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Australian Prescriber
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EDITORIAL

Changes at *Australian Prescriber*

The Executive Editorial Board

(Aust Prescr 2002;25:2)

The Executive Editorial Board of *Australian Prescriber* wants to alert readers to a significant change for the journal. If handled incorrectly this imposed change may threaten the journal's existence.

When you publish an independent drug bulletin, you expect to attract criticism from a range of sources, including the pharmaceutical industry. It can therefore be difficult to find a 'home' that both promotes the journal's primary role of publishing independent information, and insulates it from attack.

Australian Prescriber started life in 1975 in the Department of Health, within what is now the Drug Safety and Evaluation Branch of the Therapeutic Goods Administration (TGA). Publication has been continuous except for a period from 1982 to 1983 when it was halted as an economy measure. This resulted in a national and international outcry which quickly led to the journal's revival. The Department transferred *Australian Prescriber* from the TGA to the Pharmaceutical Benefits Branch in 1993, partly due to pressure from the pharmaceutical industry. In 2001, following the shake-up of the Pharmaceutical Benefits Advisory Committee, the funding of *Australian Prescriber* became the responsibility of the Pharmaceutical Access and Quality Branch of the Department of Health and Aged Care.

Despite these upheavals, *Australian Prescriber* continues to be a valued source of independent therapeutic information. This presumably reflects the fact that the Department has never interfered with the editorial process, which remains firmly in the control of the Executive Editorial Board of practising clinicians.

The circulation of the journal, which is sent to all practising and student doctors, pharmacists and dentists in Australia, is the largest of any medical journal in Australia. The extraordinary success of the electronic version of the journal is attested to by the large number of visitors to the *Australian Prescriber* web site (200 000 hits per month). This is no doubt because the public funding of *Australian Prescriber* enables it to be one of the few journals that makes its full text freely available on the internet. Readership surveys have also attested to the popularity of the journal, with the new drugs section being particularly valued by the readers.

Given the success of *Australian Prescriber* it is surprising that the Department has outsourced the journal to the National Prescribing Service (NPS) on a short-term contract. This change was not sought by the NPS, and is not consistent with the recommendations of a departmental review carried out under the supervision of the Pharmaceutical Health and Rational use of Medicines (PHARM) committee. The Executive Editorial Board was not consulted until well after the outsourcing decision had been made. No particularly cogent reason for the transfer has ever been given to the Board. The cost of *Australian Prescriber* should not be a concern as it is, of course, minute when compared with the $3.8 billion annual cost of the Pharmaceutical Benefits Scheme.

Although the Executive Editorial Board was not consulted it did not immediately reject the proposal. If the focus of the change is to promote the quality use of medicines the transfer could be beneficial. However, if the focus is on cost cutting and making it easier to cease funding the journal when the outsourcing contract expires, the move could lead to the demise of *Australian Prescriber*.

The Executive Editorial Board is committed to ensuring that:

- sufficient funding is allocated to the NPS to allow *Australian Prescriber* to continue to be published at least as frequently and with the same size and quality as at present
- *Australian Prescriber* continues to be sent free of charge to all practising and student doctors, pharmacists and dentists in Australia
- formal arrangements are made between the Department and the NPS to allow continuing access to resources of information currently available to *Australian Prescriber* by virtue of it being housed within the Department
- negotiations occur with the current editorial staff to ensure the editorial continuity essential for a journal such as *Australian Prescriber*.

The Executive Editorial Board is determined to defend *Australian Prescriber* and the international reputation it has developed over 26 years. We will have no hesitation in challenging the Department and the NPS over any issues we think have not been addressed, until they are satisfactorily resolved for the benefit of our readers.

In this issue...

This issue is larger than planned as the Executive Editorial Board wanted to inform readers of its concerns for the journal. The members of the Editorial Board have also invited Andrew Herxheimer to explain the importance of independent drug bulletins.

While the future of the journal is uncertain we can be sure that patients will be enquiring about influenza immunisation in the next few months. Robert Hall analyses some of the evidence supporting the use of the vaccine. Allan Molloy also tells us there is little evidence for using pethidine to treat chronic pain.

We can also be certain that patients will forget to take their medication. Andy Gilbert, Libby Roughead and Lloyd Sansom tell us about some of the strategies which can be used to manage this problem.

EDITORIAL

The importance of independent drug bulletins

Andrew Herxheimer, Emeritus Fellow, UK Cochrane Centre, founding Editor, Drug and Therapeutics Bulletin, and past Chairman, International Society of Drug Bulletins

Index words: drug information, drug regulation.

(Aust Prescr 2002;25:3–4)

Medicine changes considerably during the working life of a doctor or pharmacist. Lifelong learning and unlearning is therefore a professional necessity and must be an integral part of normal work, not something to add on in spare moments.

Doctors, pharmacists and the public receive a flood of promotional information and suggestions that cannot be accepted at face value. Pharmaceutical promotion is advocacy that aims to create sales by presenting a product to its best advantage while playing down disadvantages. Something similar happens when over-enthusiastic colleagues talk about their preferred treatment.

When a new treatment or a new way of managing a problem appears, we need to ask:

- is the treatment that is offered worth considering and trying to understand?
- should I adopt it or recommend it to patients?

Often the answer to the first question is no, because the suggested treatment seems unnecessary or trivial or makes no sense. If however it looks as if it could be useful, the likely benefits and disadvantages need critical assessment. However, evidence to answer specific clinical questions is often lacking. In addition, if evidence is available individual doctors often do not have the time or the skills and experience to make reliable assessments that minimise biases. In practice it is more feasible and much more efficient for appropriate independent experts to do this – some with the relevant clinical expertise, others experienced in the evaluation of experimental data, such as clinical trials. They can then present their analyses and conclusions to all prescribers and pharmacists, who can read them in detail if they wish, discuss them, and decide whether they – as individual practitioners or as a group – want to use the new treatment in some situations. The assessment of medical treatments is best published in an independent drug bulletin.

The work of preparing impartial scientifically and clinically sound assessments resembles that of the Therapeutic Goods Administration (TGA) in licensing new products, and of the Pharmaceutical Benefits Advisory Committee (PBAC) in deciding whether the Pharmaceutical Benefits Scheme (PBS) should pay for them. However, these regulatory processes are part of government and are less helpful for clinical problems. The TGA can consider only whether a product is effective and reasonably safe: its primary job should be to protect the public and to limit what drug companies may claim about their products. The PBS needs expert advice to ensure that taxpayers get value for money and do not pay over the odds for minor or uncertain improvements.

Regrettably neither the TGA nor the PBAC is allowed to publish the evidence and the arguments on which they base their decisions. This secrecy makes it easy for aggrieved companies, doctors or patients to criticise them for being arbitrary or inconsistent.

To be able to think properly about the role of different treatments for a particular problem doctors need to understand and be able to discuss the evidence and the arguments. No one has found a better place for doing this than in an independent drug bulletin. Of course in principle any general medical journal could do it, but in practice there are two difficulties:

- general journals have to cover a very wide range of topics, so they have not got sufficient space to review and assess therapies
- almost all established medical journals are heavily dependent on advertising revenue from pharmaceutical companies, and if they are too critical they risk losing advertisers.

The member bulletins of the International Society of Drug Bulletins, including *Australian Prescriber*, contain no drug adverts: they must be free to express carefully considered unvarnished opinions. Independent drug bulletins are open to discussion, debate and argument. As medicine is not an exact science, drug bulletins are willing to reconsider and if necessary update their conclusions in the light of new evidence, and to consider other points of view.

Formularies and collections of therapeutic guidelines, while important and valuable resources, do not reduce the need for an independent drug bulletin. They are compendia for reference, giving compact and reliable information that is intended to remain current for a fairly long time – usually at least one year. Formularies have no space for detailed discussion, but most guidelines summarise the underlying concepts and arguments. The formularies and guidelines appear too infrequently to be topical, and neither encourages discussion among their users. The danger of guidelines is that too many people, among them clinicians as well as administrators of health services, regard them as mandatory – which they are not. They save work and time, but they must be applied flexibly to individual cases. In some cases it is better to depart from a guideline than to follow

it. It would be valuable to build a collection of examples of such justified departures from guidelines, and this could be another role for independent drug bulletins.

Informing health professionals and the public about drugs and drug treatments is an important way to encourage the quality use of medicines. While drug bulletins such as *Australian Prescriber* clearly have a role, their message is reinforced if it also comes from other sources. It is important to ensure that information from different sources such as the *Therapeutic Guidelines* and the *Australian Medicines Handbook* is compatible. This user-friendly information should also be reinforced by other activities such as those of the National Prescribing Service. Integrated independent information, perhaps via the internet, will be well received by both health professionals and their patients.

E-mail: andrew_herxheimer@compuserve.com

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.

Evidence-based medicine

Editor, – I refer to the article 'Are we there yet? – Travel along the information highway seeking evidence-based medicine' (Aust Prescr 2001;24:116–9). I enjoyed this problem-based article on influenza vaccination but was surprised that the authors did not suggest consulting the *Australian Immunisation Handbook* as their first search strategy. To solve the problem I pulled the 7th edition (2000) off the shelf, looked up the index on influenza, flicked to page 140, skimmed to recommendation 4 regarding pregnant women on page 144 and found:

'Influenza vaccine is safe for pregnant women. Pregnant women who fall into one of the above risk categories should be vaccinated. In addition, there is evidence from a number of studies that pregnant women, particularly during the second and third trimester, are at increased risk of influenza-associated complications. The US Centers for Disease Control estimates that an average of 1–2 hospitalisations among pregnant women could be prevented for every 1,000 pregnant women immunised. It is therefore recommended that all women who will be in the second or third trimester of pregnancy during the influenza season be vaccinated **in advance**, so that they will be protected during that period.'

Time: 45 seconds!

The *Australian Immunisation Handbook* is also available on the internet at: http://www.health.gov.au/pubhlth/immunise/publications.htm (albeit as a 2.6 meg PDF file)!

To me, this exercise shows the clear value of independent immunisation/therapeutic guidelines produced by expert colleagues who have distilled the evidence into authoritative recommendations. It also shows the deficiencies of the Commonwealth Department of Health web search engine which apparently does not currently index their own PDF documents!

