COVER

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EDITORIAL

It's natural so it must be safe

Anthony Smith, Emeritus Professor of Clinical Pharmacology, University of Newcastle, Newcastle, New South Wales

Index words: *Aristolochia*, guarana, St John's wort.

(Aust Prescr 2002;25:50–1)

Background

In her recent book 'The Poison Principle'[1], Gail Bell makes a discursive commentary on poisons and poisoners through the ages. After reading the book I realised that almost all the deadly substances she discusses could be classified as 'natural'. Gail Bell clearly separates common poisons from medicines but Paracelsus in the 16th century would not make this distinction. He contended, with some justification, that it was all a question of dose!

Many complementary medicines have a long history of traditional use, and are generally regarded as safe. That is why they are sold through a range of outlets, often without the need for the advice of a health professional. Does this mean that we can make a clear distinction between poisons and medicines, and uncritically accept the mantra 'natural = safe'? Recent examples of previously unsuspected toxicity tell us of the need for continuing vigilance.

Aristolochic acids (found in the plant genus *Aristolochia*) have recently been shown to cause nephropathy and, probably, renal (urothelial) cancer.[2] They should not be, but occasionally are, adulterants in traditional Chinese and other medicines available in Australia. As a safety precaution, the analytical laboratories of the Therapeutic Goods Administration (TGA) reviewed the chemical composition of around 100 herbal products which might have been contaminated by aristolochic acids. The results for the majority of these products were reassuringly negative. However, a small number of products were urgently recalled. Even stricter controls around these 100 herbal medicines have now been put in place.

Immediate toxicity is relatively easy to detect but linking natural substances with outcomes such as cancer is more difficult because of the time between exposure and the onset of symptoms. Without being alarmist, it is perfectly possible to claim that some so-called 'idiopathic' diseases could be the unrecognised results of taking complementary, or prescription, medicines.

Another recent concern is St John's wort (*Hypericum perforatum*) which some people take for depression.[3] The plant contains substance(s) which increase the production of drug metabolising enzymes found in the gut and liver (in particular cytochrome P450 3A4[4]). This may increase the metabolism of some prescription medicines, leading to interactions which result in organ rejection (cyclosporin), worsening of HIV-AIDS (indinavir), inadequate anticoagulation (warfarin) and breakthrough bleeding (combined oral contraceptives).[5]

Concealment of known potential toxicity is rare, but the requirement for complementary medicines containing guarana to declare their caffeine content on the label has only recently become mandatory. Guarana's 'energising' effects relate to its caffeine content. You probably would not buy a product for yourself or your children with 'added caffeine', but without this important labelling you might not realise that caffeine is what you get with guarana – a 'natural' product.

Reviewing the quality and safety of complementary medicines is the responsibility of the TGA. It is advised by the Complementary Medicines Evaluation Committee (CMEC), a Commonwealth Government committee established in 1997. All complementary medicines included on the Australian Register of Therapeutic Goods (ARTG) are evaluated for quality and safety. Manufacturers and sponsors are only required to 'hold the evidence' for preparations for which minor therapeutic claims are being made. These claims are not routinely evaluated for a listable preparation (a preparation carrying the symbol AustL, with a number,

In this issue...

Many people believe that complementary medicines are safe. Tony Smith explores this myth, while Stephen Myers alerts us to some of the interactions between complementary medicines and warfarin.

Warfarin can interact with alcohol. This may complicate the management of some of the heavy drinkers discussed by Greg Whelan.

Thrombosis is a known complication of oestrogen therapy. While Edith Weisberg discusses this risk, Paul Neeskens questions whether hormone replacement therapy has any benefit beyond symptom relief.

The benefits of some of the drugs mentioned in the article by Daniel O'Brien and Beverly Biggs may be limited in the prevention of malaria. When designing a regimen for a traveller to a malarious area, the adverse effects of chemoprophylaxis need to be considered. Rohan Jayasinghe and Pramesh Kovoor remind us that some of these antimalarial drugs can prolong the QT interval on the ECG.

on its packaging). Compounds which make more serious claims (disease prevention, modification or management) are evaluated for efficacy in addition to the mandatory review of safety and quality. If these claims are accepted a registered compound will have AustR, with a number, on its packaging and label.

