, as the signs, symptoms, and precipitants became more widely recognised. Although severe cases have been reported with an overdose of a single drug, they usually only occur with a combination of two or more 'serotonergic' drugs (even when each is at a therapeutic dose), presumably leading to an excessive rise in serotonin concentrations. The true incidence of serotonin syndrome is unknown, because of a lack of large case series, a wide spectrum of symptoms and variations in the definition.

Pathophysiology

Serotonin (5-hydroxytryptamine, 5-HT) is synthesised from the amino acid tryptophan. It has central and peripheral effects and there are at least seven different types of serotonin receptors. Centrally, serotonin acts as a neurotransmitter with influences on mood, sleep, vomiting and pain perception. Depression is often associated with low concentrations of serotonin. Peripherally, the primary effect of serotonin is on muscles and nerves. The majority of serotonin is synthesised and stored in the enterochromaffin cells of the gut where it causes contraction of gastrointestinal smooth muscle. Serotonin is also stored in platelets and promotes platelet aggregation. It also acts as an inflammatory mediator.

The pathophysiology of serotonin syndrome remains poorly understood. It is thought to result from stimulation of the 5-HT_{1A} and 5-HT_{2} receptors, and the drug classes implicated in serotonin syndrome reflect this theory. These include serotonin precursors, serotonin agonists, serotonin releasers, serotonin reuptake inhibitors, monoamine oxidase inhibitors (MAOIs) and some herbal medicines (Table 1). Commonly used migraine medications such as sumatriptan and dihydroergotamine are also regarded as 'serotonergic' drugs. There are isolated case reports of mild/moderate serotonin syndrome associated with these drugs. Most cases will involve either an SSRI or an MAOI and at least one other medication. Generally, drugs with two different mechanisms of action on serotonin must be present for a severe serotonin syndrome to develop.

Table 1

Drugs implicated in severe serotonin syndrome*

Drug	*Mechanism*
L-Tryptophan	Serotonin precursor
Selective serotonin reuptake inhibitors	Inhibit serotonin reuptake
Tricyclic antidepressants	Inhibit serotonin reuptake
Monoamine oxidase inhibitors (A>B)	Inhibit metabolism of 5-HT
Pethidine	Serotonin agonist
Tramadol	Inhibits serotonin reuptake
LSD	Partial serotonin agonist
Buspirone	Partial serotonin agonist
Amphetamines and anorectics	↑ 5-HT release & ↓ reuptake
Atypical antidepressants	Various
St John's wort	All of the above?
Lithium	Unknown

* Note: Interactions are more severe between drugs with different mechanisms of increasing serotonin.

Some other drugs may cause serotonin syndrome although how this happens remains unclear. Drugs with effects on catecholamines, tryptamine and dopamine may have secondary effects on serotonin release or reuptake.

Diagnosis

The diagnosis of serotonin syndrome is purely clinical. It is based upon recognising a varied combination of signs and symptoms in the presence of selected 'serotonergic' medications. The diagnosis should not be made without identifying a cause. Serotonin syndrome most commonly occurs after a dose increase (or overdose) of a potent serotonergic drug or shortly after a second drug is added. Some of the drugs involved have very long half-lives (e.g. fluoxetine) and may have been ceased weeks before. There may be a history of recent overdose or use of illicit drugs, particularly ecstasy, amphetamines or cocaine. Herbal medicines may be implicated (St John's wort, ginseng, S-adenosyl-methionine).

The clinical features of serotonin syndrome are highly variable, reflecting the spectrum of toxicity (Table 2). The onset can be dramatic or insidious. The most useful features in the diagnosis of serotonin syndrome are hyperreflexia and clonus (inducible/spontaneous/ocular). However, many patients taking SSRIs may display one or more of the clinical features without gross toxicity.

Investigations are generally unhelpful in the diagnosis of serotonin syndrome, but may assist in treatment and in ruling out a differential diagnosis. The white cell count is often mildly raised and elevations in creatine kinase levels may occur.

The differential diagnosis includes neuroleptic malignant syndrome, dystonic reactions, encephalitis, tetanus, thyroid storm and sepsis, as well as poisoning by anticholinergic drugs, amphetamines, cocaine, lithium, MAOIs, salicylates and strychnine. Serotonin syndrome can also be confused with the withdrawal of antidepressant treatment.[2] Serotonin syndrome and the other agitated deliriums share many clinical features, but clonus, hyperreflexia and flushing are the most specific signs.

Time course/complications

In most cases, serotonin syndrome is a self-limiting condition and will improve on cessation of the offending drugs. Mild to moderate cases usually resolve in 24–72 hours. In severe cases patients require intensive care as the syndrome may be complicated by severe hyperthermia, rhabdomyolysis, disseminated intravascular coagulation and/or adult respiratory distress syndrome.

Treatment

Recognising the possibility of serotonin syndrome and diligent supportive care are the mainstays of treatment. All patients with moderate or severe serotonergic symptoms should be admitted to hospital. Those with hyperthermia should be admitted to an intensive care unit. All serotonergic medications should be ceased, and care taken that other precipitants are not inadvertently administered. Intravenous hydration is given, to ensure an adequate output of urine. Careful monitoring of temperature, pulse, blood pressure and urine output is required. Aggressive cooling techniques may be required for hyperthermia. This may involve cool water sprays, ice packs, and even paralysis and ventilation. Benzodiazepines may be used to control seizures and muscle hyperactivity. Specific treatment of hypertension is usually not required.

