CONTENTS

Australian Prescriber
Volume 23
Number 5
2000

EDITORIAL

Long-term hormone replacement therapy

Alastair H. MacLennan, Associate Professor, Obstetrics and Gynaecology, University of Adelaide, Adelaide

Index words: menopause, cancer, oestrogens, osteoporosis.

(*Aust Prescr 2000;23:90–2*)

Introduction

The risks and benefits of taking hormone replacement therapy (HRT) for more than five years are uncertain. There are no large long-term randomised placebo-controlled trials to guide the duration of therapy. Large trials are expensive, difficult to run and can only examine a limited number of regimens and routes of HRT.

Until the results of large trials (see box on facing page) are reported we can only guess at the potential primary effect of HRT on major postmenopausal morbidity and mortality from the much weaker designs of observational studies (cohort and case control). These trials are not randomised and are open to bias and confounding. When the results of observational trials are expressed as relative risk, there is generally less chance of a result being due to bias or confounding if the relative risk is more than halved (<0.5) or more than doubled (>2.0). The increased relative risk of lung cancer in smokers is 43.0 and thus the association is very strong. Hot flushes are reduced by HRT to a relative risk of 0.2. Both results suggest the findings are likely to be causally related. A relative risk of 1.0 suggests no effect either way.

In this issue...

Hormone replacement therapy is good at relieving menopausal symptoms, but Alastair MacLennan explains why more research is needed about its long-term effects. Consumers will be particularly interested in the adverse effects of treatment, according to Helen Hopkins, Tony Wade and Derek Weir.

Adverse reactions may not be the focus of a visit from a pharmaceutical detailer, but these representatives of the pharmaceutical industry usually have a lot of useful information. Ric Day advises us on how to get the most from a detailer's visit.

Drug company representatives rarely discuss old drugs such as digoxin. Although digoxin is no longer a first-line drug in the treatment of heart failure, Daniel Ninio tells us that it still has a role in atrial fibrillation.

Breast cancer

A reanalysis of the data from 51 observational studies showed a relative risk of 1.023 (95% CI* 1.01–1.04) for each year of HRT use. The relative risk for HRT use of five years or longer (average 11 years) was 1.35 (95% CI 1.21–1.49).[1] These small increases in relative risk (i.e. under 2.0) could be due to detection bias, for example the HRT users could have had more breast examinations and mammograms. HRT users also have more independent risk factors, such as higher social class, Western diet, fewer pregnancies, later first pregnancy, and a higher alcohol intake, which could also account for small changes in the relative risk of breast cancer. However, if the increased risk is real it would equate to an extra two detected breast cancers per 1000 women who use HRT for five years. Paradoxically, most observational studies show a significant reduction in deaths from breast cancer in HRT users. Selection and detection bias can confound all these results.

There is no good evidence that HRT users with a family history of breast cancer further increase their risk compared to non-users with a similar history. Women taking HRT do not need to have mammography more often than other women.

Recent observational studies on the role of added cyclical and continuous progestogens given with oestrogen therapy have not clarified if these regimens have any effect on breast cancer rates.[2,3] The relative risks were again small in both studies with overlap of the confidence intervals for oestrogen alone versus oestrogen/progestogen regimens. Thus, no recommendations can yet be made as to whether added progestogens influence breast cancer risk.

Bowel cancer

The most recent meta-analysis of 23 observational trials suggests that in postmenopausal women who have ever taken HRT the relative risk is 0.80 (95% CI 0.72–0.92).[4] This is a 20% reduction in colorectal cancer, however this result is open to the biases of non-randomisation. The effect needs to be confirmed in long-term randomised placebo-controlled trials.

Endometrial cancer

The relative risk that taking unopposed oestrogen for 10 years causes endometrial cancer is 9.5 (95% CI 7.40–

* CI = confidence interval

New randomised placebo-controlled long-term trials

Two large randomised controlled trials have recently commenced. The Women's Health Initiative includes 27 000 American women who will receive HRT or placebo treatment. It is a nine-year study which started two years ago with funding of nearly US$1 billion. The other primary prevention study of HRT is the Women's International Study of long Duration Oestrogen after Menopause (WISDOM). It is a placebo-controlled study of women taking oestrogen, or oestrogen and progestogen for 10 years with a further 10-year follow-up of clinical end-points such as fracture, cardiac events, cancer, dementia, thromboembolism, quality of life and death. WISDOM will enrol 36 200 women internationally. In the UK, WISDOM is funded for 22 000 entrants, and funding for a cohort of 2000 Australian women is currently being sought to contribute to this important trial. This collaboration will help validate the extrapolation of the results of WISDOM to the Australian population.

12.30) and so this is likely to be a true effect. Additional progestogen greatly reduces this risk, but the degree of this protection is not accurately known. Currently the recommended regimen for women with a uterus is to take oestrogen and cyclical progestogens before the menopause and for 1–2 years after menopause. Continuous combination therapy can be introduced after four years of cyclical therapy or when the woman is definitely postmenopausal. This reduces the amount of initial bleeding that is normally seen for several months when commencing a combined continuous HRT regimen.

Thromboembolism

Current observational studies suggest that although this is a relatively rare potential complication, the absolute risk rises from 1 in 10 000 to 3 in 10 000 in HRT users (relative risks in four studies ranged from 2.1–6.9). A past history of thromboembolism before the menopause is not an absolute contraindication to postmenopausal HRT, but might prompt the prescriber to consider testing for thrombophilia.[5]

Cardiovascular disease

Observational and animal studies suggest a potential benefit for HRT. A recent meta-analysis of these epidemiological studies reports a relative risk of 0.70 (95% CI 0.65–0.75) for oestrogen therapy alone and 0.66 (0.53–0.84) for combined HRT.[6] However, many researchers argue that the studies have the potential bias of a 'healthy user' effect. A three-year randomised placebo-controlled trial (PEPI)[7] has suggested a potential benefit in the primary prevention of ischaemic heart disease. Secondary prevention studies do not suggest that HRT can reverse the early risk of established ischaemic heart disease.[8] Currently HRT may be offered to women with risk factors as a potential (but not established) primary cardioprotective agent to complement other established drug therapies and lifestyle changes.

Stroke

HRT was not consistently associated with a change in the relative risk of stroke in observational studies.

Osteoporosis

Short-term randomised controlled trials consistently show that HRT improves low bone density, and when used prophylactically it inhibits loss of bone after the menopause. However, long-term randomised trials are still needed to show that improved bone density results in a major reduction in osteoporotic fractures, particularly at the hip. Improvements in surrogate end-points suggest that a reduced risk of fractures will be one of the main benefits of taking oestrogen for many years.

All therapies for osteoporosis require long-term compliance to achieve their effect. In South Australia in 1997 the median length of use in all women on HRT was five years with 70% continuance rate at five years. In women with a diagnosis of osteoporosis the median length of use was six years.[9]

Alzheimer's dementia

A meta-analysis of 10 observational studies showed a reduction of this dementia in HRT users. The relative risk was 0.71 (CI 0.52–0.98).[10] Although there are plausible neuroprotective mechanisms for HRT, long-term randomised placebo-controlled trials are awaited to see if HRT has a primary preventative role in this disease which is becoming more common with increasing longevity. A recent secondary prevention trial does not suggest that HRT can reverse established disease.[11]

Other risks and benefits

Potential long-term risks still need to be defined by long-term randomised controlled trials. They include increased risks of gall bladder and uterine surgery.

Other potential benefits may include a reduction in tooth loss, dry eyes, dry skin, arthritic symptoms, urge incontinence, frequency, nocturia, urinary tract infections, dry vagina, dyspareunia, memory loss and possibly some types of depression. All of these need to be assessed in large trials, but if a woman experiences sustained symptom relief from HRT then long-term therapy may be appropriate to maintain her quality of life.

Current options for length of HRT use

With all the caveats about the weaknesses of observational data, these data are all we can use when advising a woman about the potential risks and benefits of long-term HRT. Until the results of the Women's Health Initiative and WISDOM are available it is not possible to make general recommendations for the duration of treatment. Probably, for menopausal

symptom control, up to five years therapy is appropriate, with the option of another five years if still symptomatic when weaned off HRT. Longer therapy would be necessary for other potential indications such as the prevention of cardiovascular disease, dementia, some urological problems and osteoporosis. Phytoestrogens have yet to be shown in published rigorous scientific trials to be of greater benefit for menopausal symptoms than a placebo or to prevent osteoporotic fractures and cardiovascular events.

A woman's informed choice for long-term HRT should be based on unbiased information, explanation of the current data and its limitations and an understanding of her individual needs, risks and preferences. It should not be based on myth, selected information, vested interests in HRT or other products for the menopause and especially not on the lack of skill or knowledge of the adviser.

REFERENCES

1. Beral V, Bull D, Doll R, Key T, Peto R, Reeves G, et al. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047-59.
2. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 2000;283:485-91.
3. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: Estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000;92:328-32.
4. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: A review and meta-analysis. Am J Med 1999;106:574-82.
5. Greer IA, Walker ID. Hormone replacement therapy and venous thromboembolism. Climacteric 1999;2:224-31.
6. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. Annu Rev Public Health 1998;19:55-72.
7. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women [published erratum appears in JAMA 1995;274:1676]. JAMA 1995;273:199-208.
8. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280: 605-13.
9. MacLennan AH, Wilson DH, Taylor AW. Hormone replacement therapies in women at risk of cardiovascular disease and osteoporosis in South Australia in 1997. Med J Aust 1999;170:524-7.
10. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. JAMA 1998;279:688-95.
11. Mulnard RA, Cotman CW, Kawas C, van Dyck CH, Sano M, Doody R, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. JAMA 2000;283: 1007-15.

E-mail: alastair.maclennan@adelaide.edu.au

Self-test questions

The following statements are either true or false (answers on page 111)

1. Hormone replacement therapy increases the risk of stroke.
2. Women taking hormone replacement therapy should have mammography more often than other women.

How we prepare articles

Australian Prescriber aims to provide an independent, expert review of therapeutics and to provide objective, balanced, impartial, reliable, up-to-date information for its readers.

The Executive Editorial Board of *Australian Prescriber* decides which topics will be reviewed in the journal. In addition to its own discussions, the Executive Editorial Board also considers suggestions for articles from the Advisory Editorial Panel and the readership.

All the editorials and articles are commissioned. Unsolicited articles are not accepted. When commissioning an author, the Executive Editorial Board selects someone who not only has a detailed knowledge of a topic, but can also write a balanced review.

Once commissioned papers are received by *Australian Prescriber*, they are sent to independent referees for peer review. The referees' reports are considered when the Executive Editorial Board discusses the papers for the first time.

After the Executive Editorial Board's discussions papers may be rejected, or returned to the authors. This allows the authors to respond to comments from the Executive Editorial Board and the referees. Once the authors have responded, the Executive Editorial Board decides whether to accept or reject their articles for publication in *Australian Prescriber*.