Dr Ken Harvey
Senior Lecturer
School of Public Health
La Trobe University
Bundoora, Vic.

Dr Peteris Darzins and Ms Majella Pugh, co-authors of the article, comment:

Dr Ken Harvey reports being surprised that the authors did not suggest consulting the *Australian Immunisation Handbook* (NHMRC)[1] as their first search strategy. However, not everyone has the latest version of the Handbook on their shelf. Even so, Dr Harvey has overlooked Table 2 which shows that the very first place the medical practitioner conducting the search looked was in the NHMRC web site. It is interesting that the search conducted by browsing the NHMRC web site, and also by using the search terms 'vaccination' and 'guidelines', separately, did not lead to the immunisation guidelines. This shows that information retrieval by electronic means from readily accessible sources is still seriously limited. This may be because the needed information is simply not in the electronic databases or, if it is there, it cannot be readily found by people who are not accustomed to using that particular database.

We agree with Dr Harvey that more attention could be devoted to proper indexing of databases. Poorly indexed databases have a number of deleterious effects. First, they do not provide the information searchers are looking for. Second, they provide a strong negative incentive to searchers to look for information in the databases when next they want to find something. In our opinion, it would be preferable to have fewer, readily accessible, items in the databases, rather than masses of information that is not readily accessible. Proper structuring of databases requires discipline and the active involvement of content experts in deciding what should or should not be included. Many web sites sacrifice function for form and appear to be designed by computing experts without adequate supervision from content experts. It is time those who care about evidence-based medicine invest the required effort to attend to this serious barrier to the optimal provision of health care.

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Influenza immunisation

Robert Hall, Communicable Disease Control, South Australian Department of Human Services, Adelaide

SYNOPSIS

Many flu-like illnesses are not caused by influenza, however influenza is a significant cause of morbidity. Its complications include pneumonia, and increase mortality particularly during pandemics. Elderly people are particularly vulnerable and vaccination is recommended for everyone over 65 years old. The efficacy of the vaccines depends on how well they match the circulating strains of the virus. A systematic review suggests the efficacy for preventing infection may be as low as 24%. The vaccine may be more efficacious at preventing complications in the elderly. Neuraminidase inhibitors and ion channel inhibitors are not very effective treatments for influenza.

Index words: pneumonia, vaccines, amantadine, neuraminidase inhibitors.

(Aust Prescr 2002;25:5–7)

Introduction

Influenza is an infectious disease of humans, horses, pigs, and both wild and domesticated birds. It is highly infectious for humans and epidemics in European populations have been recorded since the early sixteenth century. Pandemics have occurred 3–5 times each century since 1700.[1]

Clinical features

Influenza is an acute viral respiratory infection characterised by febrile illness, myalgia, unproductive cough, headache, severe malaise, sore throat and rhinitis. The incubation period is 1–4 days. While the median duration of illness is three days, this may vary by viral serotype. Cough and malaise can persist for weeks. Complications include otitis media, pneumonia, bronchiolitis and exacerbations of chronic respiratory disease. Other consequences include febrile convulsions, Reye's syndrome and myocarditis.[2,3] The complications account for the considerable morbidity and mortality of influenza.

Virology

The viruses causing human influenza were discovered in the 1930s.[4] The virus has an RNA core, a protein shell and a lipid membrane. There are two glycoproteins on the membrane, a haemagglutinin (H) and a neuraminidase (N). The haemagglutinin assists viral entry into the cells of the respiratory epithelium while the neuraminidase also facilitates release of new virions from infected cells.

There are three serotypes of influenza virus (A, B and C) determined by the antigenic make-up of the core, but only serotypes A and B are of importance in human disease. Serotype A viruses are further characterised by serological identification of the H and N proteins. Since 1977 the commonly circulating A serotypes have been H1N1 and H3N2. There is further variation and individual strains are named after the place, serial number and year of first isolation, e.g. influenza A/Sydney/5/97 (H3N2).[2]

The virus has a marked capacity to mutate, undergoing antigenic drift, with incremental changes over time, and antigenic shift, where large changes occur over a short interval. For example, in 1957 the predominant influenza A virus changed from H1N1 to H2N2. Antigenic shifts were associated with the pandemics in 1919, 1957 and 1968.

Most new varieties appear to originate in southern China in ducks or pigs, and the high population numbers and densities in that region then promote rapid transmission to the rest of the world. A recent example of an antigenic shift is the A/Hong Kong/156/97 (H5N1) virus, and despite fears at the time of a pandemic this did not eventuate.[2]

Epidemiology

Defining a case of influenza is difficult without virological or serological testing, and clinical diagnosis is unreliable. Surveillance for influenza is based on laboratory data resulting in high specificity (cases identified tend to be true cases), and low sensitivity (many true cases are not identified). Surveillance data therefore do not tell us about the burden of disease.[5] Influenza possibly accounts for 13% of cases of respiratory tract infection, and 9% of the world's population may catch influenza each year. Infection peaks in winter, with a typical season lasting 6–8 weeks.[6]

Mortality and morbidity

Generally, the incidence of influenza is higher in children, the elderly, and those living in close proximity to each other. Influenza and pneumonia (of all types) are among the 10 leading causes of death, mostly in the elderly. In the USA estimates of 'excess' mortality due to 'pneumonia and influenza' have ranged from 1800 to 11 700 in the period 1979–92 (in a population of some 250 million). Interestingly, only A H3N2 'is regularly associated with excess mortality'.[7]

Complications of influenza are not evenly distributed over the population. High-risk population groups for mortality include the elderly and those with chronic morbidity.[5] The risk of hospitalisation varies according to age and pre-existing health status.[3] During pandemics the burden of disease can be very high indeed.[2]

Preventive strategies

Preventive strategies for influenza include immunisation and the use of antiviral agents.

Vaccines

Currently available influenza vaccines are inactivated split virus vaccines manufactured from virus stock grown in chick embryos. They are trivalent, containing two A types (H1N1 and H3N2) and one B type. They are standardised to contain 15 microgram of haemagglutinin of each virus and are given by deep subcutaneous injection (the National Health and Medical Research Council (NHMRC) recommends a 25 mm 23 gauge needle). Immunity to haemagglutinin appears to be a strong determinant of protection.[2]

The efficacy of influenza vaccine is determined by several factors[8], including:

- the immunogenicity of the vaccine
- the degree of match between vaccine and wild virus
- the age and health of recipient.

During ageing, primary T-cell dependent antibody responses decline, but secondary responses tend to be maintained. Some of this effect may be due to prior exposure to similar wild virus. Persons with chronic medical conditions tend to respond less well, leading to a problem of low response in nursing homes.[9] The vaccine prevents complications (death, hospitalisation) in recipients[4], but does not prevent transmission in aged-care settings.[7]

To be efficacious, vaccines have to be tailored to the circulating serotypes of the influenza virus. The World Health Organization (WHO) has established a system for predicting which serotypes will be in circulation. This surveillance system is based on 110 laboratories in 79 countries and four reference centres (London, Atlanta, Tokyo and Melbourne). Each year WHO recommends the composition of vaccine for the influenza season in each hemisphere. This recommendation is then considered by the Australian Influenza Vaccine Composition Committee, which decides on the composition of the vaccine to be used during the influenza season in Australia.

Influenza vaccine effectiveness

Influenza vaccination appears to have 70–90% strain-specific effectiveness in healthy adults for 1–3 years[4] when vaccine and circulating strains are well matched. Vaccination of healthy adults is associated with reduced absenteeism and reduced demand on healthcare resources.[3] Vaccine effectiveness does not rapidly wane, however there is considerable antigenic drift from year to year in the circulating strains of influenza virus, so there is a need to immunise each year to cover the circulating virus. The timing of immunisation is not critical, provided the vaccine is the current strain and is given more than two weeks before the expected exposure to risk.

In elderly people the protection conferred against influenza is lower at about 30–60%, but protection against complications and death is higher.[4] The efficacy of influenza vaccine for preventing hospitalisation and pneumonia in the elderly is around 50–60%.[3]

In the military, respiratory disease is the second highest cause of morbidity and the sixth highest cause of reduced productivity. In the British Army in 1996–97, 40% of this respiratory disease was due to influenza, particularly in new recruits. This problem led to a Cochrane evaluation of influenza vaccine[10,2], which found 10 acceptable trials that showed a reduction of 29% in 'influenza cases' (95% CI* 12–42%), and a saving in time off work of 0.4 working days. Sixteen acceptable trials showed a vaccine efficacy for a clinical case definition of 24% (95% CI 15–32%), and for a serological and clinical case definition of 68% (95% CI 49–79%). Mismatches between vaccine and circulating strains appeared to explain most of the lack of efficacy. The review concluded that 'the results of this study seem to discourage the utilisation of vaccination against influenza in healthy adults as a public health measure.'[10]

Adverse events

Around 10–65% of influenza vaccine recipients report pain at the injection site, and occasionally more generalised myalgias. Local and systemic reactions, usually fever, malaise and myalgia, occur rarely. They are usually mild, maybe of 1–2 days duration.[4] Immediate hypersensitivity reactions, ranging from urticaria to anaphylaxis, are rare and are probably caused by hypersensitivity to egg protein. Guillain-Barré syndrome has been reported after influenza immunisation, first being noted with the 1976 vaccine. Analysis of adverse events with subsequent vaccines shows a much lower increase in risk (an increase of about 1–2 cases per million recipients above background), but these results are not statistically significant and are at the limits of epidemiological methods. Whether Guillain-Barré syndrome is caused by influenza vaccination has not been established.[11,3]

Contraindications

Influenza vaccine should not be given to people with anaphylactic hypersensitivity to eggs or hypersensitivity to any influenza vaccine component. Vaccination should be deferred in people with a current acute febrile illness (>38.5°C) and caution should be exercised if there is a history of Guillain-Barré syndrome.[3,11]

Drugs

The ion channel inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (zanamivir and oseltamivir) have some effectiveness in influenza treatment and prophylaxis. Amantadine and rimantadine both interfere with the replication of type A influenza virus, but have no action on type B viruses. Neuraminidase inhibitors inhibit the entry of viruses into cells and the exit of virus particles from cells. They are active against types A and B.[2] None of these drugs is widely used in Australia and, while their use may be of value in individual cases, they confer little public health benefit.[2]

* CI confidence interval

Costs and benefits

Influenza is expensive to the community. The cost of influenza in the USA has been estimated to be US$1–3 billion in direct costs per year, and US$10–15 billion in indirect costs, mostly due to time off work.[6]

In the USA a demonstration project was carried out between 1989 and 1992 to determine the costs to Medicare (the US health insurance program for the elderly) of immunising the elderly against influenza.[12] This concluded that immunisation of persons over 65 years of age was likely to be cost-effective.