Table 2

Clinical features of serotonin syndrome

Cognitive	Confusion, agitation, hypomania, hyperactivity, restlessness
Autonomic	Hyperthermia, sweating, tachycardia, hypertension, mydriasis, flushing, shivering
Neuromuscular	Clonus (spontaneous/inducible/ocular), hyperreflexia, hypertonia, ataxia, tremor

Hypertonia and clonus are always symmetrical and are often much more dramatic in the lower limbs.

Serotonin antagonists have been used in management of moderate to severe serotonin syndrome. Cyproheptadine is possibly the most promising drug.[3] The initial dose is 4–8 mg orally. This may be repeated in two hours. If no response is seen after 16 mg it should be discontinued. If there is a response then it may be continued in divided doses up to 32 mg/day (e.g. up to 8 mg four times daily). Other drugs that have been suggested include chlorpromazine and propranolol, but these have more contraindications and adverse effects.

After the patient has recovered reconsider the ongoing treatment of the condition for which the serotonergic drug was prescribed.

Prevention

The prevention of serotonin syndrome involves awareness of the toxic potential of serotonergic drugs. The manufacturer's advice about washout periods should be carefully considered when switching antidepressants and patients should also be educated about possible drug interactions.

E-mail: michael.hall@act.gov.au

REFERENCES

1. Data produced by Drug Utilisation Sub-Committee, Pharmaceutical Benefits Branch, Health Access and Financing Division, Commonwealth Department of Health and Ageing, Canberra, 2002.
2. Tiller JWG. Medicinal mishaps: serotonin states. Aust Prescr 1998;21:63.
3. Chan BS, Graudins A, Whyte IM, Dawson AH, Braitberg G, Duggin GG. Serotonin syndrome resulting from drug interactions. Med J Aust 1998;169:523-5.

FURTHER READING

Gillman PK. The serotonin syndrome and its treatment. J Psychopharmacol 1999;13:100-9.

Gillman PK. Serotonin syndrome: history and risk. Fundam Clin Pharmacol 1998;12:482-91.

Conflict of interest: none declared

ABNORMAL LABORATORY RESULTS

B-type natriuretic peptide: a new diagnostic tool for congestive heart failure

Ben Ewald, Lecturer in Epidemiology, and General Practitioner, Centre for Clinical Epidemiology and Biostatistics, University of Newcastle, Newcastle, New South Wales

SYNOPSIS

B-type natriuretic peptide is released from the ventricle of patients with heart failure. High concentrations help to distinguish heart failure from other causes of dyspnoea. The test is sensitive in congestive heart failure but it cannot distinguish if the dysfunction is diastolic or systolic. B-type natriuretic peptide is not used as a routine test in Australia, but if it becomes available it may be helpful in ruling out the diagnosis of congestive heart failure. It is also being investigated as a screening tool for heart disease in the community.

Index words: echocardiography, dyspnoea, screening.

(Aust Prescr 2003;26:64–5)

Introduction

The diagnosis of congestive heart failure rests on three elements. These are suitable signs and symptoms, objective evidence of ventricular dysfunction, and response to treatment. While the diagnosis is generally clear when the patient has obvious clinical or radiological pulmonary oedema, it can be difficult to make when the condition is less advanced or the patient has comorbidities such as lung disease. The Framingham criteria are a way of scoring symptoms and clinical signs, but cannot be regarded as giving a definitive diagnosis of congestive heart failure. In one recent study the Framingham criteria were compared with the diagnosis made by two cardiologists with access to echocardiographic results for 1586 acutely dyspnoeic patients presenting to emergency wards. The criteria and the final diagnosis were concordant in only 73% of patients.[1] Improved ways of detecting congestive heart failure would therefore be of great clinical benefit.

Objective evidence of ventricular dysfunction is currently obtained from echocardiography, catheter studies, or nuclear medicine studies. Catheter studies and nuclear medicine are invasive, quite expensive and not widely available. Echocardiography is more widely available, however it still requires waiting for, and travel to, an appointment. This can be a problem for the frail aged or patients in rural areas. Detection of ventricular dysfunction by a simple blood test would therefore be a very attractive alternative.

Physiology

Four neurohormonal systems are activated by ventricular dysfunction. These are the sympathetic nervous system, the renin-angiotensin-aldosterone system, the endothelin pathway, and the natriuretic peptides. All these systems maintain systemic tissue perfusion and the first three also maintain blood pressure, which is advantageous in the short term but deleterious to the heart in the long term.

The natriuretic peptides produce diuresis, natriuresis and vasodilatation. These effects reduce the load on the heart, and work in opposition to the renin-aldosterone system and the sympathetic nervous system. Although natriuretic peptides are increased in heart failure, their effects are overwhelmed by the activated renin-angiotensin-aldosterone system and sympathetic nervous system. Three peptides have been identified:

- A (or atrial) natriuretic peptide is secreted by the atrium in response to dilatation
- B natriuretic peptide (BNP, originally called 'brain natriuretic peptide' as it was found in the brains of pigs) is produced by the ventricle in response to increased end diastolic pressure or volume
- C natriuretic peptide is produced widely by endothelial cells in response to shearing stresses.