Having all papers reviewed by the members of the Executive Editorial Board and independent referees can be a lengthy process. This thorough peer review helps to maintain the high quality of the material published in *Australian Prescriber*.

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.

Drugs in sport

Editor, – I have been the representative of the Internal Medicine Society of Australia and New Zealand on the Advisory Editorial Panel of *Australian Prescriber* for some time. I am writing to you both in this capacity and as a clinical pharmacologist who has had considerable interest in drugs and sport over a long period of time.

The recent article by Professor Fricker (Aust Prescr 2000;23:76–8) is certainly interesting and timely, but it really deals with drugs in elite sport rather than addressing the more serious problem of drug abuse in sport as it relates to the wider community. Many years ago, I wrote an article for *Australian Prescriber* on this topic.[1]

There is an error in Professor Fricker's article which does need correction. On two occasions he quotes the prohibited urinary caffeine concentration as >12 nanogram/mL. This is incorrect; the correct concentration is >12 microgram/mL.

Fortunately the error was not in the 'other' direction, as such articles can often be quoted as a defence in tribunals. In a recent article published in the Medical Journal of Australia[2], I have added a disclaimer so that such errors do not carry over into the rather complex setting of sports tribunals.

Michael Kennedy
Consultant Physician
Internal Medicine Society of Australia and New Zealand
Sydney

REFERENCES

1. Kennedy M. Drugs and sporting performance. Aust Prescr 1989; 12:57-9.
2. Kennedy MC. Newer drugs used to enhance sporting performance. Med J Aust 2000;173:314-7.

Cisapride: new restrictions

Editor, – In view of the safety concerns about cisapride (Aust Prescr 2000;23:59), the Pharmaceutical Benefits Advisory Committee has considered details of the use of the drug in Australia. This included a summary of the situation overseas in relation to the incidence of cardiac arrhythmias or sudden cardiac arrest associated with cisapride.

The Committee recommended that the current Pharmaceutical Benefits Scheme restricted benefit listing for gastroparesis and reflux oesophagitis be amended to an authority required listing for the treatment of gastroparesis where the diagnosis has been made or confirmed by a consultant physician. In addition, the Committee recommended that the caution: 'Cisapride may cause serious cardiac arrhythmias' be added to the amended listing. This amendment is to be implemented in the November 2000 Schedule of Pharmaceutical Benefits. A 'Dear Doctor' letter of explanation will also be included in this edition of the schedule.

The Committee considered that cisapride only has a role in the treatment of gastroparesis. Members were of the view that it is inferior to the proton pump inhibitors in the treatment of reflux oesophagitis.

The Therapeutic Goods Administration has restricted the approved indication for cisapride in reflux oesophagitis to patients with severe disease who have not responded to a proton pump inhibitor. There are, however, no data to show that cisapride is cost-effective for this indication.

Although the dosage of cisapride recommended in Australia differs from the product information in the USA, no evidence was provided by the sponsor to show that lower doses are used in Australia.

Diana MacDonell
Secretary
Pharmaceutical Benefits Advisory Committee

Methotrexate

Editor, – I refer to the interesting article 'Perils and pitfalls of methotrexate prescription' (Aust Prescr 2000;23:44–5) in which Dr Kanagarajah highlights the significant compliance problems that a prescriber should be aware of when using this therapy in elderly patients. Indeed, the increasing use of methotrexate is likely to centre on older patients, who may have concurrent multi-organ system impairments. Renal function is impaired in many of these patients, even though the serum creatinine remains in the normal range. A similar situation exists in other organ systems where reduced reserve function remains silent and subclinical until challenged and exposed by disease or medication.

Underlying deficits in haematological, nutritional (including folate) and immunological reserve may become overt when challenged with a potent immunomodulator such as methotrexate. A sinister danger is that, through the mechanism of convergence, where multiple system factors impact on key physical functions, an older person may not present with adverse effects usually ascribed to that drug, but rather with ailing function. The use of ever more powerful medications, aiming for symptom reduction in an ageing patient population, requires increasing levels of clinical awareness and prudence.

Tuly Rosenfeld
Senior Staff Specialist
Department of Geriatric Medicine
Prince of Wales Hospital
Sydney

Treating acute sinusitis

Editor, – I appreciate such articles as Professor Wormald's (Aust Prescr 2000;23:39–42). I have been a general practitioner for all of my working life, but I have a particular interest in otorhinolaryngology.

I was slightly irked when I read that antihistamines and antihistamine-pseudoephedrine combinations were downgraded and were considered to be of little use. This attitude to histamine and the allergic processes in the body's defence mechanisms against environmental factors is prevalent today. However, it ignores some basic physiology, pathophysiology and pharmacology. Mucosal cell inflammation, whatever the cause, results in cell damage. This results in the release of histamine and other inflammatory mediators. The pharmacological properties of histamine are numerous, the most significant being inflammation of surrounding tissue and more tissue damage. To ignore this pathological sequence of events when tissue damage occurs is basically erroneous.

When treating acute sinusitis, would it not be of great help to know about how the patient reacts to environmental pollutants. This knowledge could be of great help in recurrent sinusitis. I'll not get into IgE levels in various periods in a person's life, nor the RAST screens (very limited these days), and other tests for allergy. The article says to leave these to the specialists.

When considering the need for antibiotic therapy with or without antihistamine-decongestant medication, I would also look for post-nasal discharge during my examination.

Celine Aranjo
General Practitioner
Kingsgrove, NSW

Editor, – The excellent article by Professor Wormald makes no mention of the use of bromhexine as an adjunct to the treatment of sinusitis. *Respiratory Medicine*[1] discusses the use of bromhexine to alter the physical characteristics of the mucus and to give an increase in sputum amoxycillin levels. A number of local general practitioners order this combination and in our practice we recommend the use of bromhexine for milder cases. Could Professor Wormald please comment?

John W.M. Williams
Pharmacist
Mosman, NSW

REFERENCE

1. Taskar VS, Sharma RR, Goswami R, John PJ, Mahashur AA. Effect of bromhexeine on sputum amoxycillin levels in lower respiratory infections. Respir Med 1992;86:157-60.

Editor, – I wish to add some facts to Professor Peter John Wormald's article 'Treating acute sinusitis' (Aust Prescr 2000;23:39–42).

Firstly, I would like to re-emphasise the fact that dental infections can cause maxillary sinusitis. Selden referred to such a manifestation as the endo-antral syndrome (EAS).[1] This is a pathological condition resulting from the spread of infection from the root canal apices near the maxillary sinus into both the antral and periapical tissues. The degree of sinus involvement is related to the proximity of the involved apex to the sinus.[2] Reported frequencies of sinusitis of dental origin vary considerably, between 4.6 and 47.0%.[3]

Because of these facts, I would like to suggest that patients suffering from maxillary sinusitis be referred to the dental surgeons to rule out dental infection as the source of their problem.

Dr Wei Cheong Ngeow
Department of Oral & Maxillofacial Surgery
Faculty of Dentistry
University of Malaya
Kuala Lumpur
Malaysia

REFERENCES

1. Selden HS. The endo-antral syndrome: an endodontic complication. J Am Dent Assoc 1989;119:397-8, 401-2.
2. Matilla K. Roentgenological investigations into the relation between periapical lesions and conditions of the mucous membrane of maxillary sinuses. Acta Odontol Scand 1965;23 Suppl 42.
3. Melen I, Lindahl L, Andreasson L, Rundcrantz H. Chronic maxillary sinusitis. Definition, diagnosis and relation to dental infections and nasal polyposis. Acta Oto-Laryngologica 1986;101:320-7.

Professor P.J. Wormald, the author of 'Treating acute sinusitis', comments:

In reply to Dr Aranjo, I am not aware of any scientific evidence that antihistamines or antihistamine-pseudoephedrine combinations provide any benefit in the management of acute sinusitis.

The study quoted in Mr Williams' letter showed that bromhexine increased the levels of amoxycillin in the sputum significantly and that the clinical outcome in the short term was better in this group of patients. Unfortunately there were one or two problems in the methodology of this study, so these findings would need to be repeated and corroborated before being accepted. In addition, it is unknown whether levels of amoxycillin in nasal mucus would be similarly increased and whether this would have a clinical impact on the outcome of sinusitis. I feel that saline douches would probably afford as much benefit as any other medication regarding the viscosity of mucus.

In response to Dr Ngeow's comment, certainly we do see maxillary sinusitis as a consequence of root canal infections. However, I think the reported frequency of sinusitis due to dental origin would be in the region of less than 5% rather than in the higher range.

Electronic prescribing

Editor, – I refer to Frank Quinlan's editorial 'Electronic prescribing in general practice: one small step' (Aust Prescr 2000;23:50–1). More and more general practitioners are computerising their practices. With the expanding repertoire come errors in writing computer scripts. These include writing the wrong drugs, the wrong dose and strength, and errors in dose instructions and patient names.

Writing the wrong drugs can occur when a general practitioner enters the first three letters of a drug name and the software anticipates the choice without the doctor having to type the entire name. A whole list of drugs is then generated, potentially causing errors. This can be obviated by typing more than the first three or four letters to refine the selection of the drug name.

Incorrect dose strength is generated if a drug has more than one strength in the Drug Selection Screen. Using the arrow keys on the keyboard to highlight the required strength is likely to reduce such mistakes.

It is helpful to make a list of your commonly prescribed medications and save them as favourites. All subsequent prescriptions of these drugs will then have the correct dose, frequency and instructions at the click of a mouse.

An incorrect patient name on a script can be minimised by making sure that the correct new patient's name appears on the screen after the previous patient has left.

Obviously the surest way of avoiding prescribing errors is to check the script after it has been printed to make sure it is for the right patient, the right drug, the right strength and with instructions clearly marked.

Farooq Qureshi
General Practitioner
Glenelg East, SA

Editor, – Dr Nolan's article on advertising in electronic prescribing (Aust Prescr 2000;23:52–3) suggests Australians have yielded to the natural and fashionable idea that drug ads might be to some degree acceptable. The bulk of evidence is leaning the other way. The monitoring network we have in France has consistently shown for 10 years that industry-based information is misleading and biased. I refer your readers to the recent eLetter launched by Public Citizen in Worst Pills Best Pills (www.citizen.org/eletter/currentissue.htm) about the impact of ads on the prescribing habits of psychiatrists. They can also refer to the Medical Lobby for Appropriate Marketing (www.camtech.net.au/malam).Do you really expect advertising is going to be any different in an electronic format?

C. Kopp
La Revue Prescrire
Paris
France

Treating head lice

Editor, – I refer to Dr Orli Wargon's article 'Treating head lice' (Aust Prescr 2000;23:62–3). I was surprised by the recommendation that all clothes, head gear etc. be washed on the grounds that head lice can survive away from the host for three days and eggs can survive for 10 days.

I had understood this advice to be outdated on the basis that live lice which become detached from the head are at the end of their days anyway. Eggs should not be acquired from fomites as there is no glue to attach them to a hair shaft. Further, egg hatching is highly dependent on temperature and humidity with few eggs hatching at under 22ºC. If a few do, they would need lottery-winning style luck to find a human for that all-important first blood meal.