Recommendations for the use of vaccine

In the USA, the Advisory Committee on Immunization Practices recommends that 50–65 year-olds should receive vaccine because 24–32% have chronic medical conditions which confer a higher risk of influenza-related hospitalisation and death. Immunisation coverage of high-risk individuals under 65 years old is not high and the Advisory Committee on Immunization Practices considers that an age-based strategy will achieve higher levels of immunisation of at-risk individuals than a 'high-risk' strategy.[3] This is not currently recommended in Australia, but the Australian Technical Advisory Group on Immunisation is reconsidering its recommendations to the NHMRC on influenza immunisation, including the issue of immunising everyone 50 years of age and older.

The vaccine should be offered to patients a few months before the influenza season, which in most of Australia usually starts between June and September. The NHMRC currently recommends that annual influenza vaccination, with a vaccine registered for use in the current season, be offered to the following groups[11]:

- everyone 65 years of age and older
- Aboriginal and Torres Strait Islander people 50 years of age and older
- people six months of age and older with chronic illnesses requiring regular medical follow-up or hospitalisation in the previous year
- people six months of age and older with chronic illnesses of the pulmonary or circulatory systems (except asthma)
- residents of nursing homes or long-term care facilities
- children and teenagers aged six months to 18 years on long-term aspirin therapy (because aspirin treatment puts them at risk of Reye's syndrome if they develop a fever)
- healthcare and other workers providing care to the high-risk groups above.

Other groups for whom influenza immunisation should be considered include pregnant women, overseas travellers and persons infected with HIV.

Commonwealth-funded vaccine is available for:

- those 65 years of age and older
- Aboriginal and Torres Strait Islander people 50 years of age and older
- Aboriginal and Torres Strait Islander people with chronic medical conditions.

E-mail: robert.hall@dhs.sa.gov.au

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 23)

1. Influenza vaccine has an efficacy of 98% in protecting people against influenza.
2. Influenza vaccine contains a live virus so is contraindicated in people infected with HIV.

Abnormal laboratory results

Dunstan R, editor. Abnormal laboratory results. Sydney: McGraw-Hill Book Company Australia Pty. Ltd.; 2001. 216 pages.
Price $32.95 + $6.60 postage. 20% discount for *Australian Prescriber* readers.

Australian Prescriber has for many years published a series of articles on abnormal laboratory results. These articles have now been collected and edited for publication by Dr Robert Dunstan.

Hypertension in diabetes

Julia Lowe, Director of General Medicine, Department of Endocrinology, John Hunter Hospital, Newcastle, New South Wales

SYNOPSIS

Good management of blood pressure is at least as important as good control of blood glucose and the reduction of cholesterol in preventing the complications of diabetes. The degree to which blood pressure is lowered and the choice of drugs must be influenced by the doctor's awareness of the patient's other health problems and the potential adverse effects. Age alone should not be a factor in determining the target blood pressure. Controlling the blood pressure often requires more than one antihypertensive drug. Tight control of the patient's blood pressure reduces macrovascular complications, but may not significantly reduce all-cause mortality. Treatment therefore includes the management of the patient's other risk factors.

Index words: cardiovascular, complications, ACE inhibitors, calcium antagonists.

(Aust Prescr 2002;25:8–10)

Introduction

About half the diabetic population are hypertensive and, depending on the ethnic group, between 5% and 25% of people with hypertension have diabetes. Hypertension and diabetes are a critical combination for the development of both micro- and macrovascular disease. The major cause of excess mortality in diabetes is cardiovascular disease. Nephropathy is also a major consequence of diabetes and hypertension; diabetic nephropathy is a major contributor to the growing need for renal transplants. The addition of diabetes to even mild grade hypertension (WHO-ISH guidelines 140/90 to 159/99 mmHg) immediately places the patient in a high-risk category. Such patients require a comprehensive assessment of their vascular risk factors including history of previous cardiovascular events.

South Asians who have migrated to countries such as Australia and the UK have an especially high mortality from coronary heart disease. The low proportion of deaths from coronary heart disease in Japanese people with diabetes, despite high rates of smoking and hypertension, suggests that the more favourable lipid profiles of the Japanese are protective. This emphasises the importance of managing lipids in hypertensive patients with diabetes.

The Diabetes Control and Complications Trial and the UK Prospective Diabetes Study (UKPDS) showed the importance of good blood glucose control in the prevention of microvascular complications. Neither study was able to show that tight blood glucose control reduced heart attacks and strokes. The role of hypertension, smoking and hyperlipidaemia as precipitants of macrovascular disease in people without diabetes is well established. Logically, all these factors must be attacked to prevent complications of diabetes due to large vessel disease. This involves lifestyle changes (see box) as well as drugs.

Does a policy of tight blood pressure control reduce the risk of complications?

The impact of a tight blood pressure control policy was investigated in a UKPDS sub-study.[1] This randomly allocated nearly 1200 patients to tight control (target blood pressure less than 150/85 mmHg) or less rigorous control (less than 180/105 mmHg). Reductions in risk in the group assigned to tight control, compared with the group assigned to less tight control, were 44% (95% confidence interval 11–65%, number needed to treat (NNT) 22) for strokes and 32% (6–51%, NNT 18) in deaths related to diabetes. However, the reductions in deaths due to myocardial infarction and all-cause mortality were not statistically significant. Although the risk of amputations was reduced by 49% this was not a statistically significant effect. When all macrovascular events (myocardial infarction, sudden death, stroke and peripheral vascular disease) were combined, the group assigned to tight blood pressure control had a statistically significant 34% risk reduction (NNT 18). These results are comparable with the outcomes of:

- a meta-analysis of clinical trials of improved blood pressure control in the general population
- patients with diabetes in the Hypertension Optimal Treatment (HOT) study[2]
- the sub-group of patients with type 2 diabetes in the Systolic Hypertension in the Elderly Program (SHEP).

Is such a policy cost-effective?

These studies of hypertension and diabetes all confirm the importance of good blood pressure control as well as good blood glucose control. A cost-effectiveness analysis of the

Lifestyle strategies to reduce cardiovascular risk

Stop smoking
Lose weight
Reduce sodium intake (less than 2 g or 88 mmol per day)
Moderate alcohol intake (no more than 2 drinks per day)
Regular exercise
Relax and manage/relieve stress *
Use less saturated fat, more fish oils *
Maintain adequate potassium, calcium and magnesium intake *

* Objective evidence equivocal

UKPDS data concluded that tight control of blood pressure in hypertensive patients with type 2 diabetes substantially reduced the cost of complications, and increased the interval without complications. The cost-effectiveness ratio compared favourably with accepted healthcare programs to reduce cardiovascular risk such as cholesterol lowering and advice on lifestyle. The costs ranged between £390 and £1049 per extra year free from diabetic end-points and between £261 and £720 per life gained.[3]

How tight is tight control?

The prospective observational part of the UKPDS[4] hypertension sub-study showed a clear reduction in end-points associated with diabetes if the systolic blood pressure was reduced by 10 mmHg. Practitioners have three sets of guidelines to assist them (see Table 1) but must ultimately be guided by common sense and their knowledge of the patient when setting individual targets. Factors such as renal disease, previous treatment, risk of falling and compliance with medication have to be balanced against the significant benefits to be gained by rigorous blood pressure control. Home blood pressure monitoring may help to guide the effectiveness of therapy.

Elderly diabetic patients with the highest systolic and pulse pressure have the highest absolute risk of adverse cardiovascular outcomes. They therefore have the most to gain from tight blood pressure control and should not be undertreated simply because of their age.

Are all drugs equal or are some more equal than others?

There is now agreement that thiazide diuretics[5] and beta blockers are effective in reducing morbidity and mortality in patients with diabetes and hypertension.[6,7] These drugs should be first-line therapy in spite of the fact that the patient has diabetes. The two areas of uncertainty are whether there are particular risks in using calcium antagonists, or particular benefits in using ACE inhibitors. This choice is controversial in the treatment of hypertension even in patients without diabetes. Two recent meta-analyses[6,7] using the same trials, but different selection criteria, reached conflicting conclusions. Both studies are consistent with the recommendations of the sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, that diuretics or beta blockers are first-line therapy for the treatment of uncomplicated hypertension. The studies support the option of ACE inhibitors as first-line treatment, and suggest that they may have particular benefits in patients (such as those with diabetes) who are at high risk of heart failure.

The evidence about calcium antagonists in hypertension is much less clear. One review[8] suggested that calcium antagonists reduce the risk of both major cardiovascular events and cardiovascular death by 28% compared to placebo. However, a more recent study, comparing calcium antagonists with other antihypertensive drugs, found that they had similar rates of cardiovascular mortality, but a significantly increased risk of myocardial infarction (26%), congestive heart failure (25%) and major cardiovascular disease (combined 10%).[9]

Table 1

Recommended blood pressure targets in the treatment of hypertension

WHO-ISH*	JNC VI †	NHF ‡
<130/85 mmHg (young, middle-aged, diabetic)	<140/90 mmHg (lower if tolerated)	<130/85 mmHg (under 65 years, diabetes, renal disease)
<140/90 mmHg (elderly)		<140/90 mmHg (over 65)

* World Health Organization-International Society of Hypertension

† Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure

‡ National Heart Foundation

Not surprisingly, systematic reviews of studies that have reported outcomes in patients with diabetes and hypertension are equally confusing. All agree in concluding that intensive control of blood pressure reduces cardiovascular morbidity and mortality. They also agree that combination therapy is frequently required and may be more beneficial than monotherapy, but like the studies of hypertension overall, they disagree on the role of calcium antagonists. Perhaps the safest advice in these circumstances is to be cautious about using calcium antagonists as first-line drug therapy in patients, such as those with diabetes, who are at high risk of coronary heart disease and heart failure. This does not preclude the use of calcium antagonists when combination therapy is required to achieve optimal blood pressure control. To achieve a target of less than 130/85 mmHg will require combination therapy in more than 60% of patients.