B-type natriuretic peptide

When stimulated by stress or stretch, ventricular myocytes activate transcription of the relevant gene and produce a 108 amino acid peptide (Pro BNP). Before excretion by the myocyte this peptide is cleaved to produce an inactive 76 amino acid N-terminal fragment and the C-terminal 32 amino acid with hormonal activity (BNP).[2] Plasma half-life of BNP *in vivo* is 18 to 22 minutes so concentration promptly reflects changes in cardiac status.

Available assays measure either the inactive N-terminal fragment or the active 32 amino acid peptide. There are currently several assays available that do not give directly comparable results. Individual laboratory reference ranges should therefore be used.

Of all the neurohormones, BNP is the best candidate for use as a diagnostic test. When BNP rises it tends to go very high,

which gives it good discriminatory power in separating ventricular causes of dyspnoea from other causes. In one series of patients presenting to an emergency ward with shortness of breath, those without heart failure had a mean BNP concentration of 38 pg/mL while in those with heart failure it averaged 1076 pg/mL. [3]

Four studies* (totalling 1994 patients) have compared the test performance of BNP with the diagnosis of congestive heart failure made by echocardiography and consideration of all clinical details.[1,3,4,5] The results show BNP has a sensitivity of 90–97% and a specificity of 76–92%. There have also been four studies* (totalling 6109 people) which investigated using BNP to screen for pre-clinical heart disease in the community.[6,7,8,9] Three of these studies showed good test performance with sensitivities ranging from 77% to 100% and specificities from 70% to 96%. Recent results[9] contradict these findings and show sensitivity in detecting any left ventricular systolic dysfunction of only 53% in men and 26% in women. For moderate to severe left ventricular systolic dysfunction these values are 65% and 80%, well below those found in the other studies. This suggests that although BNP shows good test performance in acutely sick hospital patients it is less accurate in the detection of ventricular dysfunction in asymptomatic individuals.

Only two of the studies (involving 232 patients) investigated the use of BNP as a diagnostic tool for suspected congestive heart failure in general practice. Further research is needed to validate the test in the milder spectrum of disease seen in general practice. One such study is currently under way in Newcastle, New South Wales.

Congestive heart failure can be due to either systolic or diastolic ventricular dysfunction. While there are guidelines[10] and a wealth of good evidence from randomised controlled trials on the management of systolic dysfunction, there is scant evidence on how to manage diastolic failure. BNP is increased in both systolic and diastolic dysfunction so many patients will still need echocardiography in order to plan therapy. The value of the test may eventually be in its capacity to rule out heart failure as a cause of a patient's illness.

BNP has been shown to be a powerful predictor of prognosis in patients with heart failure. A high concentration is associated with a poor prognosis. Some centres are therefore using BNP concentrations to guide therapy, however this usage is still experimental.

E-mail: ben.ewald@newcastle.edu.au

REFERENCES

1. Maisel A, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161-7.
2. Clerico A, Del Ry S, Giannessi D. Measurement of cardiac natriuretic hormones (atrial natriuretic peptide, brain natriuretic peptide, and related peptides) in clinical practice: the need for a new generation of immunoassay methods. Clin Chem 2000;46:1529-34.
3. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol 2001;37:379-85.
4. Davis M, Espiner E, Richards G, Billings J, Town I, Neill A, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. Lancet 1994;343:440-4.
5. Cowie MR, Struthers AD, Wood DA, Coats AJS, Thompson SG, Poole-Wilson PA, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997;350:1349-53.
6. McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998;351:9-13.
7. Hobbs FDR, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. Br Med J 2002;324:1498-500.
8. Nakamura M, Endo H, Nasu M, Arakawa N, Segawa T, Hiramori K. Value of plasma B type natriuretic peptide measurement for heart disease screening in a Japanese population. Heart 2002;87:131-5.
9. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PWF, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction. The Framingham heart study. JAMA 2002;288:1252-9.
10. Krum H, National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand Chronic Heart Failure Clinical Practice Guidelines Writing Panel. Guidelines for management of patients with chronic heart failure in Australia. Med J Aust 2001;174:459-66.

Dr Ewald's research into BNP is funded by the Hunter Medical Research Institute.

* Details of studies of BNP are available in the electronic version of this article.
See http://www.australianprescriber.com

Self-test questions

The following statements are either true or false (answers on page 71)

7. Changes in end diastolic pressure stimulate the secretion of B-type natriuretic peptide from the brain.
8. In congestive heart failure concentrations of B-type natriuretic peptide increase.

Adverse drug reactions reporting online

Australian Prescriber readers are now able to report adverse reactions to medicines directly to the Adverse Drug Reactions Advisory Committee (ADRAC). Health professionals who are likely to use the new service regularly can become 'registered reporters'. Those who just wish to report reactions occasionally can do so as 'unregistered reporters'. To access the service, reporters can connect to the website of the Therapeutic Goods Administration (www.tga.gov.au). The link to adverse drug reaction reporting is on the home page.