Fraser M. Hadden
Suffolk
UK

Editor, – Dr Orli Wargon's article 'Treating head lice' (Aust Prescr 2000;23:62–3) was useful, as this is a common problem which disrupts schools and disturbs parents, but it was not comprehensive enough in its approach.

Professor Richard Speare of James Cook University has conducted extensive tests to determine the effectiveness of current products on the market to treat head lice and has concluded that, while resistance is growing towards permethrin and maldison, those products containing pyrethrum together with aromatic oils and natural repellents not only kill the head lice, but also dissolve the glue that sticks them to the hair.

This is advantageous for children with long hair, where fine-tooth combing with vinegar/water solution to remove the eggs after treatment is a painful experience. Herbal oils which dissolve the glue allow simple shampooing after treatment to remove the eggs.

A recent addition to the market is preventive headbands, cap inserts and scrunchies impregnated with pyrethrum, rosemary and citronella. These can be worn to school and discourage the spread of head lice by direct contact in much the same way as a dog flea collar!

Richard Lord
Pharmacist
Narooma, NSW

Dr Orli Wargon, the author of 'Treating head lice', comments:

In reply to Dr F. Hadden, there are references to support washing clothes and headgear, for example, the most recent edition (1999) of Fitzpatrick's Dermatology in General Medicine (page 2683) which also refers (page 2681) to transmission by shared towels, brushes and combs playing a significant role.

Regarding Richard Lord's interesting letter, the textbook also mentions that natural pyrethrin products containing refined kerosene or petroleum distillates may cause eye irritation and that care must be exercised to avoid eye contact, but this is difficult in children. Other references mention using 30–40 g of standard petrolatum to the entire surface of the hair and scalp left overnight with a shower cap to clog the respiratory spiracles of the adult louse and block efficient air exchange.[1] This, however, then requires 7–10 days of diligent shampooing to remove the residue.

REFERENCE

1. Schachner LA. Treatment resistant head lice: alternative therapeutic approaches. Pediatr Dermatol 1997;14:409-10.

The ethics of rational prescribing

Editor, – The Health Insurance Commission encourages doctors to prescribe rationally and cost-effectively. The golden rule of medicine is to do one's best for the patient. The silver rule is to do so without bankrupting the country. For those who take the silver rule seriously, it is profoundly depressing to prescribe a cheap non-steroidal anti-inflammatory drug and have the patient return with an unfilled prescription and a request for a COX-2 inhibitor because the pharmacist has told the patient that this new (and four times as costly) drug is better and is subsidised by private health funds. Pharmacists are a necessary and welcome safeguard against prescribing error, but this type of occurrence is more than an isolated incident. Is this type of advice to patients a new form of marketing which is neither socially responsive nor ethical?

Max Kamien
Professor and Head
Department of General Practice
University of Western Australia
Perth

Warwick Plunkett, Pharmaceutical Society of Australia, comments:

Professor Kamien raises the difficult subject of the dilemma facing both medical practitioners and pharmacists every day of the 'cost' versus 'technology' weighting in best care delivery to the patient. To fulfill both his gold and silver rules in the incident quoted by Professor Kamien, the pharmacist's advice to the patient was probably correct having first ascertained the patient's private health fund status. The patient would receive the newest anti-inflammatory therapy with arguably less adverse effects and at no cost to the public purse.

The possible error committed by the pharmacist was the lack of professional courtesy in not discussing his advice first with the medical practitioner concerned. Of course, sometimes titles can be intimidating. Perhaps, therefore, the real issue demonstrated by this anecdote is that the general standard of inter-professional communication remains poor and should be a priority for both practitioners and their professional organisations to resolve.

Morphine and methadone use in cancer pain

Editor, – Changing to methadone may be beneficial for some patients with cancer pain who are suffering the adverse effects of morphine. We are concerned that there is confusion about the dose of methadone to prescribe when making this change.

Methadone is a useful second-line analgesic for cancer pain but has its own problems. A report into methadone-related deaths in South Australia between 1984 and 1994 showed that while methadone used for drug dependence was relatively safe, this was not the case when methadone was used for pain.[1] A potential danger is the view that the dose of methadone, required to produce the same analgesic effect, is identical to the dose of oral morphine.

The view that the dose ratio is 1:1 was mainly developed from single dose studies. Individual variation in the pharmacokinetics of methadone should raise concern about using this ratio when replacing morphine with methadone.[2,3] Studies focusing on chronic opioid use in cancer pain have reported varying equianalgesic dose ratios. These reports suggest that:

- the comparative pharmacology of morphine and methadone is incomplete
- the equianalgesic dose ratio varies with the dose of morphine before the change to methadone (at higher morphine doses methadone is relatively more potent)[4,5]
- for analgesia, the dose of methadone should be carefully titrated, preferably in hospital.[6]

We believe that there is currently no reliable morphine to methadone equianalgesic dose ratio. There is little evidence to support any protocols for starting methadone. The safest way to replace morphine with methadone is therefore by individual titration over a number of days, preferably in a hospital setting. Furthermore, we suggest that this titration should only be carried out by a clinician experienced in prescribing methadone.

If the titration takes place in hospital the patient's general practitioner must be informed of the possibility of late onset adverse effects (half-life may vary from 40 to 600 hours).

Mary Brooksbank
Director, Palliative Care
Guy Bannick
Fellow in Palliative Care
Michael Briffa
Fellow in Palliative Care
Palliative Care Unit
Royal Adelaide Hospital
Adelaide

REFERENCES

1. Williamson PA, Foreman KJ, White JM, Anderson G. Methadone-related overdose deaths in South Australia, 1984-1994. How safe is methadone prescribing?. Med J Aust 1997;166:302-5.
2. Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM. Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. Clin Pharmacol Ther 1987;41:392-401.
3. Meresaar U, Nilsson MI, Holmstrand J, Anggard E. Single dose pharmacokinetics and bioavailability of methadone in man studied with a stable isotope method. Eur J Clin Pharmacol 1981;20:473-8.
4. Ripamonti C, Groff L, Brunelli C, Polastri D, Stavrakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? [see comments in J Clin Oncol 1998;16:3213-5]. J Clin Oncol 1998;16:3216-21.
5. Bruera E, Pereira J, Watanabe S, Belzile M, Kuehn N, Hanson J. Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. Cancer 1996;78:852-7.
6. Ripamonti C, Zecca E, Bruera E. An update on the clinical use of methadone for cancer pain [see comments in Pain 1997;73:114-5]. Pain 1997;70:109-15.

How to make the most of a visit from a pharmaceutical company representative

Richard Day, Professor of Clinical Pharmacology and Toxicology, St Vincent's Hospital and University of New South Wales, Sydney

SYNOPSIS

Representatives of pharmaceutical companies visit health professionals principally to promote the prescription of their products. While the visit aims to change the prescriber's behaviour, it is also an opportunity for the health professional to obtain important information. Modern representatives are well trained and should be able to answer questions about a drug's efficacy, safety, utility and cost. However practitioners should be aware that the purpose of the visit is to alter their prescribing and there is the potential that the information they receive will be biased in favour of the product. Most representatives follow a code of conduct drawn up by the Australian Pharmaceutical Manufacturers Association. Complaints can be made to this association if the representative promotes a product inappropriately.

Index words: advertising, drug industry, prescribing.

(Aust Prescr 2000;23:97–9)

Introduction

Whether we like it or not, visits from the representatives of pharmaceutical companies influence our prescribing practices.[1] For many prescribers, drug company representatives are the main source of information about new drugs and an important factor in changing prescribing behaviour. Although most doctors when asked do not believe they are unduly influenced by pharmaceutical representatives, research shows that they are.[1]

Doctors can choose not to see drug company representatives. This has the advantages of saving time and money.[2] If we do decide to accept a visit from a pharmaceutical representative (and about 85% of general practitioners do) is it possible to gain more value from the visit?

Who are the representatives?

Pharmaceutical representatives, or detailers, have been selected from applicants who may have degrees in nursing, pharmacy or science. Increasingly, they undertake the Australian Pharmaceutical Manufacturers Association (APMA) sponsored course for pharmaceutical representatives. This course is run by an Australian university and has been rated highly in independent annual reviews. It covers a range of important topics including a detailed study of the APMA's voluntary code of conduct on promotional practices.[3]

Each pharmaceutical representative receives intensive instruction about the product they will be promoting and how to market it. If there are competing products, obviously the characteristics favouring their own company's product will be focused upon and contrasts drawn with the competitors. Information about the diseases for which the drug is indicated will almost always be taught to the pharmaceutical representative. The depth and quality of the education and preparation of the pharmaceutical representative will vary with the pharmaceutical company, the importance of the product and the stage in the 'life-cycle' of the drug. Most effort will be expended when a new drug is being released. The representative may also be involved in briefing and familiarisation programs aimed at relevant specialists who are influential because of the letters they write and the opinions they give to general practitioners.

Detailing is just one part of a sophisticated marketing effort but it is very influential and a substantial investment for pharmaceutical companies. Each visit probably costs the company around $200.

What to ask

Doctors need to know about the efficacy, safety and utility of new products. The fact that a drug has been registered for a particular indication means that the evidence for the efficacy and safety of the drug for that indication has been accepted by our regulatory authority, the Therapeutic Goods Administration (TGA). However, what about efficacy, safety and utility in our own patients? This is the question we should return to often.

Efficacy

The question to ask is how does the new drug compare with the drug you usually use for that condition? If it does not seem much better, why would you prescribe the new drug? The pharmaceutical representative needs to know that you would like to be convinced by good evidence that the new drug is worth consideration. Remember that the product information (PI) for the drug is the equivalent of the Bible when it comes to key information about the drug. The PI has been reviewed, amended and finally approved by the TGA after much negotiation with the pharmaceutical company. Increasingly, the PI contains useful details about the 'pivotal' clinical trials of the new drug. These are the trials that are used to support the registration of the drug. The pivotal trials may compare the new drug with standard, accepted therapy.

Although a drug might be efficacious and registered for a particular indication it may be inappropriate to use it in all cases of that indication. For example, a new drug might have an indication for pneumonia approved by the TGA, but if it is a broad spectrum and expensive antibiotic it would be an inappropriate first choice for the average patient with pneumonia. Another useful question is to ask what a reputable and well-known guidelines publication, such as 'Antibiotic Guidelines'[4], says about the place of this drug in the management of the condition. Often such guidelines do not recommend new drugs, certainly not as the first choice.

Safety

Pharmaceutical representatives are less likely to dwell on adverse effects or interactions. This is not surprising, but it means that you may need to ask. The PI is helpful as it lists contraindications and the reported frequencies of adverse effects. It is often helpful to run through these parts of the PI with the pharmaceutical representative. Apart from the known adverse drug reactions, you would also want to hear about critical drug interactions, for example with warfarin.