The MICRO-HOPE sub-study[10] of the heart outcomes prevention evaluation study included 3577 people with diabetes. They had at least one other risk factor or a previous cardiovascular event, but had no clinical proteinuria, heart failure or low ejection fraction. The study had a combined primary outcome of myocardial infarction, stroke or cardiovascular death. After adjustment for the changes in systolic blood pressure (2.4 mmHg) and diastolic blood pressure (1.0 mmHg) an ACE inhibitor lowered the risk of the combined primary outcome by 25% (12–36%). As the study was not designed to be a trial of the effect of lowering blood pressure, and medication was not titrated to achieve prespecified target blood pressure levels, only general comparisons can be made with other studies. It suggests that the benefits of treatment may result from mechanisms other than the lowering of blood pressure. Whether these mechanisms are unique to ACE inhibitors is unclear.

While AT_1 receptor antagonists (commonly referred to as angiotensin II antagonists) may have the same benefits as ACE inhibitors, this has yet to be shown in clinical trials. The new combinations of an ACE inhibitor or an AT_1 receptor

antagonist with a thiazide may be of value when there is the need to add a thiazide to improve blood pressure control after titration of the other drug to the maximum tolerated dose.

Conclusion

While current evidence may be difficult to interpret in some areas of the treatment of hypertension in diabetes, there is no conflict in recommending tight blood pressure control and the use of combination therapy if necessary to achieve this result. The final choice of drugs and optimal blood pressure control for each patient must be influenced by knowledge of the potential harms and benefits to each individual. It is no different in this respect from the control of blood glucose. Blood pressure and glucose both need to be individually tailored as part of a comprehensive cardiovascular risk management strategy. This includes a discussion of the aims and potential problems of treatment with the patient.

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

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FURTHER READING

See resources on the following web site:

'Diabetes on the Internet 2001' www.diabetes.org.au/ct_2001.htm

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Self-test questions

The following statements are either true or false (answers on page 23)

3. Tight control of blood pressure may not significantly reduce fatal myocardial infarctions in patients with diabetes.
4. To achieve a target blood pressure of 130/85 mmHg most patients with hypertension and diabetes will require only one antihypertensive drug.

Patient support organisations

Diabetes Australia

Diabetes Australia consists of twelve organisations:

- the eight State and Territory Associations of Diabetes Australia
- Australian Diabetes Society
- Australian Diabetes Educators Association
- Kellion Diabetes Foundation
- Diabetes Research Foundation – Western Australia.

All funds raised by or on behalf of Diabetes Australia are re-invested into research, health services, provision of self-management products and services, and public awareness.

Contacts

National office

1st Floor, Open Systems House
218 Northbourne Avenue
BRADDON ACT 2612

Tel: 1800 640 862 (toll-free); (02) 6230 1155
Fax: (02) 6230 1535
E-mail: admin@diabetesaustralia.com.au
Web site: www.diabetesaustralia.com.au

Australian Capital Territory

The Grant Cameron Community Centre
Mulley Street
HOLDER ACT 2611
Tel: (02) 6288 9830
Fax: (02) 6288 9874
E-mail: diab.act@diabetesaustralia.com.au

New South Wales

GPO Box 9824
SYDNEY NSW 2001
Tel/Fax: 1300 136 588 (toll-free)
E-mail: marketing@diabetesnsw.com.au

Northern Territory

2 Tiwi Place
TIWI NT 0810
Tel: (08) 8927 8488; (08) 8927 8482
Fax: (08) 8927 8515
E-mail: ceo@diabetesnt.org.au

Queensland

Cnr Ernest and Merivale Streets
SOUTH BRISBANE QLD 4101
Tel: (07) 3239 5666
Fax: (07) 3846 4642
E-mail: daqld@daq.org.au

South Australia

159 Sir Donald Bradman Drive
HILTON SA 5033
Tel: (08) 8234 1977
Fax: (08) 8234 2013
E-mail: dasa@da-sa.com.au

Tasmania

57E Brisbane Street
HOBART TAS 7000
Tel: (03) 6234 5223
Fax: (03) 6234 5828
E-mail: lclark@datas.org.au

Victoria

7th Floor, 100 Collins Street
MELBOURNE VIC 3000
Tel: (03) 9654 8777
Fax: (03) 9650 1917
E-mail: mail@dav.org.au

Western Australia

48 Wickam Street
EAST PERTH WA 6004
Tel: (08) 9325 7699
Fax: (08) 9221 1183
E-mail: dawaproducts@dawa.asn.au

Book review

Drugs and Pregnancy. Melbourne: Pharmacy Department, The Royal Women's Hospital, Women's and Children's Health; 2001. 144 pages. Price $27.50.

Jane Talbot, General Practitioner, Kalamunda, Western Australia

The aim of this guide is to collate the available information on the effects of a comprehensive list of drugs registered in Australia as well as a list of commonly encountered herbal medicines during pregnancy and the recommendations on their safety.

The guide has been concisely written, thoughtfully organised and is indeed a very handy little tome. For those of us who deal regularly with pregnant women, the Australian Drug Evaluation Committee's 'Prescribing medicines in pregnancy' 4th edition has been an obligatory addition to our medical bookshelf. This guide retains all that information but provides more comprehensive information as well.

The Alphabetical Drug Listing is perhaps the handiest section of the guide as a quick reference. As well as listing all the drugs alphabetically, there are then five columns for each drug which indicate the Australian risk category for drugs used in pregnancy, specific trimester recommendations (may be used, caution, not recommended, contraindicated) and the page later in the guide where the particular drug is discussed.

The section of the guide titled 'Further information on drugs' is excellent. Brief and to the point it is also highly referenced (200 references in all). The authors obviously have researched what is the evidence for classes and groups of drugs and provide this support in the text. This part of the guide is very user-friendly and easy to navigate around to find the information needed.

A section on drug addiction during pregnancy is timely, helpful and factual as is the section on the herbals contraindicated during pregnancy and why they should be avoided. The guide concludes with the comprehensive set of references.

Drugs and Pregnancy is a valuable tool on any doctor's bookshelves and would be highly recommended for any professional involved in the care of pregnant patients.

Does pethidine still have a place in therapy?

Allan Molloy, Director, Chronic and Cancer Pain Program, University of Sydney Pain Management and Research Centre, Royal North Shore Hospital, Sydney

SYNOPSIS

In chronic pain management, the general consensus at present is that pethidine has no role to play. There is a myriad of other options including spinal implants, long-acting opioid preparations for nociceptive pain or the newer drugs for neuropathic pain. In all cases ruling out new or undiagnosed pathology and early consideration of the role of psychosocial factors is important. Pethidine can be used to treat acute pain for a short time. After this time other options should be considered due to the risk of accumulation of norpethidine and the potential adverse sequelae. If pethidine is used in episodes of recurrent pain such as migraine, patients can become overly reliant on this medication. The resultant drug-seeking behaviour can be very difficult to treat.

Index words: analgesia, morphine, pain.

(Aust Prescr 2002;25:12–3)

Introduction

Pethidine is a synthetic opioid analgesic. There is no doubt that it is an effective analgesic but there is a significant potential for the development of dependence and drug-seeking behaviours. Once these are established they may be very difficult to address. The other significant concern is the potential for toxicity due to the accumulation of its metabolite norpethidine after repeated administration.

Pharmacology

The effects of pethidine are generally similar to those of morphine, despite its different structure. It also has local anaesthetic and atropine-like effects. Pethidine is readily absorbed orally, but its bioavailability is only about 50%. In the acute pain setting, pethidine can be administered by intramuscular injection, patient controlled analgesia, and also intraspinally, for example epidurally after Caesarean section.

Pethidine has a half-life of 3–5 hours and useful analgesia lasts between 2 and 4 hours after parenteral administration. Given at this frequency the active metabolite norpethidine (half-life 8–21 hours) accumulates (particularly in renal failure). This may lead to potentially serious adverse effects including tremor, twitching, agitation, confusion and (rarely) fitting. Norpethidine is estimated to possess half the analgesic potency of pethidine but twice the convulsive potency.[1]

Pethidine has some clinically significant drug interactions. Phenobarbitone and chlorpromazine enhance the production of norpethidine, and pethidine should not be given to patients taking monoamine oxidase inhibitors because of the risks of respiratory depression, hypertension and possibly coma.

Acute pain

Pethidine is effective for intra-operative and postoperative analgesia and is used as a premedication. In acute pain pethidine acts on opioid receptors to inhibit pain-generating impulses in afferent Aδ and C fibres. At equi-analgesic doses pethidine produces less smooth muscle contraction in the biliary tract and less of a rise in the common bile duct pressure than morphine.[1] It also causes less urinary retention and constipation than morphine. Pethidine is not recommended for conditions such as migraine.[2]

Alternatives to pethidine for acute pain

For acute pain states there are a number of alternatives including other opioid analgesics, non-steroidal anti-inflammatory drugs, simple analgesics, regional anaesthetic techniques and intraspinal techniques (intrathecal and epidural administration). While pethidine remains a useful drug in the peri- and postoperative period it should not be used for more than 72 hours, with further caution exercised in those patients requiring higher than normal doses, or in those with renal failure.[3] Such patients should be changed to a different analgesic regimen and if necessary assessed by an acute pain team if one is available. However, the evidence for the risk of adverse events attributable to norpethidine is not clear. Patients may experience adverse effects due to norpethidine toxicity in shorter time frames and with relatively low concentrations of norpethidine.[3]

Chronic pain

Epidemiological data show that 20% of the population experience chronic pain and that approximately 10% of the population are significantly distressed and disabled by chronic pain.[4] In contrast to acute pain, research suggests that chronic pain is likely to be less sensitive to opioids. For example, nerve injuries are associated with up to a 70% reduction in presynaptic opioid receptors and the presence of substances such as cholecystokinin, which may reduce opioid sensitivity.[5]

There is a surprising lack of clinical studies showing that opioids reduce pain and improve function in patients with chronic pain. One study found nearly 60% of patients attending a pain clinic were taking opioid analgesics. Many reported taking above the recommended dose despite no reported benefit. In this study the use of opioids correlated well with

measures of distress and disability, but not with objective physical signs.[6]

There are no long-term controlled studies on the efficacy or adverse effects associated with the use of opioids in chronic non-malignant pain.[7] An Australian review found that opioids were often prescribed for patients with social problems, high levels of emotional distress and unclear medical diagnoses. Escalation occurred in those patients prescribed short-acting opioids such as pethidine or dextromoramide.[8]

Guidelines on management strategies for the use of oral opioids in patients with chronic non-malignant pain were published in 1997.[9] This followed an earlier consensus statement on the 'Use of opioids for the treatment of chronic pain' by the American Academy of Pain Medicine and the American Pain Society.[10] These guidelines do not support the use of regular parenteral opioids in the management of chronic pain.