Medicines Australia Code of Conduct

Medicines Australia (formerly the Australian Pharmaceutical Manufacturers Association) has a code of conduct to guide the promotion of prescription drugs in Australia.[1] An updated version of the Medicines Australia Code of Conduct was implemented earlier this year.[2] The revisions will have taken into account some of the complaints received in the previous year.

The report of the Code of Conduct Committee for 2002 says that 49 complaints were received. Nine complaints were withdrawn and some are unresolved, so the report details the assessment of 36 cases.[3]

Most of the complaints came from rival pharmaceutical companies, but six came from health professionals and three were made by the Australian Consumers Association. Nine complaints did not involve a breach of the Code of Conduct and two more were dismissed by the Code of Conduct Appeals Committee. This leaves 25 complaints in which at least one breach of the Code was found (Table 1). Details of these breaches can be found in the report.[3]

NOTE

The Medicines Australia Code of Conduct is available from:
Medicines Australia
Level 1, 16 Napier Close
DEAKIN ACT 2600
Tel: (02) 6282 6888
Web site: www.medicinesaustralia.com.au

REFERENCES

1. Roughead EE. The Australian Pharmaceutical Manufacturers Association Code of Conduct: guiding the promotion of prescription medicines. Aust Prescr 1999;22:78-80.
2. Medicines Australia. Code of Conduct. 14th ed. Canberra: Medicines Australia; 2002.
3. Medicines Australia. Code of Conduct Annual Report 2002. Canberra: Medicines Australia; 2002.

Table 1

Breaches of the Code of Conduct July 2001–June 2002

Company	*Complaint*		*Sanction imposed by Code of Conduct Committee*
	Drug brand name	*Drug generic name*	
Abbot Australasia	Reductil	sibutramine	Withdrawal of promotional material
Alcon Laboratories	Travatan	travoprost	Withdrawal of promotional material
AstraZeneca	Oxis Turbuhaler	eformoterol	Withdrawal of promotional material, promotional material to be recovered from recipients
Aventis Pharma	Rulide	roxithromycin	Withdrawal of promotional material. Corrective letter to be sent to all general practitioners. $20 000 fine (reduced to $10 000 on appeal)
	Rulide	roxithromycin	Withdrawal of promotional material
	Tritace	ramipril	Withdrawal of promotional material. $5000 fine
	Specialist symposium (hospitality out of proportion to educational content)		$10 000 fine
Baxter Healthcare (non-member)	Suprane	desflurane	Withdrawal of promotional material. Corrective letter to be sent to anaesthetists.
Bristol-Myers Squibb	Pravachol	pravastatin	$40 000 fine (reduced to $20 000 on appeal)
CSL Ltd	Flomax	tamsulosin	Withdrawal of promotional material
	Vaqta	hepatitis A vaccine	Withdrawal of promotional material. Corrective advertising to address potentially misleading information. $20 000 fine
GlaxoSmithKline	Lamictal	lamotrigine	Withdrawal of promotional material. Corrective letter to be sent to general practitioners and neurologists.
	Seretide	fluticasone	Corrective letter to be sent to general practitioners and specialists
Lundbeck Australia	Cipramil	citalopram	Material not to be used again. Corrective letter to be sent to recipients of the material.
Merck Sharp & Dohme	Fosamax	alendronate	Withdrawal of promotional material
Novartis Pharmaceuticals	Famvir	famciclovir	Withdrawal of promotional material
	Zelmac	tegaserod	Withdrawal of promotional material
Pfizer	Aricept	donepezil	Withdrawal of promotional material. Corrective advertising required and a corrective letter to be sent to all doctors.
	Aricept	donepezil	Withdrawal of promotional material
	Norvasc	amlodipine	Withdrawal of promotional material. Corrective advertising required and a corrective letter to be sent to all general practitioners. $50 000 fine
	Zeldox (unapproved product)		Promotional activity should not occur again. $15 000 fine
Pharmacia Australia	Somac	pantoprazole	Withdrawal of promotional material. $50 000 fine for repeating previous breaches
Roche Products	Xenical	orlistat	Withdrawal of promotional material
Servier Laboratories (non-member)	Coversyl	perindopril	Withdrawal of promotional material. Corrective letter to be sent to all general practitioners.
Wyeth Australia	Educational meeting (hospitality out of proportion to educational content)		Activity should not occur again

The story of one complaint

John S. Dowden, Editor

Shortly after a review of tegaserod[1] was prepared for *Australian Prescriber*, one of the editorial staff noticed an advertisement for the drug in a medical newspaper. The advertisement appeared to show a young man and a young woman complaining about their symptoms of irritable bowel syndrome. Unfortunately, the young man would not be able to get relief from tegaserod as it was only approved for women. Without studying the product information, health professionals may not have been aware of this restriction from the advertisement.

I wrote to the Code of Conduct Committee to say the advertisement could be misinterpreted. I did not specify which section of the Code might have been breached, but the Australian Pharmaceutical Manufacturers Association (APMA, now Medicines Australia) identified three possible breaches.

On the day the APMA informed me the complaint would be considered, I was surprised to receive a telephone call from the manufacturer of tegaserod. Obviously the APMA had promptly informed the company of the source of the complaint.