Increasingly, it is important to know about the metabolism of a new drug and the potential drug interactions which can result. For example, drugs that are metabolised by or block the hepatic cytochrome P450 enzyme system are subject to a large number of potential interactions. As these details are often used in comparing one drug with another, having access (perhaps via the pharmaceutical representative) to a good, recent review or article in a reputable journal is useful.

Utility

Usually the combination of a drug's efficacy and safety features determines its value in our patients. Its efficacy may be similar to older drug therapies, but an advantage that might induce us to prescribe the drug for some of our patients could be a better safety profile. Claims of greater utility, that is the efficacy to safety ratio combined with factors such as convenience due to a better dosing schedule, or a cost advantage for the individual or the taxpayer, may be the argument for prescribing a new drug. You will also want to know other practical details, such as dosing with food, and whether you need to adjust the dose in the elderly or those with impairment of kidney or hepatic function.

Some of the claims made by the pharmaceutical representative will be supported with evidence beyond that found in the PI. This is where you might ask for a copy of the evidence to peruse later, for example original papers. Pharmaceutical representatives are generally very pleased to provide you with scientific papers or to seek additional information from their medical information departments to support their position. They should also be able to provide you with a copy of the consumer medicine information.

Precautions

Most of us with experience of interacting with pharmaceutical representatives recognise some of the sales methods they commonly use. These include appealing to your pride, for example 'Of course you know the latest treatment for this condition', or telling you that your colleagues are switching to the detailed product. The representative may also tell you that well-known leaders in the relevant specialties are switching their prescribing to the drug. Offering samples is a familiar ploy to induce some feeling of commitment from you to try the drug out on a few of your patients. This feeling is perhaps assisted with the giving of some practice-relevant gifts or brand reminders, such as pens and notepads.

Complaints

There may be situations where you feel that the pharmaceutical representative has displayed inappropriate bias or given you misleading information. If this is the case then complain to the pharmaceutical company (usually the medical department is best) or, if this proves unsatisfactory, the APMA.* Every month the APMA has a meeting to discuss such complaints.[3] More complaints about the practices of pharmaceutical representatives will be extremely effective in improving the quality of pharmaceutical representatives' visits, and their value to prescribers.

Conclusion

By now time is almost up. About 5–15 minutes is all you might allocate to a pharmaceutical representative. Essentially the pharmaceutical representative's visit can be used to boost your knowledge concerning efficacy, safety and utility of drugs. Remember that pharmaceutical representatives are well-trained individuals, generally with good communication skills and knowledge, who are keen to assist you in understanding the advantages of their product. Respectful communication combined with an enquiring and critical attitude will allow you to obtain the maximum benefit possible from the time you invest in the meeting. Indeed, you might reasonably be aggrieved if the visit is not helpful, at least in part, because you have forgone the income from a consultation while talking to the representative. Increasingly, undergraduate medical courses provide training including role-play to help future prescribers understand and perhaps profit more from seeing representatives. Given the significance of detailing to prescriber education, perhaps more attention needs to be paid to equipping current prescribers to deal more effectively with detailers.

REFERENCES

1. Avorn J, Chen M, Hartley R. Scientific versus commercial sources of influence on the prescribing behavior of physicians. Am J Med 1982;73:4-8.
2. Griffith D. Reasons for not seeing drug representatives [editorial]. Br Med J 1999;319:69-70.
3. Roughead EE. The Australian Pharmaceutical Manufacturers Association Code of Conduct: guiding the promotion of prescription medicines. Aust Prescr 1999;22:78-80.
4. Writing Group for Therapeutic Guidelines: Antibiotic. Therapeutic Guidelines: Antibiotic. 10th ed. Melbourne: Therapeutic Guidelines Limited; 1998. http://www.tg.com.au

* Australian Pharmaceutical Manufacturers Association
Telephone 02 9922 2699; fax 02 9959 4860

FURTHER READING

Australian Pharmaceutical Manufacturers Association. Code of Conduct of the Australian Pharmaceutical Manufacturers Association. 13th ed. Sydney: Australian Pharmaceutical Manufacturers Association Inc; 2000.

Roughead EE, Harvey KJ, Gilbert AL. Commercial detailing techniques used by pharmaceutical representatives to influence prescribing. Aust N Z J Med 1998;28:306-10.

Sandhu GS, Day RO. Factors affecting prescribing in general practice – a role play. Med J Aust 1992;157:621-2.

Day R. Pharmaceutical company promotion: striking a balance [editorial]. Aust N Z J Med 1998;28:291-3.

E-mail: R.Day@unsw.edu.au

Self-test questions

The following statements are either true or false (answers on page 111)

3. Pharmaceutical promotion has no effect on prescribing patterns.
4. The Code of Conduct of the Australian Pharmaceutical Manufacturers Association covers the interaction between health professionals and drug company representatives.

Your questions to the PBAC

I note the list of generic brands in the 'New drugs' section of each edition. I wonder how many will have the same bioavailability as their competitors?

The matter of bioavailability is of concern to my patients who frequently speak of coercion to accept a strange brand currently stocked in the pharmacy. The reported variability of effect experienced by patients, for example in swapping brands of frusemide, cannot be lightly dismissed as anecdotal.

I am very doubtful that equal weights of drugs translate to bioequivalence, but would be pleased to be reassured that this is so. If generic drugs are not bioequivalent, then the parties concerned should be aware of the differences.

Perhaps *Australian Prescriber* could provide a service to its readers by documenting the bioavailability studies done on each generic registered for inclusion on the Pharmaceutical Benefits Scheme? The name of the testing laboratory, its ownership, the techniques used, the quality control standards employed and the number of samples taken, should all be on the public record and available to all.

John Mackellar
General Practitioner
Mooroopna, Vic.

Dr Leonie Hunt, Drug Safety and Evaluation Branch, Therapeutic Goods Administration, comments:

The Therapeutic Goods Administration (TGA) is the body responsible for the registration of medicines in Australia, including generic equivalents of prescription medicinal products. Applications for generic products, which are claimed to be essentially similar to an innovator product, must include bioavailability data which demonstrate that the proposed product is bioequivalent to a leading brand of the medicine available in Australia. Guidance in relation to how a bioequivalence study should be conducted is available to sponsors of medicinal products in the document issued by the Commission of the European Communities entitled 'Investigation of Bioavailability and Bioequivalence'. Further information is available from the TGA web site (www.tga.health.gov.au/) and the Committee for Proprietary Medicinal Products web site (www.eudra.org/humandocs/humans/qwp.htm).

In general, a comparison of the time course of the blood concentrations of the drug resulting from administration of the two brands to a group of volunteers is required. Comparison of the rate and extent of absorption of the drug from the two products is conducted by a statistical analysis using internationally recognised methods. A decision whether to register the generic product is then made taking these results into account. Modified-release products, such as delayed-release tablets and slow-release tablets, may require studies to be conducted under a variety of conditions to confirm equivalence. Where there is any doubt as to the bioequivalence of the two products, the TGA is able to seek advice from the independent expert committee, the Australian Drug Evaluation Committee.

The actual data sets, on which decisions to register individual products are made, may contain commercially confidential information. They are not usually available to the public.

Associate Professor R. Moulds of the Executive Editorial Board, comments:

Dr Mackellar's concern is a common one. The regulatory processes outlined by Dr Hunt are good at ensuring the plasma concentrations of a generic drug are similar to those obtained with the 'innovator' brand of the drug, usually the market leader. The limits allow for differences of no more than 20% in the overall plasma concentration versus time curves of the two drugs.

It is a more difficult question whether or not such allowable differences might be noticed by a patient. The intraindividual variation in plasma levels of a drug when it is taken on different occasions is usually greater than 20%. So a patient will probably only genuinely notice a difference between various brands of a drug if they also notice a difference when they take the same brand on different occasions.

A patient is also only likely to notice a difference between brands if the drug has a steep concentration-effect curve, so that a 20% change in concentration results in a significant change of effect. Few drugs have such a steep curve.

There are very few clear examples where differences between brands of a drug are clinically important. One very important exception, however, is that of warfarin, and patients should not shift from one brand of warfarin to another.

Contemporary management of atrial fibrillation

Daniel M. Ninio, Research Fellow, Department of Clinical Pharmacology, Alfred Hospital, Melbourne

SYNOPSIS

Atrial fibrillation is responsible for considerable morbidity in our population. Management of persistent atrial fibrillation of acute onset involves electrical or pharmacological cardioversion to restore sinus rhythm and the use of antiarrhythmic drugs to maintain sinus rhythm. The duration of atrial fibrillation is an important determinant of the timing and success of cardioversion and the risk of embolic complications. When sinus rhythm cannot be maintained, control of ventricular rate and the prevention of stroke become the goals. This is also the case in patients in whom conversion to sinus rhythm is impractical or likely to be unsuccessful. The choice of aspirin or warfarin depends on each patient's individual risk of stroke.

Index words: arrhythmia, cardioversion, antiarrhythmic drugs, anticoagulants.

(Aust Prescr 2000;23:100–2)

Introduction

Atrial fibrillation is the most common arrhythmia presenting to cardiologists and general practitioners. Its prevalence is 0.4% in the general population, increasing to 9% of people over the age of 80. As our population ages, the prevalence of atrial fibrillation in Australia will continue to rise.

Despite being considered a benign arrhythmia, atrial fibrillation is a major cause of morbidity. Patients suffer a wide variety of symptoms including palpitations, dizziness, dyspnoea, angina and worsening heart failure. The most feared complication is systemic embolism, particularly embolic stroke. Optimal management of atrial fibrillation can improve patients' symptoms and reduce their risk of stroke substantially.

There are two approaches to therapy. One involves restoring and maintaining sinus rhythm. When this is not practical, the focus turns to the control of ventricular rate and anticoagulation to prevent embolism.

Assessment

In patients discovered to have atrial fibrillation treatable conditions contributing to the arrhythmia should be identified (Table 1). Comorbidities which may influence the decision to use warfarin and the choice of antiarrhythmic drug should be considered. The assessment should include a thorough history and examination, a 12 lead ECG, echocardiography and thyroid function tests.

One of the most important factors influencing treatment is the duration of atrial fibrillation. Most patients with atrial fibrillation of less than 24 hours duration will spontaneously revert to sinus rhythm. The longer the patient has been in atrial fibrillation, the lower the success rate for both pharmacological and electrical cardioversion. The risk of atrial thrombus and embolic stroke also increases with time.

Establishing the exact duration of atrial fibrillation can be difficult. While some patients are highly symptomatic with the onset of the arrhythmia, others can be completely asymptomatic. If the onset of atrial fibrillation is unclear from the history, it must be assumed that the atrial fibrillation has been present for longer than 48 hours.

Restoration of sinus rhythm

DC electrical cardioversion

Consensus of cardiological opinion is that patients who present within 48 hours of the onset of atrial fibrillation can be cardioverted without the need for warfarin (Fig. 1). When the atrial fibrillation has been present for longer than 48 hours, the risk of atrial thrombus is too high and cardioversion should be delayed until the patient has been anticoagulated for at least three weeks. Anticoagulation is continued for four weeks following successful cardioversion as normal atrial function is not immediately restored (atrial stunning).