Alternatives to pethidine for chronic non-malignant pain

Those receiving regular pethidine for chronic pain should have their condition re-evaluated. Preferably this re-evaluation should be by a multidisciplinary pain management team where one is available. If there is a delay in obtaining a multidisciplinary assessment, attempts should be made to identify and start to address any unhelpful beliefs and behaviours in addition to any nociception or neuropathy present. In most cases this approach will broaden the treatment options to include a clinical psychologist or psychiatrist with expertise in pain management.

If the patient has evidence of tissue damage such as lytic lesions associated with cancer or joint degeneration (e.g. rheumatoid arthritis) then nociceptive pain can be inferred. Treatment options include non-steroidal anti-inflammatory drugs, simple analgesics such as paracetamol and long-acting opioid preparations providing steady blood concentrations of opioids such as morphine, oxycodone, hydromorphone or fentanyl. In the same way, a patient who has had a major nerve or spinal cord injury should be assessed for neuropathic pain and consideration given to drugs such as sodium valproate[11], gabapentin[11] or mexiletine. In carefully selected cases an intrathecal drug delivery system or spinal cord stimulator may be considered.

Pethidine is often used for conditions such as low back pain and radicular pain which may have nociceptive or neuropathic components or be a combination of both. A similar approach to that described above is recommended. These patients will require the early involvement of a multidisciplinary pain management team.

Self-help

As pain is a multidimensional experience, treatment should not be continued with one modality unless there is a rapid and sustained response. Failure to instruct patients on self-management approaches risks reinforcing an external locus of control (excessive reliance on others instead of managing their own pain). Usually this is the province of a clinical psychologist but medical practitioners can make a start with self-help books such as *Manage your pain* which is written to be used as a manual for patients to work with their doctor, physiotherapist or other health care worker.[12] In many cases this approach will not be sufficiently intensive and treatment may be required in a good quality pain management program.[13]

Summary

Pethidine is an effective analgesic for acute pain, but has no role in chronic pain. Patients reliant on regular pethidine require a multidisciplinary assessment. A round-table conference should follow to consider treatment options. There may be options to address the pain and also options to help the individual to manage their pain more successfully. In many cases a co-ordinated multidisciplinary cognitive behavioural pain management program will be required. Maintenance of gains made during such programs requires an understanding that patients will continue to experience pain and that their function and quality of life requires the active use of pain management strategies that they have learnt. This requires the support of their doctor or other healthcare worker. As this approach aims to 'de-medicalise' the management of their pain, practitioners have to be careful not to inadvertently undermine this approach by switching the focus back to pain, rather than promoting function by encouraging the use of 'well behaviours'.

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See resources on the following web site: www.painmgmt.usyd.edu.au

Dr Molloy is a co-author of 'Manage your pain'.

Clinical intuition: more than rational?

Glyn Brokensha, Senior Lecturer, Medical Education Unit, University of Adelaide, Adelaide

SYNOPSIS

Clinical intuition is controversial, not least because of a confusion of definition. Excluding mysticism, three categories of intuition are identified; the spurious, the inferential and the holistic. Intuition is located in the understanding that the patient is much more than the disease. To question our assumptions about how the evidence-base informs our decisions, rehabilitates intuition and recovers reason from rationalisation.

Index words: decision-making, consumers.

(Aust Prescr 2002;25:14–5)

Introduction

'*Intuition is a sacred gift. Rationality its faithful servant.*' [1]

Why, in the full flow of an epidemic of gastroenteritis, did I choose to admit that child for a lumbar puncture? There were so many others, apparently just the same.

Why, at the end of an exhausting day, did I ask the mother of *that* child with feeding difficulties to bring him in? He had only recently had a normal six-week examination. Why, having found nothing remarkable in my examination did I unaccountably send him immediately to our base hospital?

The first baby had viral meningitis, the second an undiagnosed coarctation of the aorta. In both instances I had a bad case of grateful bewilderment!

'Clinical intuition', the sages nod, as if such categorisation revealed more than it actually conceals. Naming a process brings such comfort to our ignorance of it.

What is intuition?

Many clinicians would agree that intuition plays a part in diagnosis and management, although few would concur on how much. What exactly do we mean by clinical intuition? The scarce literature is blighted by confusion even over definition.[2]

Intuition seems to be used mainly in four senses:

- mystical
- spurious
- inferential
- holistic.

Mysticism

Mystical intuition refers to the notion that there are forces at work which have no rational explanation. By some direct means, the *intuiter* is influenced in ways that are inexplicable either by introspection or by empirical research.

In other words, my clinical intuitions in respect of the two babies were the result of *something* occurring in me which neither I nor scientific inquiry can understand. A mystical transmission of information, as if by 'the hand of God'.

Spurious

Spurious intuition argues that we often act illogically. When our questionable actions are vindicated we egocentrically attribute the success to ourselves, calling it 'intuition'. When events prove otherwise, we rationalise our mistake and repress self-doubt, preferring denial to the painful reality of imperfection.

In other words, my two decisions were elevated *post-facto* to shining successes. Many other clinical blunders were ignored and repressed.

Inferential

Inferential intuition recognises that much more sensory information impinges upon us than can ever be comprehended. These sensory impressions could be unconsciously integrated and form the basis for intuitive judgment and action.

'A judgment in which visual and verbal cues are so rapidly and subliminally observed that their contributions to the final decision are virtually forgotten.'[3]

In other words, my clinical intuitions were as a result of sensory factors such as the smell of the house, the appearance of each baby or the demeanour of the parents. Sadly for my place in the Diagnostician's Hall of Fame, I will only ever be sketchily aware of what these factors were.

Holism

Holistic intuition supposes that in our 'modelling' of the world, we can be unconsciously influenced by gaps, redundancies and hidden connections in the data. Unobserved, they influence our thinking and impact upon our decisions.

'Where gaps, missing pieces, or hidden relationships are detected within … the whole array of perceptual information'.[3]

In other words, my diagnostic acumen was unknowingly built on an unconscious 'modelling', not only of the clinical presentation, but also of the prevailing social milieu and even of the process of being a general practitioner. Presumably these 'models' are built through time spent in the discipline, which is why intuition has been traditionally regarded as the preserve of the expert.[3]

That such processing could occur out of awareness is unsurprising given our extraordinary sensory capacity and the computational immensity of our neurology. Indeed, there is rational evidence to support such an intuitive view of intuition.[2]

An elegant psychological experiment demonstrated the unconscious development and use of intuition. Volunteers played a gambling game which 'simulates real life

decision-making in the way it factors uncertainty, rewards and penalties'. They quickly developed and utilised advantageous strategies without realising. 'Moreover, they began to develop anticipatory skin conductance responses whenever they pondered a choice that turned out to be risky, before they knew explicitly that it was a risky choice.'[4]

Controversial or contrary?

The persistent controversy about clinical intuition is unsurprising, given our empiricist traditions. However, a wealth of rational evidence attests to the prevalence of intuitive thinking in clinical situations and much evidence also points to its practicality.[2,5]

Unfortunately, the evidence often muddles the many meanings of intuition and confuses rather than clarifies. Intuition occurs in the context of discovery. Once the existence of an intuition has been noticed, entirely different strategies are required to evaluate the content of the intuition. 'The largely unconscious process involved in generating hunches is quite different from the conscious processes required to test them'.[6]

In other words the objective validity of intuitions, in terms of whether they work out to be true or not, is an irrelevancy. The value of an intuition lies not in its accuracy, but in its ability to intrude itself into consciousness.

There is also a widespread and mistaken notion that intuition is necessarily irrational. An 'esoteric talent available only to a few initiates'[7], 'that gifted minority'[8] and 'not legitimate knowledge'.[3] This notion is itself irrational, based on a 'belief that intuition is an irrational process … as a consequence it is assumed that intuition can neither be fully understood nor explained'.[2]

Although by definition irrational to the intuiter, intuition is evidently a process capable of rational investigation and explication. It seems that in evaluating intuition, we are often not rational.

A certain uncertainty

It seems that our quest for certainty, to have the 'right answers', has often caused us to ask the wrong questions. Clinical trials, the source of evidence-based medicine, are often unhelpful, because they pose the wrong questions.[9]

Our disease-centred view causes us to lose sight of the person. 'Information scientists are keen to know [the] information [that] physicians would like to have available when they tackle clinical decisions. The results of their studies are intriguing, yet ultimately predictable: physicians want information that is relevant to *specific* questions about *specific* patients.'[9]

'Mrs Jones may have an illness but she also has a predicament.'[9] It is an individual predicament, which reminds us that we too have an individual predicament: what are we to do now?

We fail Mrs Jones, by clinging mindlessly to evidence-based medicine without '… understanding the limits of generalisability in our clinical experience and in the research we read.'[10] Without such understanding, our evidence becomes orthodoxy and our practice a religion.