The head of marketing politely discussed the issues I had identified. I was reassured that there had been no intention to misinform health professionals. The manager suggested that as any breach of the Code of Conduct would be a minor technicality it may be appropriate to withdraw my complaint. He also pointed out that the Code of Conduct Committee has a big workload and it would be helpful if the Committee did not have to consider inadvertent breaches.

The manager followed up his telephone call with a civil electronic mail message asking me to consider withdrawing the complaint. If other companies take this very persuasive approach it may help to explain why relatively few complaints from health professionals reach the Code of Conduct Committee.

I was on the verge of withdrawing the complaint when tegaserod started appearing in the general media. The stories hailed tegaserod as a breakthrough treatment and featured Kirstie Marshall (Olympic skier, now turned Victorian MP) as the celebrity sufferer. Unfortunately, the message that tegaserod was only approved for women with a less common form of irritable bowel syndrome was not clear. Perhaps the marketing materials did need clarification? I decided not to withdraw the complaint.

The Code of Conduct Committee found the advertisement had breached all three sections of the Code. In keeping with APMA policy[2], I was asked to keep the verdict confidential in case the company appealed the decision. I heard nothing more about the complaint until it was published in the annual report of the Code of Conduct Committee.[3]

REFERENCES

1. Tegaserod. Aust Prescr 2002;25:74-5.
2. Marley J. Complaints: a personal view. Aust Prescr 1999;22:80.
3. Medicines Australia. Code of Conduct Annual Report 2002. Canberra: Medicines Australia; 2002.

Patient Support Organisations

Continued from page 61

State and Territory AIDS Councils

AIDS Council of NSW
9 Commonwealth Street
Surry Hills NSW 1300
Phone: (02) 9206 2000
Web site: www.acon.org.au

Northern Territory AIDS Council
46 Woods Street
Darwin NT 0800
Phone: (08) 8941 1711
Web site: www.octa4.net.au/ntac

AIDS Action Council of the ACT
16 Gordon Street
Acton ACT 2601
Phone: (02) 6257 2855
Web site: www.aidsaction.org.au

West Australian AIDS Council
664 Murray Street
West Perth WA 6872
Phone: (08) 9482 0000
Web site: www.waaids.com

AIDS Council of South Australia
64 Fullarton Rd
Norwood SA 5067
Phone: (08) 8362 1611
Web site: www.aidscouncil.org.au

Victorian AIDS Council
6 Claremont Street
South Yarra VIC 3141
Phone: (03) 9865 6700
Web site: www.vicaids.asn.au

Tasmanian Council on AIDS and Related Diseases
319 Liverpool St
Hobart TAS 7000
Phone: (03) 6234 1242
Web site: www.tascahrd.org.au

Queensland AIDS Council (QuAC)
32 Peel Street
South Brisbane QLD 4101
Phone: (07) 3017 1777
Web site: www.quac.org.au

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 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.

Arcitumomab

CEA-Scan (Australian Radioisotopes)

vials containing 1.25 mg lyophilised arcitumomab for reconstitution with sodium-pertechnetate in saline

Approved indication: imaging of advanced colorectal cancer

Carcinoembryonic antigen (CEA) is found in the serum of patients with colorectal cancers. It can be used in monitoring these patients for local recurrences or metastases. Attaching a radioactive label to an antibody (arcitumomab) to CEA helps to localise where the tumour cells producing the CEA are.

Arcitumomab is made by exposing mouse spleen cells to human CEA. These cells produce an antibody from which the arcitumomab fragment is extracted. Arcitumomab is mixed with a technetium-containing radionuclide and diluted before being injected intravenously. The technetium disintegrates giving off gamma rays. It has a half-life of six hours and 28% of the radiolabel is excreted in the urine within 24 hours. Imaging should take place 2–5 hours after the injection.

In one trial, 40 patients with resected rectal cancer were followed up for five years with CEA immunoscintigraphy in addition to routine surveillance. Sixteen patients developed recurrent cancer. Although only six of these patients had increased serum CEA, immunoscintigraphy identified 82% of the tumours. The sensitivity for finding lesions was 94% and the specificity was 97%. This resulted in six patients having further surgery which could improve their survival. These patients had a mean survival of 35 months compared to 21 months in a group of historic controls.[1]

The adverse reactions to the injection have included itching, urticaria and other rashes. Some patients will develop antibodies to mouse protein.

Although CEA immunoscintigraphy can help to identify local recurrences, it may not give surgeons all the information they need. In a comparison with positron emission tomography (PET), CEA immunoscintigraphy did not detect all metastases in bone, lung and lymph nodes.[2] Another small study found that PET is better at predicting which patients have resectable recurrent disease. In 16 patients having resections, PET had predicted resectable tumours in 81% while CEA immunoscintigraphy identified only 13% as resectable. CEA immunoscintigraphy was unable to show which patients had unresectable disease whereas PET predictions were correct in 90% of patients with unresectable disease.[3]

REFERENCES

1. Lechner P, Lind P, Goldenberg DM. Can postoperative surveillance with serial CEA immunoscintigraphy detect resectable rectal cancer recurrence and potentially improve tumor-free survival? J Am Coll Surg 2000;191:511-8.
2. Willkomm P, Bender H, Bangard M, Decker P, Grünwald F, Biersack HJ. FDG PET and immunoscintigraphy with ^{99m}Tc-labeled antibody fragments for detection of the recurrence of colorectal carcinoma. J Nucl Med 2000;41:1657-63.
3. Libutti SK, Alexander HR, Choyke P, Bartlett DL, Bacharach SL, Whatley M, et al. A prospective study of 2-fluoro-2-deoxy-D-glucose/positron emission tomography scan, ^{99m}Tc-labeled arcitumomab (CEA-scan), and blind second-look laparotomy for detecting colon cancer recurrence in patients with increasing carcinoembryonic antigen levels. Ann Surg Oncol 2001;8:779-86.