Electrical cardioversion is very successful in restoring sinus rhythm, but the recurrence rate without medication is high, particularly in the presence of underlying heart disease. Drugs may be used to improve the success of cardioversion and the long-term maintenance of sinus rhythm.

Pharmacological cardioversion

An attempt can be made to restore sinus rhythm pharmacologically, avoiding the need for hospital admission and general anaesthetic. Flecainide, sotalol and amiodarone improve the rate of conversion to sinus rhythm when compared to placebo, but each drug has its limitations. The role of digoxin in acute cardioversion remains controversial.

The new class III agent, ibutilide, is effective in terminating atrial fibrillation and flutter of up to 90 days duration.[1] It has

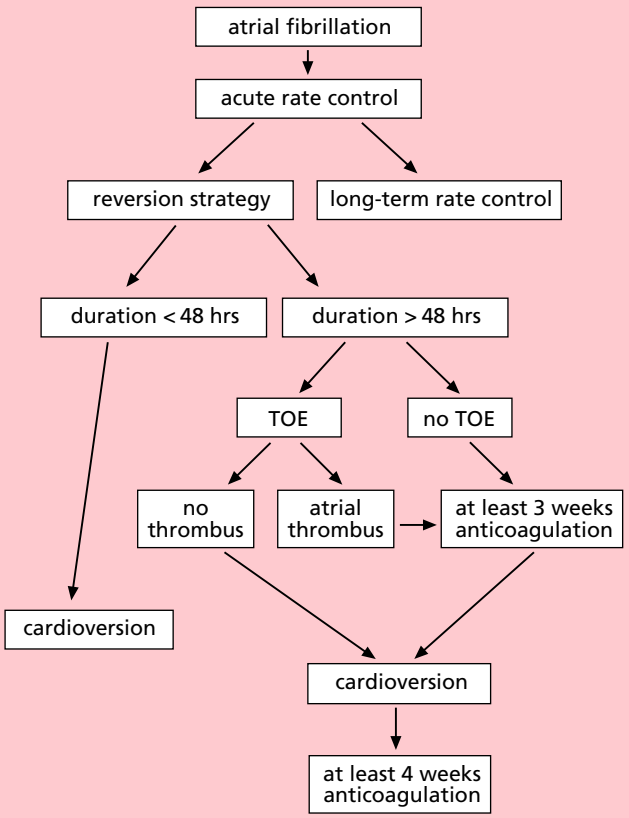
Table 1

Common conditions contributing to atrial fibrillation

hypertension	coronary disease	valvular heart disease
heart failure	alcohol excess	pericarditis
infection	thyrotoxicosis	chronic lung disease

Fig. 1

Management of newly diagnosed atrial fibrillation



TOE = transoesophageal echocardiography

a half-life of only six hours and is given intravenously over 10 minutes. A second dose is given 10 minutes later if necessary. Success rates of up to 63% have been reported. This must be weighed against the increased risk of polymorphic ventricular tachycardia (4%) so ECG monitoring is required. Ibutilide has also been used to improve the success rate of electrical cardioversion.

If pharmacological cardioversion is unsuccessful, electrical cardioversion should be considered.

Anticoagulation and cardioversion

In hospitals where transoesophageal echocardiography (TOE) facilities are available, 'accelerated cardioversion' may be performed. Patients without atrial thrombus on TOE can be cardioverted with relative safety, without the need for pretreatment with warfarin. Anticoagulation is still necessary following the procedure. Unfortunately, a negative TOE does not entirely rule out the possibility of stroke.

Maintenance of sinus rhythm

Class Ia (e.g. quinidine), class Ic (e.g. flecainide) and class III antiarrhythmic drugs (e.g. amiodarone, sotalol) reduce the recurrence of atrial fibrillation. Digoxin does not prevent recurrent atrial fibrillation and may be withdrawn once sinus rhythm is restored unless indicated for concomitant heart failure.

Class I drugs

The class Ia drugs (e.g. quinidine) have fallen out of favour because of the suggestion of an increased mortality with long-term use. This is probably due to proarrhythmic adverse effects.

The Cardiac Arrhythmia Suppression Trial also raised doubts about the safety of flecainide. The risk appears to be greatest for patients with underlying heart disease. With very few exceptions, flecainide should only be considered for the prevention of recurrent atrial fibrillation if left ventricular function is normal.

Class III drugs

The class III drugs have gained popularity because of their efficacy and relative safety.

Sotalol is as effective as the class I drugs but has a better safety profile. The main concern is QT prolongation and the risk of torsades de pointes which is increased by hypokalaemia. QT intervals and electrolytes should therefore be checked regularly.

Amiodarone is at least as effective as sotalol but its non-cardiac adverse effects can limit its long-term use. Initially reserved for patients with resistant arrhythmias, it is now being used more widely. Lung function, liver enzymes and thyroid function should be checked regularly to monitor for toxicity. Amiodarone is the drug of choice for patients with concomitant left ventricular dysfunction.

New class III drugs

In contrast to sotalol and amiodarone, dofetilide is a pure class III drug. It is effective at stopping atrial fibrillation and maintaining sinus rhythm. Dofetilide has no overall negative inotropic effect and few non-cardiac adverse effects, but it does cause QT prolongation and torsades de pointes.

The safety of dofetilide in heart failure was studied in the DIAMOND-CHF trial.[2] Dofetilide reduced the incidence of atrial fibrillation but had no effect on mortality. When starting treatment at least 72 hours of inpatient ECG monitoring is advised. Careful dose adjustment for renal impairment (as used in the trial) is also recommended.

Rate control

If acute atrial fibrillation precipitates severe hypotension, ischaemia or heart failure, immediate electrical cardioversion is usually needed. If the patient is stable, drugs can be used to slow the ventricular response.

Digoxin is most frequently used for this purpose but may be insufficient when used alone, particularly if there is sympathetic activation (e.g. exercise or after surgery). Combining digoxin with either verapamil or diltiazem, or a beta blocker (e.g. atenolol) can overcome this problem. These additional drugs are also very effective as monotherapy for controlling the rate of atrial fibrillation. They are particularly useful for patients with coexisting hypertension or angina. Digoxin is the treatment of choice if the patient has heart failure.

In the occasional patient in whom rate control cannot be achieved pharmacologically, atrioventricular node ablation,

with rate responsive ventricular pacing, may be considered. Anticoagulation is still required.

Rate control versus rhythm control

It is unclear whether chronic atrial fibrillation is best managed with rhythm control (repeated cardioversion and antiarrhythmic drugs to restore and maintain sinus rhythm) or rate control (controlling ventricular rate and anticoagulation). This is the subject of ongoing, randomised controlled studies. While we await these results, both approaches are reasonable and patient preference may be the deciding factor.

In general, the approach adopted should reflect the likelihood of maintaining sinus rhythm following cardioversion. The two important factors predicting the recurrence of atrial fibrillation are the duration of atrial fibrillation and the presence of structural heart disease. It is therefore more reasonable to attempt rhythm control in patients with normal hearts and atrial fibrillation of recent onset than in patients with heart failure or valve disease who have had atrial fibrillation for many years. If sinus rhythm cannot be maintained despite repeated cardioversions and a variety of antiarrhythmic drugs, the goal of treatment becomes rate control.

Anticoagulation

Pooled data from five large studies suggest that warfarin reduces the risk of stroke by 68% (target INR 2.0–3.0).[3] This reduction of embolic stroke occurs at the expense of bleeding complications. Warfarin is more effective than aspirin, but carries a higher bleeding risk. The decision to choose warfarin or aspirin must be based on an assessment of the risks and benefits of treatment for each individual.

In general terms, warfarin is recommended for patients at high risk of embolic stroke (>10% per year) (Table 2). Warfarin could be considered for patients at moderate risk of stroke (5% per year). The benefit of warfarin is less clear in this group and aspirin is a reasonable alternative in the presence of relative contraindications to warfarin. Patients with atrial fibrillation under the age of 65 without risk factors (so-called 'lone atrial fibrillation') have a low incidence of stroke (1%). The risks of warfarin probably outweigh the benefits for these patients so aspirin is recommended.

Non-pharmacological measures for refractory cases

Ablation and surgery

One approach involves the physical interruption of the electrical circuits that sustain atrial fibrillation. The 'maze' surgical procedure and non-surgical catheter ablation based on the same principle are only available in highly specialised units. Both carry considerable procedural risks.

An interesting recent development is the ablation of cardiac tissue around the pulmonary veins to treat patients with paroxysmal atrial fibrillation. These areas may be the origin of the ectopic beats that precipitate some attacks of atrial fibrillation.[4]

Table 2

Clinical stratification of the risk of stroke in patients with atrial fibrillation

High risk >10% per year	valvular heart disease
	previous transient ischaemic attack or stroke
	heart failure or left ventricular dysfunction
	age >75 with hypertension or diabetes
Moderate risk approximately 5% per year	age >65 not high risk
	age <65 with hypertension, diabetes or vascular disease
Low risk <1% per year	age <65 no risk factors

Atrial defibrillator

Following the success of the implantable defibrillator for ventricular arrhythmias, initial experience with atrial defibrillators has brought mixed results. While they appear to be effective, the shocks are uncomfortable and may be quite frequent with paroxysmal atrial fibrillation. Patients are less likely to accept the discomfort, given the relatively benign nature of the arrhythmia. There is also a risk that the defibrillator shock may trigger ventricular arrhythmias. Dual chamber defibrillators make this less of a problem. The cost implications of wider use of these expensive devices would also be considerable.

Conclusion

The management of atrial fibrillation needs to be tailored to each patient. The risks and benefits of cardioversion, antiarrhythmic drugs and anticoagulation must be weighed up and discussed with the patient to ensure the best outcomes.

REFERENCES

1. Ellenbogen KA, Stambler BS, Wood MA, Sager PT, Wesley RC, Meissner MC, et al. Efficacy of intravenous ibutilide for rapid termination of atrial fibrillation and atrial flutter: a dose-response study [published erratum appears in J Am Coll Cardiol 1996;28:1082]. J Am Coll Cardiol 1996;28:130-6.
2. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, Kober L, Sandoe E, Egstrup K, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. N Engl J Med 1999;341:857-65.
3. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials [published erratum appears in Arch Intern Med 1994;154:2254]. Arch Intern Med 1994;154:1449-57.
4. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-66.

E-mail: DrNinio@yahoo.com

Self-test questions

The following statements are either true or false (answers on page 111)

5. Warfarin reduces mortality in patients with atrial fibrillation and heart failure.
6. Digoxin does not prevent recurrent atrial fibrillation.