So, how are we to respond to Mrs Jones' individual situation? Maybe by following the advice to think more and perhaps read less.[9]

'The process of questioning our claims and assumptions in clinical decision-making is part of a recent interpretive turn in medicine, one that stands in opposition to evidence-based medicine ... Being a good physician involves far more than an appeal to best evidence. ... A reliance on evidence alone forces us to stop too soon in our clinical reasoning.'[10]

The wealth of experience

Appreciable evidence[2,3,5] now supports the view that useful clinical intuition, far from being an 'esoteric talent', is directly related to knowledge and experience and that '… it is particularised knowledge that plays a vital role for experts, not inexplicable powers of intuition'.[11]

When we learn to ride a bicycle, drive a car or play a musical instrument we develop a practical expertise. Initially, our attention is narrowed and focused on the task. We quickly become fatigued. Later, as our competence grows, we become increasingly capable and can attend to the wider sensory environment.

This is the context of the expert practitioner's intuition. 'Complex sequences of actions can become so routine through practice and experience that they are carried out semi-automatically ... while perceptual awareness of other, possibly unusual aspects of the situation increases.' [2]

Most patients have a wealth of this experience too. This is not generally in the domains of clinical knowledge and skill, but in their own experience they are, *de facto*, experts!

Patients' intuitions about their own health are usually ignored, often discounted and occasionally denigrated, despite evidence that attention to them at the very least improves our own clinical intuition.[5] The rational, empathic, compassionate physician, the clinician to whom the individual's experience of illness is paramount, intuitively appreciates the uniqueness of the patient, the situation, and the doctor.

Clinical intuitions then, are the consequences of a particular clinician, engaged with a particular patient in a particular place. As such, we recognise that intuition is much more than rational, it is reasonable.

E-mail: glyn.brokensha@adelaide.edu.au

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I've missed a dose; what should I do?

Andrew Gilbert, Libby Roughead and Lloyd Sansom, Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, Adelaide

SYNOPSIS

More than 80% of patients occasionally miss a dose of their medication. Health practitioners ought to plan with their patients what to do if a dose is missed. Patients believe that this plan should be a required part of the information received when a medication is prescribed and dispensed. Consumer Medicine Information sheets, which are available for most commonly prescribed medications, contain a section on what to do if a dose is missed. The routine use of these sheets or similar advice may help patients to know what to do when they miss a dose.

Index words: Consumer Medicine Information, patient compliance.

(Aust Prescr 2002;25:16–8)

Introduction

Why **don't** consumers know what to do when they miss a dose of their medication? As health professionals we know that the vast majority of patients occasionally miss a dose of their medication. This unintentional non-compliance, and request for advice after the event, is very common in practice. In a study of 205 people, 90% rated having information on 'what to do if a dose is missed' as very important or important and only 1.5% did not want information on this topic.[1] A USA study[2] found that less than 50% of patients received this information.

Given our understanding of the difficulties around compliance with medication regimens, it must be our expectation that many patients will miss doses. Informing them about what to do about a missed dose at the time of prescribing, dispensing and administration would seem to be a logical step towards improved compliance.

Pre-emptive advice

Missed doses could be viewed within the framework of patient non-compliance, however the problems which arise often result because health professionals do not give enough information to allow the patient to safely use the medication. Teaching a patient what to do if a dose is missed and providing strategies to minimise the number of missed doses appears a sensible approach.[3] Providing written information, that includes what to do if a dose is missed, improves people's self-administration of medicines, including corrective action when a dose is missed.[4]

In practice, giving information on what to do if a dose is missed should not be too onerous a task for medical practitioners or pharmacists. Most of the commonly prescribed medications in Australia come with, or have available, a Consumer Medicine Information (CMI) sheet. All CMI sheets have a section entitled 'What to do if you miss a dose'. Giving patients a CMI sheet the first time they receive a medication, and using this material in discussion with patients at the time of prescribing and dispensing would prepare them for this eventuality.

Assessing the importance of a missed dose (Table 1)

The severity of the patient's condition, whether clinically significant breakthrough effects are likely to be observed, and the characteristics of the medication should be considered when deciding the most appropriate strategy following a missed dose. Vulnerable patients are easily recognisable in any practice and include those on medications of low therapeutic index*, or suffering from conditions which require constant maintenance of therapeutic concentrations (for example epilepsy and thromboembolic diseases requiring anticoagulation). On the other hand, for most people with hypertension or hypercholesterolaemia a single missed dose will be of little consequence.

The patients should be informed at the time of prescribing and dispensing, of strategies to minimise missed doses and to redeem the situation when a dose is missed. Highlighting the strategy as it appears on the CMI or writing out an action plan as a reminder to the patient may prove very useful.

While a pre-emptive approach is ideal it is recognised that requests for information about missed doses are common. Knowledge of a drug's half-life, a major determinant of the fluctuation in interdose concentrations at steady state, is useful for making recommendations on what to do if a dose is missed. Upon cessation of therapy, it takes four to five half-lives for the drug to be completely eliminated.

In general, medications, or their active metabolites, with a long half-life tend to create less problems when a dose is missed than medications with a short half-life. However, the clinical effect of some drugs is not related to the half-life. 'This usually occurs when the drug is acting via an irreversible

* The therapeutic index reflects the range of concentrations between the drug concentration which produces toxic effects and the drug concentration required for therapeutic effects. A narrow therapeutic index means only small increases in concentration can cause toxicity and small decreases in concentration can result in loss of efficacy.

Table 1

Examples of medications for which missed doses may be clinically important, and information for patients on what to do if a dose is missed

Medication	*Information for consumers*
Oral contraceptives	
Combined oral contraceptives	If one or more tablets are missed from the inactive tablets, no additional contraceptive precautions are necessary, and tablet taking should be recommenced ignoring the missed tablet or tablets. However, if all the inactive tablets are missed and then the next pack is not started on time, start as soon as it is remembered. Additional contraception (such as a condom or a diaphragm) must be used for the next 7 days. If an active tablet is forgotten take it as soon as it is remembered, within 12 hours after the time that it is normally taken. Then take the next and subsequent tablets at the usual time. If there is a delay of more than 12 hours after the time that the tablet is normally taken, contraceptive protection in this cycle may be reduced. There is more risk in becoming pregnant if tablets are missed during the first week, or at the end of the current pack. Take the missed tablet as soon as it is remembered, even if this means taking two tablets at the same time. Any earlier missed tablets are left in the pack. Continue taking a daily tablet as usual, and use additional contraceptive precautions (except for the rhythm or temperature method) for the next 7 days. If these 7 days extend into the inactive section, skip the inactive section and start a new pack in the active area on the next day instead.
Progestogen-only oral contraceptives	For women using the progestogen-only pill the recommendation for the use of other methods of contraception is extended to 14 days if the dose is delayed by three hours or more.
Anticonvulsants	
Acetazolamide Carbamazepine Ethosuximide Phenytoin Tiagabine Topiramate Vigabatrin	If it is almost time for next dose (within 4 hours), skip the missed dose and take the next dose when it is due. Otherwise, take it as soon as it is remembered, and then go back to taking the medicine as usual. Do not take a double dose to make up for the missed dose. This may increase the chance of you getting an unwanted adverse effect.
Lamotrigine Sodium valproate	Do not take a double dose to make up for the dose that you missed. (This drug has a long half-life.)
Digoxin Warfarin	If it is almost time for the next dose, skip the missed dose and take the next dose when it is due. Otherwise, take it as soon as it is remembered, and then go back to taking the medicine as usual. Do not take a double dose to make up for the dose that you missed.
Psychotropics	
Lithium	If it is almost time for the next dose (within 2 hours), skip the missed dose and take the next dose when it is due. Otherwise, take it as soon as it is remembered, and then go back to taking the medicine as usual. Do not take a double dose to make up for the dose that you missed.
Antidepressants other than monoamine oxidase inhibitors	If it is almost time for the next dose, skip the missed dose and take the next dose when it is due. Otherwise, take it as soon as it is remembered, and then go back to taking the medicine as usual. Do not take a double dose to make up for the dose that you missed.
Monoamine oxidase inhibitors Phenelzine Tranylcypromine	Do not take an extra dose. Wait until the next day and take the normal dose then.

mechanism (for example aspirin's effect on platelets), via an indirect mechanism (for example the effect of warfarin on blood coagulation), when the drug is a pro-drug (in which case it is the half-life of the active species that is important) or when the drug is converted to an active metabolite which has a long half-life.'[5]

Missing several consecutive doses raises additional problems. For example, for drugs with long half-lives it can take a significant time to re-establish therapeutic concentrations when regular dosing resumes unless loading doses are given (for example digoxin). Drugs with short half-lives will lose therapeutic effect rapidly. Further, drugs with first-dose effects, for example an ACE inhibitor in combination with diuretics, may also present clinical problems when normal dosing is resumed. Overall, surprisingly few studies have examined the clinical significance of a missed dose.

Missed doses of the oral contraceptive pill have been well studied. Women taking the pill need to be aware of the risk associated with missed doses and of what to do when a dose is missed (Table 1). Given the complexity of this information, and the risk of an unwanted pregnancy, it is important that any verbal counselling is supported with appropriate written material. Where a CMI sheet is available this can be used during the consultation. If no CMI sheet is available for the prescribed product, written notes based on the recommendations in the Australian Medicines Handbook are useful.[6]

Conclusion

For the vast majority of patients an occasional missed dose will have little impact on the outcome of therapy. Most CMI sheets include statements such as:

- If you forget to take one or more doses: take your next dose at the normal time and in the normal amount. Do not take any more than your doctor prescribed.
- If you miss one dose, skip it and continue with your normal schedule.

Having this knowledge when starting therapy may be a simple way to alleviate much patient anxiety and in some cases avoid unwanted clinical consequences.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 23)

5. Patients who miss a dose of warfarin should take a double dose when the next dose is due.
6. Contraception becomes unreliable if a progestogen-only contraceptive pill is missed by more than three hours.

Book review

Therapeutic Guidelines: Palliative care. North Melbourne: Therapeutic Guidelines Limited; 2001. 308 pages. Price (postage not included): $33, students $25.30.

Peter Keppel, General Practitioner, Yarrawonga, Vic.

'Palliative care is active care.'