Artemether and lumefantrine

Riamet (Novartis)

tablets containing 20 mg artemether and 120 mg lumefantrine

Approved indication: Falciparum malaria

Australian Medicines Handbook section 5.4.1

Plasmodium falciparum is the malaria parasite which causes most deaths. In many areas the parasite has developed resistance to chloroquine so there is a need to develop alternative treatments for malaria.

Artemisinin is a chemical found in the sweet wormwood (*Artemisia annua*), a Chinese herb used in the treatment of fever. Although artemisinin is effective against the parasite the symptoms rapidly recur unless high doses are used. To overcome the problems of monotherapy artemether, a derivative of artemisinin, has been combined with lumefantrine, an antimalarial drug developed in China. Compared to artemether, lumefantrine has a slower onset of action, but a more sustained effect against the parasite. The combination is more effective than either drug given alone.

Artemether is rapidly absorbed, but lumefantrine does not reach a peak plasma concentration until 6–8 hours after the combined tablet is swallowed. The tablets are taken after meals as food increases absorption. Artemether undergoes extensive first-pass metabolism and is mainly eliminated by the liver. It has a half-life of two hours whereas lumefantrine which is also eliminated by metabolism has a half-life of 4–6 days in infected patients.

As the metabolism of the drugs involves the cytochrome P450 system there are potential interactions with many drugs that are also metabolised by this system. The combination is contraindicated in patients taking drugs metabolised by CYP3A4 (e.g. erythromycin) or CYP2D6 (e.g. imipramine). It should also not be given with drugs, including other antimalarial drugs, that prolong the QT_c interval. Ideally all patients should have an electrocardiogram before and during treatment as prolongation of the QT_c interval is a contraindication to treatment.

Although palpitations can occur in 7.5% of patients the commonest adverse effects are headache and dizziness. Many

adverse events during treatment could be caused by malaria. They include fever, asthenia, anorexia and abdominal pain. The safety of artemether and lumefantrine in pregnancy is unknown and it is not approved for use in children less than 12 years old.

A regimen of six doses given over 60 hours has been compared with a mefloquine-based regimen in Thailand. Mefloquine was given to 55 patients with acute uncomplicated falciparum malaria and 164 were given artemether and lumefantrine. All the patients given the mefloquine-based regimen were cured within a month, while the cure rate with the combination was 95.5%. There was no significant difference between the treatments in the clearance of parasites from the blood; more than 90% of patients had a reduction in parasites by the third day of treatment.[1]

People travelling to areas where malaria is endemic need to take precautions to reduce the risk of infection (see 'Malaria prevention in the expatriate and long-term traveller' Aust Prescr 2002;25:66–9). Although artemether and lumefantrine tablets are not approved for prophylaxis they may have a role in emergency 'standby' treatment, however this use has not been evaluated. The future of malaria treatment may lie in combination regimens as they can slow the development of resistance. Artemether and lumefantrine tablets are therefore likely to be used for treatment, particularly as the manufacturer will supply the drug to developing countries at a reduced cost.

REFERENCE

1. Lefèvre G, Looareesuwan S, Treeprasertsuk S, Krudsood S, Silachamroon U, Gathmann I, et al. A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant *Plasmodium falciparum* malaria in Thailand. Am J Trop Med Hyg 2001;64:247-56.

Bosentan

Tracleer (Actelion)

62.5 mg and 125 mg film-coated tablets

Approved indication: pulmonary hypertension

Australian Medicines Handbook section 6.7.2

Primary pulmonary hypertension is a rare disease of unknown aetiology. Secondary causes of pulmonary hypertension include systemic sclerosis. Patients become dyspnoeic on exertion and the high pulmonary arterial pressure eventually leads to right ventricular failure. Most patients die within a few years of diagnosis.

Research into the cause of primary pulmonary hypertension has found that patients have increased amounts of endothelin-1. This is a peptide which causes vasodilatation or vasoconstriction depending on which receptors it activates.

Bosentan acts as an antagonist at the endothelin receptors. This reduces the pulmonary artery pressure in rats, so bosentan has been studied as an oral treatment for patients with pulmonary hypertension.

A double-blind study randomised 32 patients to take bosentan or a placebo for 12 weeks in addition to their usual therapy. Bosentan reduced dyspnoea and patients were able to walk further.[1] Similar improvements were seen in a larger study which randomised 213 patients.[2]

Patients take 62.5 mg twice daily for four weeks then increase to a maintenance dose of 125 mg twice daily. The bioavailability of the tablets is 50% and this is not changed by food. Plasma concentrations decrease during treatment probably because bosentan induces its own metabolism. This metabolism involves cytochrome P450 2C9 and 3A4 so bosentan will alter the plasma concentrations of drugs such as warfarin, glibenclamide and simvastatin. Bosentan also interacts with digoxin and ketoconazole.