'Take as directed', whatever that means

Helen Hopkins, Senior Policy Adviser, Consumers' Health Forum, Canberra; Tony Wade, Project Director, Australia's Health; and Derek Weir, Research Director, Australia's Health, Brisbane

SYNOPSIS

Many factors contribute to patients not taking medicines as directed. Australian professional research papers often investigate compliance as an adjunct to other research goals. Consumer research looks at the broader range of factors and issues that might contribute to how consumers use their medicines. This research often identifies questions people say they would like to ask their doctors, such as 'What is the medicine for?' and 'What are the likely effects?'. Sometimes patients will forget to ask, are held back by language or social barriers or are reluctant to trouble a doctor. Effective communication with doctors helps consumers to use their medicines appropriately and this improves their satisfaction with treatments and health care providers.

Index words: patient compliance, drug utilisation, consumers.

(Aust Prescr 2000;23:103–4)

Introduction

There has been considerable research measuring compliance and ways of improving it. There is less research on consumers' reasons for not taking their medicines as advised. Consumers have maintained that adequate information enables them to make better decisions about treatment.[1] To gain more insight into consumers' behaviour and experiences with prescription medicines, a literature review of both consumer and professional literature was recently completed.[2]

How the literature search was done

Literature was retrieved from both professional journals and the publications of Australian consumer organisations with an interest in health issues. Key professionals and consumer organisations were consulted to assist in constructing broad subject areas and in identifying search terms. Electronic databases and the catalogues of two major metropolitan universities were searched for relevant professional publications dating from 1980. Consumer-authored books, reports and papers were identified with the help of peak consumer organisations. Only those with a formal methodology were included in order to provide a standard consistent with the professional literature. Forty-six Australian professional papers and 24 consumer publications qualified for inclusion.

What the literature showed

The professional literature usually included the consumer perspective as a comment or an adjunct to some other research goal. Consumer publications often focused on issues around use and experience of medicines in a broader community setting that might include different experiences for women, older people, children, people with chronic conditions and people with specific illnesses. The relationships with the prescriber, other health care providers and institutional and other settings also influenced consumer experiences with medicines. The project provided an opportunity to compare the two literature sets and examine their findings for consistency and differences.

Communication

Both the professional and consumer literature identified the importance of consumers and health care providers sharing information to achieve positive health outcomes. Consumers frequently wanted to ask doctors similar questions about medicines (see box). They often wanted written information to take home and read later.

Not having a shared language was reported as a barrier to communication in both literature sets, either because the patient and the doctor came from different ethnic origins or because the medical terminology used by the doctor was unfamiliar to the patient. Communication problems also occurred between hospitals and health care providers in the community. This was a particular problem for patients when they were discharged because hospitalisation often meant more medicines or changes in medicines.

Use of medicine

Different groups of consumers have different experiences with medicines. There is a strong association between medication use, age and gender. Older people and women in particular are much more likely to have medicines prescribed. While this may be associated with particular health conditions, there are reports in both literature sets that prescribers may assume that these groups expect a prescription.[3,4]

Questions consumers want to ask

- What is the medicine for?
- What are the likely effects?
- What are the adverse effects and what do I do if I experience them?
- Will it interact with the other medicines I take, including over-the-counter and complementary medicines?
- What about the long-term effects?
- What are the instructions for taking the medicine, how do I take it, how much do I take and when do I take it?

Compliance

Compliance is probably the most commonly researched area in professional reports of consumers' use and experience of medicines, but it is not a term used in consumer research. From the consumer perspective, 'failure to comply' effectively places the responsibility for not taking the medicine on the consumer, but this may not be solely the patient's responsibility. The review indicates that 'non-compliance' may also arise from the prescriber not communicating instructions in a way the patient understands, poor explanation of adverse effects, or social barriers such as cost. In the light of evidence about over-prescribing and polypharmacy, 'non-compliance' may even represent a rational and responsible decision by the consumer.

Much of the professional literature on compliance extrapolates data from overseas studies to the Australian context. This may not be accurate since some Australian studies suggest that compliance among older people may be better than usually assumed.[5] Good compliance is associated with good communication. This in turn influences the quality of the relationship between prescriber and consumer.[6,7]

Adverse effects and adverse events

The consumer literature reports that medicines are frequently prescribed without sufficient information about alternative strategies or explanation about risks. Adverse events and adverse effects are important issues for consumers, representing a significant health risk as well as influencing compliance. Prescribers and pharmacists may unwittingly contribute to these problems through hesitating to communicate effectively with consumers about risks. Both literature sets identify polypharmacy as a significant problem particularly associated with age, gender and hospitalisation.[4,8] Despite the risks of adverse events and poor compliance associated with polypharmacy, studies suggest that prescribers may often be unaware of the number of prescription and non-prescription medicines their patients are taking.[8] Consumers might not realise it is important to tell their doctor about all their medicines, especially over-the-counter and complementary medicines.[9]

Where research is needed

A significant finding of the review was that there are very few Australian publications that directly address consumers' use or experience of medicines. The review identified considerable agreement between the two literature sets on key issues relating to consumer use. These include associations between use, age and gender, the need for improved communication and information and problems such as polypharmacy, compliance and adverse effects.

The consumer literature provided more focus on particular needs groups such as indigenous people, those of non-English speaking background, carers and the homeless. It also focused more on the broader experience of taking medicines such as social issues, access and cost. This illustrates the more holistic view taken by consumer researchers, recognising that medicine use and experience is not simply about the condition or the prescription, but includes a range of social factors.

Conclusion

The review provides evidence of a significant potential for Australian consumers to use their medicines more effectively. It shows that a key to this improved health outcome is improved clarity in communication about medicines between prescribers and consumers, particularly through better information and education. To support verbal communication doctors could provide written information for later reference. Electronic prescribing packages and electronic Consumer Medicines Information should make this easier for doctors to provide. Improved consumer outcomes also depend on better communications between health care providers and different parts of the health system. Collectively, the literature shows that when effective partnership and communication occur, the quality use of medicines improves and patients are more satisfied with their treatment and health care providers.

ACKNOWLEDGEMENT

The Literature Review Project, Understanding Consumer Behaviour and Experience in Relation to the Use of Medicines, was conducted by Consumers' Health Forum as part of the Pharmaceuticals Project with funding from the Department of Health and Aged Care.

REFERENCES

1. Graham JD, Kwok YS. What consumers want to know about medicines. Aust Prescr 1995;18:10-11.
2. Consumers' Health Forum. Understanding consumer behaviour and experiences in relation to the use of medicines. Literature review. Canberra: Consumers' Health Forum of Australia; 1999.
3. Cockburn J, Pit S. Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations – a questionnaire study. Br Med J 1997;315:520-3.
4. A script for change. A consumer perspective on the quality use of medicines. Melbourne: Health Issues Centre; 1995.
5. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. Med J Aust 1996;164:208-11.
6. Hustig HH, Norrie PD. Managing schizophrenia in the community. Med J Aust 1998;168:186-91.
7. Winefield HR, Murrell TG, Clifford J. Process and outcomes in general practice consultations: problems in defining high quality care. Soc Sci Med 1995;41:969-75.
8. Atkin PA, Stringer RS, Duffy JB, Elion C, Ferraris CS, Misrachi SR, et al. The influence of information provided by patients on the accuracy of medication records [published erratum appears in Med J Aust 1998;169:468]. Med J Aust 1998;169:85-8.
9. Consumers' Health Forum. Choosing your medicine. Making an informed decision about complementary and non-prescription therapies. Canberra: Consumers' Health Forum of Australia; 1999.

Web sites: www.chf.org.au
www.australiahealth.com

Self-test questions

The following statements are either true or false (answers on page 111)

7. In Australia, cost is not a barrier to people taking the medicines they are prescribed.
8. Health professionals are often unaware of all the medicines their patients are taking.

Compliance or concordance?

Simone Rossi, Managing Editor, Australian Medicines Handbook, Adelaide

The reasons why medicine-taking often bears little resemblance to what is written on prescriptions are numerous and complex.[1] New relationships and understandings need to be established between interested groups to achieve the best possible health outcomes for (medicine-taking) individuals and the community.

Changes in human interaction often cause changes in the way we communicate, whether we like it or not. In medicine, **compliance** is a measure of how closely a person follows a course of prescribed treatment. However, compliance is now considered to be a paternalistic concept. The search is on for a more acceptable term. Social scientists use the term **adherence**, but this has not been universally accepted. Recently **concordance** has been proposed as an alternative term[2], but is this word appropriate?

Dictionaries suggest that:

- concord comes from concordat, which is an agreement between the Pope and a secular government regarding the regulation of ecclesiastical matters
- concord refers to the matching of words within a sentence in terms of their number (singular or plural) and in terms of gender or person
- concord is two sounds making harmony together, and concordant is harmonious
- Concord(e) is also an aeroplane
- concordance refers to an alphabetical list or index of subjects or topics; its verbs are concordanced, or concordancing.

The negative of concord is discord. So if a person does not take their pills does this mean they are discordant, or are they non-concordant?

In its newly fashioned context, concordance is an agreement or partnership between patient and prescriber about obtaining the best use of treatment, compatible with what the patient desires and is capable of achieving. Non-concordance then relates to the patient-prescriber consultation, and not to the patient.

Compliance and concordance are not interchangeable terms. Achieving concordance between doctor and patient by identifying beliefs about illness, treatment and medicine-taking is a worthy concept. It should impact positively on compliance with treatment, and thus health outcomes may be improved. While we should be striving for concordance, some of us will no doubt still wish to be able to evaluate compliance. Although the terms compliance and non-compliance can have a negative connotation for some people, they remain the most useful descriptions of this process in the absence of anything better.

Concordance aficionados or those who may wish to know more should visit www.concordance.org/

REFERENCES

1. Hopkins H, Wade T, Weir D. 'Take as directed', whatever that means. Aust Prescr 2000;23:103-4.
2. Mullen PD. Compliance becomes concordance [editorial]. Br Med J 1997;314:691-2.

Book review

Australian Medicines Handbook 2000
Adelaide: Australian Medicines Handbook; 2000.
RRP Book $137
CD-ROM $135
Book and CD-ROM $159
Phone 08 8222 5861

Reduced prices for students and members of the Royal Australian College of General Practitioners, the Pharmaceutical Society of Australia and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists.

1. Julia Hanna, Intern, Royal Adelaide Hospital, Adelaide

The Australian Medicines Handbook (AMH) sets itself an immense task in the foreword, aiming to provide 'readily accessible, concise, up to date' information to 'facilitate effective, rational, safe and economical prescribing' and also to be 'an educational tool for practitioners and students'.

Does the AMH meet its stated goals? The drug information is very easy to access. Used as a reference book the text is concise, while as a textbook repetitions appear. For example the reader is told four times that an individual's response to any particular antihistamine is variable. The information provided is up to date, but occasionally the format lets this information

down. The leukotriene receptor antagonists are described in two places. When discussed under asthma therapy the lack of current data supporting a firm place for these medications is mentioned, but it is not reiterated under the drug headings where it would be more obvious to someone looking up these drugs. A segment about imminent approvals would also be useful, information provided inconsistently by this edition.