This statement rings true to me, having worked in a small rural town for over 16 years, in which the care of the dying is a large part of my practice. Whether it is severe chronic obstructive pulmonary disease, intractable congestive cardiac failure (less often seen now with newer drugs) or cancer, the process always involves a brief introduction, then breaking bad news, then a terminal phase in which shifting goals are negotiated and renegotiated.

The book attempts a lot more than a list of pharmacological options. It opens with general chapters covering principles of palliative care, ethical issues, communication, loss and grief, and analgesic guidelines. It makes the point that general practitioners are by default the co-ordinators of care, as well as being the gatekeepers to the health system. The place of self-care among providers is recognised.

With regard to pain management, the approach is one of identifying different types of pain, e.g. nociceptive (superficial somatic, deep somatic, skeletal muscle, visceral colicky, visceral constant) or neuropathic, rather than the traditional three stage 'ladder' approach.

The emotional, spiritual and social aspects of pain are not ignored. I particularly found useful the approach to delirium and confusion. The problems of the elderly demented patient are dealt with rather briefly, given the large cohort of these people now ageing. No mention is made of the practical problems accessing the newer antipsychotics because of the Pharmaceutical Benefits Scheme prescribing restrictions. The dose of morphine in terminal severe chronic obstructive pulmonary disease patients is stated to be 1 mg 4 hourly, increasing as needed. In my experience this is usually nowhere near enough.

There are useful chapters on medical oncology describing some newer regimens for particular cancers.

The book has been found useful by our active and busy palliative care team. It would not be sufficient on its own to answer all questions on the subject, but is written in a compassionate style, showing the wisdom of experience. There is extensive cross-referencing within the text. There is no list of other texts for reference that I could find.

Medicinal mishaps

Serotonin syndrome

Case

An elderly woman presented to hospital with a painful left hip following a fall. She was usually mobile and cared for herself, but she had a history of depression and panic disorder. On examination she was alert and orientated, but X-rays confirmed a left intertrochanteric fracture. Surgery was planned for the next day so she was started on intravenous fluids and traction. She was prescribed tramadol 100 mg four times daily in addition to her usual treatment of paracetamol 1 gm four times daily, fludrocortisone 0.05 mg in the morning, sertraline 200 mg at night, pericyazine 2.5 mg twice daily, and latanoprost eye drops at night.

On the night of admission she was drowsy but her speech was coherent. Preoperatively she was noted to be confused and unable to give a history. She remained confused postoperatively and developed visual and auditory hallucinations.

On the third postoperative day the nursing notes queried bilateral foot drop with spasms of both feet.

Six days after admission her mental state deteriorated (mini-mental examination score was 19/30). She had a low grade fever with plantar flexion and inversion of both feet with rigidity, tremor and dystonia. A psychiatrist diagnosed a serotonergic syndrome, precipitated by sertraline and tramadol. Tramadol, sertraline, pericyazine and fludrocortisone were ceased.

Despite treatment with benserazide/levodopa and botulinum toxin the woman had persisting disability due to contractures in her legs and feet. A full clinical assessment and relevant investigations showed no other abnormalities to account for this disability. It is possible that her disability had resulted from contractures developing as a result of prolonged dystonia caused by serotonergic syndrome.

Comment

Tramadol is an analgesic with agonist action on the μ opioid receptor. It also inhibits noradrenaline and serotonin reuptake.

Serotonin syndrome is caused by excess serotonin in the central nervous system (CNS). It commonly occurs as an interaction between two drugs, where each drug causes a rise in serotonin concentration in the CNS. The classic example is a combination of a selective serotonin reuptake inhibitor and a monoamine oxidase inhibitor, but it has occurred with selective serotonin reuptake inhibitors and tramadol.

Signs and symptoms of serotonin syndrome vary but may include change in mental status and behaviour, motor system changes and autonomic instability. Distinguishing them from depression or the adverse effects of antidepressants may be difficult.[1] Three or more of the following signs must be present after commencing or increasing the dose of a serotonergic agent:

- mental status changes, confusion, hypomania, agitation
- inco-ordination
- myoclonus
- hyperreflexia
- diaphoresis
- shivering
- tremor
- diarrhoea
- fever.

Other aetiologies (e.g. infections) need to be excluded.

Clinically, serotonin syndrome is likely to be under-reported because it is often not recognised or may be confused with neuroleptic malignant syndrome; symptoms may be mild, moderate or severe. Serotonin syndrome appears to be self-limiting, resolving quickly when the offending drugs are discontinued, but occasionally it may be fatal.

Recommendations

All patients should have a full medication history taken before being prescribed tramadol. Any drug that increases serotonin levels by any mechanism should raise the possibility of an interaction (see box). This situation is most likely to arise in patients being treated for depression.

Drugs to avoid in combination with tramadol

selective serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram)

tricyclic antidepressants

moclobemide

St John's wort (hypericum)

venlafaxine

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FURTHER READING

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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 Board 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 Board is prepared to do this. Before new drugs are prescribed, the Board 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.

Darbepoetin alfa

Aranesp (Amgen)

prefilled syringes containing 10 microgram/0.4 mL, 20 microgram/0.5 mL, 30 microgram/0.3 mL, 40 microgram/0.4 mL, 50 microgram/0.5 mL, 60 microgram/0.3 mL and 100 microgram/0.5 mL

Approved indication: anaemia of chronic renal failure

Australian Medicines Handbook Section 7.5

In chronic renal failure erythropoiesis is reduced leading to a normochromic, normocytic anaemia. This can be treated by giving the patient recombinant erythropoietin to stimulate red cell production.

Although there are genetically engineered differences in its structure, darbepoetin can be used as an alternative to erythropoietin. The structural differences give darbepoetin a half-life three times longer than that of erythropoietin. After intravenous injection the half-life ranges from 12 to 40 hours and ranges from 27 to 89 hours after subcutaneous injection. Patients therefore need less frequent injections if they use darbepoetin instead of erythropoietin. A weekly injection should raise the haemoglobin by at least 10 g/L in four weeks, if the patient has adequate stores of iron. The product information explains how to calculate the dose of darbepoetin when switching a patient from erythropoietin.

In clinical trials darbepoetin and erythropoietin have had similar efficacy in the correction of anaemia. Both drugs are also effective at maintaining the haemoglobin concentration.

The adverse effects of darbepoetin resemble those of erythropoietin. Patients find the subcutaneous injection of darbepoetin more painful, but when given intravenously it causes less thrombosis of the vein than erythropoietin. Other adverse events include hypertension and myalgia. Uncontrolled hypertension is a contraindication to darbepoetin. So far there have been no reports of serious allergic reactions or patients developing antibodies to darbepoetin.

Etanercept

Enbrel (Wyeth)

vials containing 25 mg

Approved indication: rheumatoid arthritis

Australian Medicines Handbook Section 15.2.2

The treatment of rheumatoid arthritis now involves the early use of disease-modifying antirheumatic drugs. Despite early intervention some patients will continue to have joint inflammation. Researchers have therefore been investigating how to control the cytokines involved in the inflammatory process.

Tumour necrosis factor is a cytokine found in the synovium. It stimulates cell proliferation and the production of inflammatory mediators. Etanercept blocks this action by binding to the receptors for tumour necrosis factor.

The etanercept molecule is a human tumour necrosis factor receptor fusion protein. It is produced by recombinant DNA technology.

Patients have to inject etanercept twice a week. After subcutaneous injection etanercept is slowly absorbed. It has a half-life of 70 hours, but the mechanism of elimination is unknown. There have been no pharmacokinetic studies to examine the effect of renal or hepatic impairment.

A double-blind placebo-controlled study enrolled 234 patients who had failed to respond to a disease-modifying antirheumatic drug. After six months of treatment 59% of the patients given etanercept had a 20% improvement in their symptoms and signs. In the placebo group only 11% had a similar response.

Another study investigated adding etanercept to methotrexate therapy. After 24 weeks 71% of the 59 patients taking the two drugs had at least a 20% improvement in their symptoms and signs. This was significantly greater than the response in the 30 patients taking methotrexate and placebo even though 27% of this group also improved.[1]

During the clinical trials etanercept was well tolerated, but there are post-marketing reports of serious adverse events. By inhibiting tumour necrosis factors etanercept may reduce the body's defences against infections and tumours. There were 22 serious infections and seven malignancies in 745 patients taking etanercept. Some patients with sepsis have died, so etanercept should be stopped if a serious infection develops. Extra caution is needed if etanercept is prescribed for patients who may have an increased risk of infection, for example patients with diabetes. Patients can develop autoantibodies, but no lupus-like reactions have been reported.

A common problem for patients is a reaction at the injection site. These reactions may be swelling, pain or itching and can last for several days. It is important that patients who are going to self-administer etanercept are instructed in how to prepare the injection. Other frequent adverse events include headache and upper respiratory infections.

When a patient stops injecting etanercept their arthritis usually returns within a month. At present, there is limited information about the long-term continuous use of etanercept. This therapy is likely to be very expensive and there is currently no method of predicting which patients will benefit from etanercept. It should be reserved for patients who have not responded to other drugs.

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Laureth-9

Aethoxysklerol (Smith & Nephew)

2 mL ampoules containing 0.5%, 1% and 3%

Approved indication: varicose veins

Australian Medicines Handbook Section 6.7.1

Laureth-9, also known as polidocanol, is an emulsifying agent. When it is injected into a vessel it damages the endothelium resulting in a thrombosis. In combination with compression bandaging, laureth-9 can be used to treat varicose veins in the legs. As laureth-9 has some anaesthetic effects this scelerotherapy is relatively painless.

In an Australian study laureth-9 was used to treat varicose veins, telangiectasia and venule ectasia. After treating 16 804 limbs, the investigators' subjective impressions were that the results were superior to sclerotherapy with hypertonic saline or sodium tetradecyl sulfate. Adverse reactions were also considered to be less severe.[1]

The adverse effects of laureth-9 include phlebitis, tissue necrosis at the injection site and pigmentation in the sclerosed area. Some patients will develop allergic reactions so the practitioner should be equipped to treat anaphylaxis. If the injection has been into paravenous tissue, an injection of 1% procaine hydrochloride or normal saline, and if possible hyaluronidase, is recommended.