Moderate to severe liver disease is a contraindication to bosentan and it can have serious adverse effects on the liver. Patients must therefore have regular tests of liver function during treatment. In clinical trials, 11% of patients had a more than three-fold increase in liver enzymes.

Adverse events that occur more frequently in patients taking bosentan, than in those taking placebo, include headache, flushing, palpitations and hypotension. Nearly 6% of patients will develop anaemia. Bosentan is teratogenic.

While bosentan has statistically significant effects, their clinical importance can be questioned. In the large trial, the mean treatment effect on dyspnoea, using a scale of 1–10, was 0.6.[2] After 16 weeks of treatment the patients could walk an extra 36 metres in six minutes. It is not clear how long these effects will last or if they make any difference to survival. If a patient's condition deteriorates consideration should be given to withdrawing bosentan as its efficacy in severe pulmonary hypertension is unknown. Its approval is limited to primary pulmonary hypertension and pulmonary hypertension associated with scleroderma.

Bosentan is an adjunctive treatment, but the best combination of therapies is yet to be defined.

REFERENCES

1. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001;358:1119-23.
2. Bosentan Randomized Trial of Endothelin Antagonist Therapy Study Group. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896-903.

Deferiprone

Ferriprox (Orphan)

500 mg tablets

Approved indication: iron overload in thalassaemia

Australian Medicines Handbook section 4.2

Patients with thalassaemia major develop anaemia and require blood transfusions. As the body has a limited capacity to excrete iron, frequent transfusions cause iron overload. This can lead to complications such as cirrhosis, heart failure and diabetes.

To prevent the complications of iron overload patients are treated with desferrioxamine. This is a chelating agent which forms water-soluble complexes in a 1:1 ratio with iron atoms.

These complexes can then be excreted by the kidney. Unfortunately desferrioxamine can only be given by injection and children may require prolonged subcutaneous infusions several times a week. As desferrioxamine is expensive to administer and can have serious adverse effects, there is a need for an oral iron-chelating agent.

Deferiprone is a chelating agent which is rapidly absorbed from the gut. Three molecules of deferiprone will form a complex with one iron atom. This complex is then excreted in the urine. Up to 90% of the dose is excreted within 24 hours. Deferiprone is also metabolised, but its metabolite has no chelating activity.

A prospective trial of deferiprone involved 21 patients who were unwilling or unable to take desferrioxamine. During an average of three years of treatment the patients' hepatic iron concentrations fell from a mean of 80.7 to 46.8 micromol/g. There was also a significant reduction in serum ferritin.[1]

Nineteen of the patients in the trial continued treatment. This enabled the researchers to review the efficacy of deferiprone after 4.6 years (mean duration of treatment). They found that the average concentration of hepatic iron had not decreased significantly. In some patients hepatic iron concentrations had increased.[2]

The researchers also reported that long-term treatment was associated with hepatic fibrosis. This conclusion was controversial and led to lawsuits against the principal researcher.[3]

While there is an argument about the risk of hepatic fibrosis, there is an association between deferiprone and severe neutropenia and agranulocytosis. The patient's neutrophil count should therefore be monitored weekly. More common adverse events include discolouration of the urine, nausea, vomiting and arthralgia.

While desferrioxamine treatment is inconvenient, compliance with deferiprone is also demanding. To maintain concentrations high enough to form the 3:1 complexes with iron, patients must take a daily dose of deferiprone of 75 mg/kg. This will often equate to several tablets three times a day.

It will take years before we know if deferiprone safely prevents the complications of iron overload. There are no data on the use of the drug in young children. Until there is a good quality study comparing it with desferrioxamine, deferiprone should only be used in patients who cannot tolerate desferrioxamine.

REFERENCES

1. Olivieri NF, Brittenham GM, Matsui D, Berkovitch M, Blendis LM, Cameron RG, et al. Iron chelation therapy with oral deferiprone in patients with thalassemia major. N Engl J Med 1995;332:918-22.
2. Olivieri NF, Brittenham GM, McLaren CE, Templeton DM, Cameron RG, McClelland RA, et al. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. N Engl J Med 1998;339:417-23.
3. Nathan DG, Weatherall DJ. Academic freedom in clinical research. N Engl J Med 2002;347:1368-71.

Rasburicase

Fasturtec (Sanofi-Synthelabo)

glass vials containing 1.5 mg freeze-dried powder

Approved indication: treatment and prophylaxis of acute hyperuricaemia

Australian Medicines Handbook section 15.3

Rapidly proliferating tumours increase the production of uric acid. If the tumour cells are damaged by chemotherapy the resulting hyperuricaemia can cause acute renal failure.

Humans lack the enzyme (urate oxidase) which, in other mammals, converts uric acid to a more soluble molecule. A genetically engineered form of the enzyme (rasburicase) has been developed. This can be used when there is a risk of rapid tumour lysis in a patient with a haematological malignancy.