Does the AMH facilitate effective, rational and safe prescribing? The amount of information readily at the fingertips of the reader makes the answer to this question a resounding yes. Economical prescribing? The costs of individual drugs are mentioned in an index separate from the main text and this might not routinely be consulted. Optimal prescribing is, I suppose, economical prescribing, and the AMH certainly promotes this.

I wholeheartedly recommend this book as an educational tool to trainee medical officers and medical students, who will find it wonderfully useful. As a reference book, I humbly recommend it to any clinician who wishes to obtain prescribing information for a diverse range of conditions quickly and efficiently, and to specialists who wish to access information rapidly in fields other than their own.

On a philosophical note, it is a shame that this excellent source of drug information found it necessary to carry advertising for private medical insurance. Given that the cost of the AMH places it firmly in the textbook/reference book category, perhaps a few more dollars on the price would have been preferable. This book is worth every cent of the price in the time and effort saved when researching or prescribing a new or unfamiliar drug. Once purchased it will be used time and time again.

2. Gerard Gill, General Practitioner, Launceston, Tasmania

This publication is the result of a joint project by the Royal Australian College of General Practitioners, the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, and the Pharmaceutical Society of Australia.

The handbook is available in both CD-ROM and book formats. The publication is intended for a wide audience. I will restrict my comments to its usefulness in general practice.

The AMH offers three main fields of information covering treatment considerations for common diseases, medication classes, and individual medications. It does bring together this information very well. At 4 cm thick the book version is not for the pocket or doctor's bag, but rather as a surgery reference. Where it does excel is in the CD-ROM form for the ease of use as a clinical desktop decision tool. The comprehensive but concise individual drug monographs are much easier to take in than the manufacturer's product information in my computer prescribing package. For really curly questions one may still need to consult the more complete manufacturer's product information.

This publication is not yet perfect. The CD-ROM version runs from the CD-ROM drive not from the hard disk, making its computer use less flexible. It can be installed on a server hard drive for network applications. The medication class numbering system varies from that used in the MIMS and the Pharmaceutical Benefits Scheme books. Can we not standardise our classification systems to speed up access? As details of newer medications released since the publication of the AMH are not available, one still needs to utilise these other publications.

The typeface, print size and colour made some contents, especially tables, hard to read quickly. While the purists may prefer only generic names, in the real world a complete listing of proprietary drug brand names in the index is required. The AMH index fails here.

An oversight in the psychotropics section is the lack of a table listing the washout times for antidepressants. One still needs to keep a considerable number of manufacturers' cards for this data.

There is limited coverage of the common complementary or over-the-counter medications. With the high use of such therapies by patients this is an area that needs attention in the next edition.

Where does this book fit into general practice? For the undergraduate or general practice registrar it offers an excellent introduction to medication issues. The book version would be less useful for the established general practitioner. The electronic version on the CD-ROM is superb and would form part of my ideal doctor's desktop tools. Other members of the community-based primary health care team such as pharmacists and nurses would find it most helpful. If one wishes to purchase a reference book on medication usage for Australian general practice, the AMH currently offers the best overall coverage. Purchase price concessions are available for students and members of the three sponsoring bodies.

Gerard Gill FRACGP has been in general practice in Launceston for 20 years and has held a number of appointments with national medical bodies. He is a Clinical Senior Lecturer in General Practice at the University of Tasmania.

Message to all 2000 graduates in medicine, pharmacy and dentistry

If you are graduating in Australia this year and wish to continue receiving *Australian Prescriber* to assist with your postgraduate training, please complete and send the distribution form on the inside back cover of this issue.

Health advice for travellers with chronic illness

Nicholas Zwar, Conjoint Senior Lecturer, Department of General Practice, University of New South Wales and South Western Sydney Area Health Service, Sydney

SYNOPSIS

Older people and those with chronic illnesses are travelling overseas more than ever before. Basic but important considerations are adequate supplies of medication (carried in the hand luggage), a health summary and medication list. Travel is associated with increased risk of deep venous thrombosis. Exercises can be advised, but evidence is currently lacking on the benefit of aspirin or low molecular weight heparin for prophylaxis. In assessing lung disease and cardiac disease exercise tolerance is a guide to the patient's fitness for air travel. Vaccinations are important but care is needed when giving live vaccines to immunocompromised patients.

Index words: travel, deep venous thrombosis, vaccination.

(Aust Prescr 2000;23:107–9)

Introduction

Increasingly, older people and those with chronic illnesses are among the 3.2 million Australians who travel overseas each year.[1] Doctors, especially general practitioners, are called on to assess fitness for travel and provide travel health advice to these patients.

General advice

Travel, particularly long flights, is a stressful event, especially for older people. Planning the itinerary to minimise jet lag and preparing for the journey by being fit and well-rested beforehand are helpful. The traveller should be provided with a health summary and medication list. A Medic-Alert bracelet can be a good idea especially for those conditions which may cause unconsciousness. Travel insurance is very important, but people with chronic illnesses may need to pay a higher premium for pre-existing conditions and many insurers exclude all psychiatric problems. If medical assistance is needed overseas, the International Association for Medical Assistance to Travellers publishes a directory of English speaking doctors, and advice for travellers (web site www.sentex.net/~iamat/). In urgent situations people can seek help from the Department of Foreign Affairs and Trade 24-hour consular service. *

Immunisation

Vaccination requirements for older travellers are essentially the same as for younger people except that influenza and pneumococcal vaccinations must also be considered. Influenza vaccine is indicated annually for those over 65 years of age and people with chronic diseases.[2] People going on trips where they will be in confined spaces with other travellers such as bus trips and cruise ships are at greater risk. Pneumococcal vaccine is indicated every five years for everyone over 65 years of age, people with chronic diseases and post-splenectomy.

Air travel

Mobility is important, as airline cabin staff are not permitted to assist with lifting, feeding, toileting or administering medication to passengers. If the traveller needs help with these functions they must be escorted. They may also need to request a wheelchair and a seat near the toilet. Taking sufficient supplies of medication for the whole trip is important and these should be carried in hand luggage. They are of no use if they are in the hold of the aircraft when needed or get lost with a misplaced suitcase. Increased fluid intake is helpful during the flight as this can lessen hypoxia and the confusion that this can cause, and it counteracts the dehydrating effect of low cabin air humidity. Water is the best fluid as tea, coffee and alcohol all act as diuretics and should be limited. Getting some sleep on long legs of the trip helps to prevent exhaustion. A neck cushion may help but sleeping tablets should be avoided in the elderly as they may worsen confusion.

The airlines have a Passenger Medical Information Form (MEDIF) which is used to provide information about requirements for travellers with medical problems. This form is available from travel agents and the medical departments of airlines. This information may be transmitted between airlines. If there is a concern about fitness to fly then some airlines such as Qantas have a medical department which can provide advice on an individual basis to the patient's doctor. Medical guidelines for air travel have been published by the Aerospace Medical Association.[3]

Policies on fitness to fly will vary between airlines and travellers need to check with their travel agent or airline. Airlines may be prepared to make special arrangements on an individual basis. Table 1 shows the policies that apply for Qantas for a number of common conditions (based on information supplied by Dr Ion Morrison, Qantas Airlines).

Prevention of deep vein thrombosis

There is an increased risk of deep vein thrombosis (DVT) during travel. A recent case control study[4] found a history of

* Telephone number from overseas 61 2 6261 3305

recent travel was four times more common in patients admitted with venous thromboembolic disease than patients admitted for other reasons. An increased rate of DVT is evident after travel of four hours or more. Although the risk is higher in those with other risk factors (chronic disease, smoking, obesity, oral contraceptive pill, past DVT), travel related DVT also occurs in those without recognised risk factors. Currently there is a lack of evidence of benefit for prophylaxis with aspirin or low molecular weight heparin. Aspirin may be reasonable for low risk patients and low molecular weight heparin considered for moderate risk travellers.[5] Airline passengers can be advised to exercise during flight – walk up the aisle every thirty minutes and during stop-overs – and avoid dehydration. Elevating the legs, where seating arrangements make this possible, and doing exercises will reduce dependent oedema. People should not fly after suffering a DVT until at least stabilised on anticoagulants. Airlines may require a longer period of anticoagulation.

Chronic lung disease

When an aircraft is cruising, cabin air has a partial oxygen pressure that is approximately 20–25% less than at sea level. This presents no problem to healthy people who, when breathing cabin air, will have an arterial oxygen (PaO_2) of approximately 70 mmHg and haemoglobin saturation of 90%. However, in some medical conditions this may be sufficient to produce tissue hypoxia.

The patient's exercise tolerance provides a guide to their fitness to fly. Dyspnoea at rest is generally a contraindication. If a person can climb a flight of 15 stairs and walk 50 metres (some authorities say 100 metres) without symptoms they should not experience problems during the flight. People with poor exercise tolerance need further assessment preferably in consultation with a respiratory physician.

Further assessment involves respiratory function tests and measurement of arterial blood gases. If PaO_2 is more than 70 mmHg then supplementary oxygen is not needed. The arterial carbon dioxide ($PaCO_2$) is also important as supplemental oxygen may reduce respiratory drive in hypercapneic patients. People with lung disease should not only not smoke, but also avoid alcohol during the flight as this may worsen hypoxia.

Supplementary oxygen

If this is needed the airline must be informed well in advance and the rate of flow and delivery system specified. Most international airlines will insist that they supply the oxygen cylinder and there will be a charge for this. The patient's own cylinder may be acceptable to Australian domestic carriers. If a nebuliser is needed in flight it needs to be approved by the airline in advance.

Table 1

Recommended medical exclusions from international air travel

Condition	*Recommended exclusion*
Myocardial infarction	Not within seven days. Medical information form required if travelling within 21 days
Stroke or transient ischaemic attack	Not within three days. Medical information form required if travelling within 10 days
Congestive cardiac failure	Individual assessment – failure needs to be controlled
Arrhythmia	Must be stable
Deep vein thrombosis	Individual assessment – patient needs to be stabilised on anticoagulants
Anaemia	Not fit if Hb <7.5 g/dL. Medical information form for Hb 7.5–10.5 g/dL. Not within 10 days of sickling crisis
Pneumothorax	Not within two weeks following full inflation of lung
After surgery	Not within 5–7 days depending on circumstances • appendicectomy, five days • angioplasty, not within three days, with stents five days • coronary bypass, not within 10 days

Diabetes

During travel people with diabetes should increase their fluid intake, avoid alcohol and arrange appropriate meals. Blood glucose monitoring should be increased in frequency during travel. Patients should take oral hypoglycaemic drugs as prescribed according to the local time.

People with diabetes who are taking insulin may need to adjust their dose for east or west trips with time zone changes greater than four hours and consultation with a diabetes specialist may be needed. A detailed itinerary of the trip is helpful for planning the insulin regimen. One regimen suitable for people who are familiar with managing their diabetes is to monitor the pre-meal glucometer reading and dose with short acting insulin accordingly. Longer acting insulin can be added before sleep on long flights. The traveller then returns to their usual dose the morning after arrival.