Larger veins require a higher concentration of laureth-9. Usually only 0.1–0.3 mL needs to be injected into smaller veins. Very fine needles should be used. After the injection a compression bandage is applied and the patient should walk around for 30 minutes. For medium sized veins the bandage is worn for 4–6 weeks. Repeated treatment may be required, but the veins may still not disappear completely in all patients.

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Oxcarbazepine

Trileptal (Novartis)

300 mg film-coated tablets

Approved indication: epilepsy

Australian Medicines Handbook Section 16.1.3

Carbamazepine is efficacious in the treatment of partial seizures and generalised tonic-clonic seizures. Its effectiveness is limited by its toxicity and interactions. Oxcarbazepine is an analogue of carbamazepine which has been developed to overcome some of these problems. It has been available in some parts of Europe for several years.

Oxcarbazepine is taken twice a day. The dose can be increased at weekly intervals. This is a more rapid titration than with carbamazepine. Each dose is well absorbed and then converted to an active metabolite. This metabolite has a half-life of nine hours, whereas the half-life of oxcarbazepine is two hours. Less than 1% of the dose is eliminated unchanged with most of the metabolites being excreted in the urine. Renal clearance is increased in children and reduced in the elderly.

Like other recently marketed antiepileptic drugs[1], oxcarbazepine has been used as an adjunct to other treatments. It is efficacious in adults and children with partial seizures uncontrolled by other drugs.[2]

Oxcarbazepine has also been studied as monotherapy. It is more effective than placebo at controlling partial seizures. In patients with previously untreated partial or generalised tonic-clonic seizures, oxcarbazepine was as efficacious as sodium valproate and phenytoin.

Fatigue, dizziness, drowsiness, nausea and vomiting are common adverse reactions. Hyponatraemia can develop particularly during the first three months of treatment. The product information recommends that patients with renal problems, or those taking medications such as diuretics or non-steroidal anti-inflammatory drugs, should have their serum sodium measured frequently at the start of therapy.

If patients have a history of hypersensitivity reactions to carbamazepine, there is a 25–30% chance that they will react to oxcarbazepine.

Unlike carbamazepine, the metabolism of oxcarbazepine is not affected by drugs, such as erythromycin, which inhibit CYP3A4. Oxcarbazepine can inhibit CYP2C19 so there is a potential for interactions with phenytoin. There are also interactions with calcium channel blockers and oral contraceptives because oxcarbazepine induces CYP3A4 and CYP3A5.

Although oxcarbazepine may have some advantages over carbamazepine, there is less information about its long-term safety. Oxcarbazepine is also likely to be more expensive.

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Pioglitazone hydrochloride

Actos (Eli Lilly Australia)

15 mg, 30 mg and 45 mg tablets

Approved indication: type 2 diabetes

Australian Medicines Handbook Section 10.1

Many patients with type 2 diabetes cannot control their glucose concentrations with diet alone. These patients have insulin resistance which may benefit from treatment with a thiazolidinedione.

The thiazolidinediones act on the peroxisome proliferator-activated receptor.[1] This leads to an increased sensitivity of muscle and adipose tissue to insulin. The drugs also reduce gluconeogenesis in the liver.

Although there are few published studies, pioglitazone has been approved for use as monotherapy or in combination with other drugs, including insulin, for the treatment of type 2

diabetes. This approval appears to be based on clinical trials lasting 16 or 26 weeks.

The studies using pioglitazone as monotherapy found that it had a significantly greater effect, than a placebo, on fasting blood glucose and HbA_{1C}. In combination with a sulfonylurea, or metformin, pioglitazone will produce greater reductions in fasting blood glucose and HbA_{1C} than a placebo. Similar effects were seen when pioglitazone was given to patients who were already taking insulin for their type 2 diabetes.

Patients taking insulin should start with a lower dose (15 mg) of pioglitazone. The recommended dose when pioglitazone is used in combination with other drugs is 30 mg.

Pioglitazone can be given once a day. Although it has a half-life of 5–6 hours, pioglitazone has an active metabolite which has a half-life of 16–23 hours.

Following the serious adverse reactions which lead to the withdrawal of troglitazone, there is concern about the hepatotoxicity of the thiazolidinediones. Similar adverse effects were not reported during the trials of pioglitazone, but liver function must be monitored regularly. During the first year of treatment the liver function should be tested every eight weeks.

The thiazolidinediones also alter lipid metabolism. This may include an increase in low density lipoprotein. In animal studies there has been cardiac hypertrophy. Although echocardiographic studies have not shown this effect in humans, the studies have excluded patients with heart disease.

More common adverse effects include oedema, headache and myalgia. Less than 4% of the patients in the clinical trials withdrew because of adverse effects.

Although cytochrome P450 3A4 is involved in the metabolism of pioglitazone there are no studies of interactions with other drugs metabolised by this enzyme. Pioglitazone may reduce the effectiveness of oral contraception. While it does not alter the steady-state pharmacokinetics of metformin and glipizide caution is needed when combining drugs such as these with pioglitazone. The combination with an oral hypoglycaemic drug or insulin increases the risk of hypoglycaemia.

To ascertain the role of pioglitazone there is a need for comparative studies to be published. There is currently not enough evidence to suggest that pioglitazone should become the first-line treatment after diet fails to control a patient's blood glucose.

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Sibutramine hydrochloride

Reductil (Abbott)

10 mg and 15 mg capsules

Approved indication: obesity

Australian Medicines Handbook Section 12.10

Drugs are not the first-line treatment for people who are overweight (see 'Obesity and its management', Aust Prescr 1999;22:12-6). Sibutramine can be considered for obese patients who are unable to reduce their weight despite changing their diet and taking more exercise. It should only be considered if the patient's body mass index is at least 30 kg/m^2 (27 kg/m^2 if there are other risk factors such as hypertension or diabetes).

Although depression is not an approved indication, sibutramine is a serotonin reuptake inhibitor. It also inhibits the reuptake of noradrenaline and dopamine. Sibutramine is structurally related to amphetamine and is mainly thought to act through its amine metabolites.

After its rapid absorption sibutramine undergoes extensive first-pass hepatic metabolism. As cytochrome P450 3A4 is involved in the metabolism there is a potential for interactions with drugs which induce (e.g. phenytoin) or inhibit (e.g. erythromycin) this enzyme. The active metabolites have a half-life of 14-16 hours and are also eliminated by metabolism.

Patients start treatment with a daily dose of 10 mg. If they have lost less than 2 kg after four weeks, the dose can be increased to 15 mg daily. Treatment should stop if the patient has not lost 5% of their weight after three months. Weight loss in patients with diabetes is slower so they can have a six month trial of treatment.

The maximum weight loss usually occurs after six months treatment. Approximately 60% of the patients who lose 2 kg in the first month of treatment will lose 5% or more of their body weight by six months.

In a double-blind trial 485 obese people were given dietary advice and took either sibutramine or a placebo. After a year 39% of the patients taking 10 mg and 57% of the patients taking 15 mg had lost at least 5% of their body weight, compared with only 20% of those who took a placebo.[1] Another study showed the importance of lifestyle modification. Women who just took sibutramine only lost 4.1% of their body weight after a year, whereas those who also modified their lifestyle lost 10.8% of their body weight. The weight loss was even greater if they also followed a diet.[2]

Sibutramine increases heart rate and blood pressure. Patients should therefore have their pulse and blood pressure checked at least every two weeks in the first three months of treatment and then at least once every three months. A sustained rise in heart rate of 10 beats/minute or a 10 mmHg increase in blood pressure are indications for stopping treatment. A history of coronary or cerebrovascular disease contraindicates sibutramine. Frequent adverse effects include loss of appetite, dry mouth, constipation and insomnia.

The options for the drug treatment of obesity are limited. Sibutramine does not seem to be a major advance. Although it produces statistically significant weight loss the clinical benefit of losing a few kilograms is questionable. In the year-long study the mean weight loss with 10 mg sibutramine was 4.4 kg, only slightly greater than the weight loss of 1.6 kg in the placebo group.[1] Although some patients who have responded to six months treatment have continued to take sibutramine for up to two years they do not continue to lose weight. The achieved weight loss is largely maintained while patients continue to take the drug, but they start to regain weight as soon as they stop.[3] There is no information on the long-term effects of sibutramine on the mortality and morbidity of obesity.

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Zoledronic acid

Zometa (Novartis)

vials containing 4 mg as dry powder

Approved indication: tumour-induced hypercalcaemia

Australian Medicines Handbook Section 10.4.2

Zoledronic acid is a bisphosphonate with a hydroxyl group and an imidazole side chain. This structure makes zoledronate a potent inhibitor of osteoclastic bone resorption. (See 'Bisphosphonates – mechanisms of action' Aust Prescr 2000;23:130-2).

Bone resorption is an important cause of the hypercalcaemia seen in some cancers. Rehydration and bisphosphonates such as clodronate and pamidronate can therefore be used to return calcium concentrations to normal. As zoledronic acid is a more potent bisphosphonate it may give improved results.

Clinical trials have compared a five-minute infusion of zoledronic acid with a two-hour infusion of pamidronate. Ten days after the infusion approximately 88% of patients with tumour-induced hypercalcaemia had responded to zoledronic acid while 70% had responded to pamidronate.

The median time for patients to relapse is significantly longer after zoledronic acid (30 days versus 17 days for pamidronate). This may be related to its long half-life of 167 hours. The drug is excreted unchanged in the urine so it is not recommended for patients with severe renal impairment.

In patients with cancer adverse events are common. Adverse reactions that have been attributed to zoledronic acid include nausea, fever and itching. Hypocalcaemia will occur in 6% of patients. If this is symptomatic the patient may need to be given calcium gluconate. Renal function should be monitored as it can be impaired by bisphosphonates. This risk may be reduced by giving the infusion over 15 minutes.

Zoledronic acid is an effective treatment, but it is less effective once the patient has relapsed. Retreatment with a higher dose has a response rate of 52%. Patients who are refractory to the first dose should not be retreated for at least a week. As zoledronic acid also has some antitumour effects it is being studied in patients with bony metastases or myeloma.

Answers to self-test questions

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

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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

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

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