Rasburicase is infused when the patient starts chemotherapy. The daily infusion is given over 30 minutes for 5–7 days. Ideally, it should not be given through the same line as the patient's chemotherapy. The half-life of rasburicase is approximately 19 hours and like other proteins it is broken down by hydrolysis.

Allopurinol (which reduces uric acid production by inhibiting xanthine oxidase) can be used as prophylaxis against hyperuricaemia. An open-label randomised trial has therefore compared rasburicase to oral allopurinol in 52 children starting chemotherapy for leukaemia or lymphoma. Rasburicase reduced the concentration of uric acid significantly faster than allopurinol during the first four days of chemotherapy. Uric acid concentrations fell by 86% within four hours of a dose of rasburicase, compared to 12% after allopurinol. This more rapid reduction resulted in patients having 2.6 times less exposure to uric acid in the first four days of therapy.[1]

Attributing adverse effects, such as fever, nausea and vomiting, to rasburicase in patients receiving chemotherapy can be difficult. There is a problem in patients with a deficiency of glucose-6-phosphate dehydrogenase as the oxidation of uric acid may precipitate a haemolytic anaemia. As rasburicase is a protein it has the potential to cause allergic reactions. Some patients will develop antibodies to rasburicase.

Clinical experience with rasburicase is limited and it is not approved for use in subsequent courses of chemotherapy. An intravenous drug may be expected to have a more rapid effect than an oral drug so some caution is needed when interpreting the comparative study. This study was also too small to show any significant differences in renal failure or the need for dialysis.[1]

REFERENCE

1. Goldman SC, Holcenberg JS, Finklestein JZ, Hutchinson R, Kreissman S, Johnson FL, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood 2001;97:2998-3003.

Vardenafil

Levitra (Bayer Australia)

5 mg, 10 mg and 20 mg tablets

Approved indication: erectile dysfunction

Australian Medicines Handbook section 13.3

Vardenafil is the third inhibitor of phosphodiesterase type 5 to be marketed in Australia. Like sildenafil and tadalafil it raises concentrations of cyclic guanosine monophosphate in the corpus cavernosum of the penis. This increases the likelihood of an erection in response to sexual arousal.

Patients take vardenafil 25 to 60 minutes before attempting intercourse. Although nearly 50% of men with erectile dysfunction will respond to a placebo, vardenafil will produce an erection in 68–80% depending on the dose. Response rates are lower in men with diabetes and those who have had their prostate removed.

Vardenafil and sildenafil have similar half-lives (approximately four hours). Like the other phosphodiesterase inhibitors, vardenafil is metabolised by cytochrome P450 3A4. This results in potential interactions with drugs such as erythromycin. Vardenafil should not be prescribed for patients taking potent CYP3A4 inhibitors such as ketoconazole and ritonavir. A low dose is recommended for people with reduced hepatic function. The drug is contraindicated in patients taking nitrates.

As vardenafil has vasodilatory effects it can cause headache, flushing and reduced blood pressure. It is contraindicated in patients with severe cardiovascular disorders, including unstable angina and a recent history of myocardial infarction.

Studies comparing the three oral treatments for erectile dysfunction are needed. A literature review found that there are no relevant differences in their selectivity for phosphodiesterase type 5 and they have similar efficacy in helping patients achieve an erection.[1]

REFERENCE

1. Gresser U, Gleiter CH. Erectile dysfunction: comparison of efficacy and side effects of the PDE-5 inhibitors sildenafil, vardenafil and tadalafil. Eur J Med Res 2002;7:435-46.

Answers to self-test questions

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

www.australianprescriber.com

Australian Prescriber is available on the internet in full text, free of charge. Go to Contact Us/New issue notification to be sent an e-mail each time a new issue goes online.

Australian Prescriber mailing list

Australian Prescriber is distributed every two months, free of charge, to medical practitioners, dentists and pharmacists in Australia, on request. It is also distributed free of charge, in bulk, to medical, dental and pharmacy students through their training institutions in Australia. To be placed on the mailing list, contact the Australian Prescriber Mailing Service.

Tick ☑ whichever of the following apply:

I have access to the *Australian Prescriber* web site on the internet ☐ Yes ☐ No

☐ Place me on the mailing list

☐ Delete me from the mailing list

My reference number is .....

☐ Change my address

My reference number is .....

☐ Send me all the available back issues

NAME: .....

ADDRESS: .....

.....

.....

.....

PROFESSION: .....

(general practitioner, resident, psychiatrist, surgeon, dentist, pharmacist, etc.)

Postal: Australian Prescriber Mailing Service
GPO Box 1909
CANBERRA ACT 2601
AUSTRALIA

Telephone: (02) 6241 6044 Fax: (02) 6241 4633

Editorial office

For general correspondence such as letters to the Editor, please contact the Editor.

Telephone: (02) 6282 6755

Facsimile: (02) 6282 6855

Postal: The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
AUSTRALIA

E-mail: info@australianprescriber.com

Web site: www.australianprescriber.com

NPS
National Prescribing Service

Australian Prescriber is indexed by the Iowa Drug Information Service, the Australasian Medical Index and EMBASE/Excerpta Medica.

Address correspondence to:
The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
Telephone (02) 6282 6755

Printed in Australia by
National Capital Printing
22 Pirie Street, Fyshwick, ACT 2609

Published by the
National Prescribing Service