It is important to have snacks on hand in case of delays to meal times. Travellers should not only carry insulin and other medications in their hand luggage, but also spare insulin in their suitcase or with a travelling companion. Insulin is stable for months at room temperature and should not be given to the airline crew to put in the fridge in case it is mislaid. Informing the travel company and wearing a Medic-Alert bracelet are wise precautions especially if travelling alone.

Cardiovascular disease

The most common cause of Australians dying overseas is coronary heart disease[6], but it is also one of the most common reasons for dying at home. Most patients with stable cardiovascular disease can travel safely. Again assessment of exercise tolerance is helpful. If the person is asymptomatic during normal activity and can walk 50 metres or climb 15 stairs without symptoms then they should be able to cope with cabin air pressure without difficulty. People with severe angina or congestive cardiac failure who are symptomatic on

minimal exertion need oxygen supplementation (usually 2 L or 4 L per minute either intermittently or continuously). Referral to a cardiologist for advice and contacting the airline before travel should be considered.

As well as a letter summarising their medical problems and medications, people with cardiac disease should also take a copy of a recent electrocardiograph. Patients with pacemakers should be advised to inform airport staff of its presence as electronic security screening may interfere with programming of the device.

Immunocompromised patients

Travellers who are on short courses of corticosteroids (less than two weeks) should be treated as immunocompetent. Patients with surgical or functional asplenia are at increased risk of malaria and ideally should avoid travel to malaria endemic areas.

HIV infection

People with HIV have both increased susceptibility to infection and an altered response to vaccination. Caution is needed with live vaccines as these may cause progressive infection. Current National Health and Medical Research Council (NHMRC) guidelines[2] are that yellow fever and live attenuated typhoid vaccination are contraindicated. Inactivated poliomyelitis vaccine (IPV) is preferable to oral polio vaccine. Measles, mumps, rubella vaccine has been used in HIV infected children without evidence of harm, but has caused disease in adults.[7]

Vaccines without live organisms such as hepatitis A, polysaccharide typhoid vaccines and hepatitis B are safe but efficacy may be lessened. Other killed vaccines for travel are also safe. The NHMRC recommendation is to give double the normal dose of hepatitis B vaccine at the normal dosage intervals. As well as vaccination, passive protection against hepatitis A with human immune globulin may be indicated. Annual influenza vaccination is recommended. Response rates in HIV are around 80% and less than 50% in those with AIDS.[7] Pneumococcal vaccine is also recommended for HIV infected adults and children over two years.

Conclusion

In travellers, as in the rest of the community, respiratory disease, cardiovascular disease and diabetes are common chronic illnesses. The ability to climb a flight of 15 stairs and walk 50 meters without symptoms is an indication that a patient with cardiac or respiratory disease will cope with the relative hypoxia of air travel. Travellers with chronic illness and their doctors need to plan well in advance of their journey. Issues to be considered include the itinerary, travel insurance, fitness for travel, immunisations and medications. Providing the traveller with a health summary and medication list can be helpful.

REFERENCES

1. Australian Bureau of Statistics. Overseas arrivals and departures. Canberra: ABS; 1998.
2. National Health and Medical Research Council.The Australian immunisation handbook. 7th ed. Canberra: Commonwealth of Australia; 2000.
3. Medical Guidelines for Airline Travel. Alexandria (VA): Aerospace Medical Association; 1997. http://www.asma.org
4. Ferrari E, Chevallier T, Chapelier A, Baudouy M. Travel as a risk factor for venous thromboembolic disease: a case-control study. Chest 1999;115:440-4.
5. Dawson AG. Aircraft Travel and Related Illness. In: DuPont HL, Steffen R. Textbook of Travel Medicine and Health. Hamilton: BC Decker; 1997.
6. Prociv P. Deaths of Australian travellers overseas. Med J Aust 1995;163: 27-30.
7. Yung AP, Ruff TA. Manual of Travel Medicine. A guide for practitioners at pre-travel clinics. Melbourne: Victorian Infectious Diseases Service, Royal Melbourne Hospital; 1999.

E-mail: n.zwar@unsw.edu.au

Self-test questions

The following statements are either true or false (answers on page 111)

9. At cruising height modern jets are pressurised to ensure the partial oxygen pressure is the same as at sea level.
10. Patients with HIV should not be immunised with vaccines made from killed organisms.

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.

Fosphenytoin

Pro-Epanutin (Pfizer)

10 mL vials containing 75 mg/mL

Approved indication: epilepsy

Australian Medicines Handbook Section 16.1.3

Phenytoin sometimes has to be given parenterally, for example to stop status epilepticus. Intramuscular injections are not recommended because of local adverse reactions and unpredictable absorption. The injection is not very soluble and can be precipitated if given with other intravenous infusions. Injectable phenytoin is pH 12 so the intravenous line must be flushed with saline to reduce local venous irritation. Fosphenytoin has been developed to try and reduce these practical problems.

Fosphenytoin is a prodrug. It is converted rapidly (half-life 15 minutes) to phenytoin. Fosphenytoin is less alkaline than phenytoin and can be given by intramuscular injection. This route is not recommended in status epilepticus as peak plasma concentrations are not reached for 30 minutes.

The pharmacokinetics are complex. Fosphenytoin is highly bound to plasma proteins. It displaces phenytoin from binding sites, increasing the unbound fraction of phenytoin. To reduce confusion about the dose of fosphenytoin it is expressed as phenytoin equivalents. (A fosphenytoin concentration of 75 mg/mL is equivalent to 50 mg/mL of phenytoin sodium.)

When the prodrug is converted to phenytoin, formaldehyde and phosphate are also produced. These compounds are not thought to cause adverse reactions, but the phosphate load needs to be considered in patients with renal impairment. Renal and hepatic dysfunction can also result in changes to protein binding. Many drugs can alter phenytoin concentrations, but none are known to affect the conversion of fosphenytoin.

Adverse reactions include hypotension and central nervous system depression. Some patients will complain of itching or paraesthesia. The safety (and effectiveness) of fosphenytoin has not been assessed for longer than five days.

In Australia fosphenytoin has been approved for use in generalised convulsive status epilepticus and the prevention and treatment of seizures occurring in connection with neurosurgery and/or head trauma.

Rivastigmine

Exelon (Novartis)

1.5 mg, 3 mg, 4.5 mg and 6 mg capsules

Approved indication: Alzheimer's disease

Australian Medicines Handbook Section 16.5.1

Acetylcholinesterase inhibitors have been studied in Alzheimer's disease as they enhance the remaining cholinergic neurotransmission. Rivastigmine is the third inhibitor to be marketed. Tacrine and donepezil are already available.

Rivastigmine inhibits acetyl- and butyrylcholinesterase resulting in increased acetylcholine at cholinergic synapses. It is rapidly metabolised by cholinesterases and has a plasma half-life of one hour. Most of a dose is excreted by the kidneys with no unchanged drug appearing in the urine. The pharmacokinetics are non-linear; the bioavailability triples when the dose is doubled.

A multicentre trial studied 725 patients with mild to moderate Alzheimer's disease. These patients were randomised to receive rivastigmine 1–4 mg/day or 6–12 mg/day or a placebo. The dose of rivastigmine was titrated in the first 12 weeks of the 26-week trial. There were 'meaningful' improvements of cognitive function in 24% of the 242 patients given the higher dose of rivastigmine and in 16% of the 238 patients given a placebo.[1] The outcome for the lower dose was not significantly different from placebo.

Over 30% of the patients randomised to take the higher dose of rivastigmine discontinued, with approximately 23% withdrawing because of adverse events.[1] Common adverse effects are nausea, vomiting, anorexia and dizziness. These adverse effects often occur while the dose is being titrated.

Although rivastigmine had advantages over placebo in the rating scales used in the trial[1], their clinical relevance is uncertain. Significantly more patients taking higher doses of rivastigmine had an improvement of at least 10% on the progressive deterioration scale, however this difference is relatively small. In the placebo group 19% of the patients improved compared with 29% of those taking rivastigmine. As the clinical response cannot be predicted in the patients who can tolerate rivastigmine, treatment should stop if there is no benefit after 12 weeks. Alzheimer's disease is chronic and progressive so studies lasting longer than six months are needed.

REFERENCE

1. B303 Exelon Study Group. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. Br Med J 1999;318:633-8.

NEW FORMULATIONS

Diltiazem hydrochloride

Cardizem (Aventis Pharma)

60 mg tablets

Gabapentin

Neurontin (Pfizer)

800 mg tablets

Olanzapine

Zyprexa Zydis (Eli Lilly)

5 mg and 10 mg wafers

Ursodeoxycholic acid

Ursofalk (Orphan)

250 mg/5 mL suspension

NEW COMBINATIONS

Oestradiol/norethisterone acetate

Estalis 50/140 (Novartis)

Patches delivering 50 microgram oestradiol and 140 microgram norethisterone acetate daily

Estalis 50/250 (Novartis)

Patches delivering 50 microgram oestradiol and 250 microgram norethisterone acetate daily

Estalis Sequi 50/140 (Novartis)

Patches delivering 50 microgram oestradiol daily for weeks one and two, and 50 microgram oestradiol and 140 microgram norethisterone acetate daily for weeks three and four

Estalis Sequi 50/250 (Novartis)

Patches delivering 50 microgram oestradiol daily for weeks one and two, and 50 microgram oestradiol and 250 microgram norethisterone acetate daily for weeks three and four

Perindopril/indapamide

Coversyl Plus (Servier)

perindopril 4 mg/indapamide 1.25 mg tablets

NEW PROPRIETARY BRANDS

Hepatitis A vaccine, inactivated

Avaxim (Aventis Pasteur)

0.5 mL pre-filled syringes

Insulin aspart

NovoRapid (Novo Nordisk)

3 mL penfill cartridges for use in NovoPen 3, NovoPen 3 Demi and Innovo

NovoLet (Novo Nordisk)

3 mL pre-filled syringes

Answers to self-test questions

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

Distribution and back issues

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

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

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

NAME: .....

ADDRESS: .....

.....

.....

.....

PROFESSION: .....

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

The full text of *Australian Prescriber* is available on the internet, free of charge, at www.australianprescriber.com

Tick ☑ whichever of the following apply:

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

☐ Place me on the mailing list

☐ Delete me from the mailing list

My reference number is .....

☐ Change my address

My reference number is .....

☐ Send me all the available back issues (from Vol. 21 No. 4, 1998)

☐ Send me the following back issue/s

.....

Editorial office

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

Telephone: (02) 6289 7038

Facsimile: (02) 6289 8641

Postal: The Editor
Australian Prescriber
PO Box 100
WODEN ACT 2606
AUSTRALIA

E-mail: info@australianprescriber.com

Web site: www.australianprescriber.com

PRODUCTION

Production Co-ordinator
Reid, S.

Desktopping
Barnes Desktopping and Design

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

Address correspondence to:
The Editor
Australian Prescriber
PO Box 100
Woden ACT 2606
Telephone (02) 6289 7038

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

Published by the Commonwealth
Department of Health and Aged Care