Good manufacturing practice is comparatively easy to assess and ensure; safety on the other hand is often dependent on the **absence** of data in any of the worldwide databases. The Adverse Drug Reactions Advisory Committee has a close link to CMEC, and wants to increase reporting of suspected adverse responses to complementary medicines. In Australia, we rely on voluntary reporting from health professionals, many of whom do not yet ask about what patients are taking apart from their prescription drugs.

There is little readily available and reliable information on complementary medicines for health professionals. Free information lines such as the Therapeutic Advisory Information Service* of the National Prescribing Service are helpful, and the recommendations of CMEC are accessible on the TGA web site.†

* Freecall 1300 138 677, e-mail tais@nps.org.au

† http://www.health.gov.au/tga/cm/cm.htm

If 50% of our patients are taking complementary medicines, neither patients nor prescribers can afford to be ignorant. Unbiased education is required for health professionals and consumers alike. Who is to collate and provide it? Perhaps this is a future task for the National Prescribing Service in conjunction with its member organisations?

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ACKNOWLEGEMENTS

I thank Dr Fiona Cumming, Director of the TGA Office of Complementary Medicines, and Professor David Roberts, former Chair of CMEC, for helpful advice.

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Emeritus Professor Smith is Chair of the Complementary Medicines Evaluation Committee.

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.

Hypertension in diabetes

Editor, – I refer to the article 'Hypertension in diabetes' (Aust Prescr 2002;25:8-10).

The author suggests that while AT_1 receptor antagonists may have the same benefits as ACE inhibitors, this has yet to be shown in clinical trials. I would draw your attention to the recently published PRIME program[1,2], which evaluated the effects of irbesartan on morbidity and/or mortality in patients with hypertension and type 2 diabetes across the continuum of early and advanced stages of diabetic renal disease.

The PRIME program consisted of two trials, IRMA 2 and IDNT.

In IRMA 2, the irbesartan 300 mg group demonstrated a 70% relative risk reduction in the primary end-point of progression to overt proteinuria, compared with a control group (placebo in addition to other non-excluded antihypertensive therapies), $p = 0.0004$.[1]

In IDNT, the primary end-point was the time until the first occurrence of doubling of serum creatinine, or end-stage renal disease, or all-cause mortality. The irbesartan group demonstrated:

- a 20% relative risk reduction in the primary end-point compared with the control group (placebo in addition to other non-excluded and antihypertensive therapies), $p = 0.02$
- a 23% relative risk reduction versus the amlodipine group, $p = 0.006$.[2]

In a recently updated position statement by the American Diabetes Association on diabetic nephropathy[3], the recommendation is that in treatment of albuminuria/nephropathy both ACE inhibitors and the AT_1 receptor antagonists can be used. The recommendations are as follows:

- in hypertensive and non-hypertensive type 1 diabetic patients with microalbuminuria or clinical albuminuria, ACE inhibitors are the initial treatment of choice
- in hypertensive type 2 diabetic patients with microalbuminuria or clinical albuminuria, AT_1 receptor antagonists are the initial drugs of choice.

While the AT_1 receptor antagonists are a newer class of drug, and data in the past have been limited, there is certainly a growing body of evidence such as PRIME on their use in hypertensive diabetic patients.

Victoria Elegant

Medical Director

Sanofi-Synthelabo Australia

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2. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60.
3. American Diabetes Association. Diabetic nephropathy: position statement. Diabetes Care 2002;25(Suppl 1):S85-S89.

Dr Julia Lowe, author of the article, comments:

I am grateful for the opportunity to comment on three studies which have evaluated the effects of AT_1 receptor antagonists on morbidity and/or mortality in patients with hypertension and diabetes. These studies were published after I had completed my article for *Australian Prescriber* and are concerned with patients who already have either microalbuminuria[1] or overt nephropathy.[2,3] My article was concerned solely with cardiovascular outcomes in patients with hypertension and diabetes, rather than the more specific question of patients who have already developed complications such as microalbuminuria or nephropathy. I note that none of these studies used an ACE inhibitor in the placebo group. Comparison with amlodipine in one of these trials[2] was interesting given the uncertainty about the value of calcium channel antagonists in prevention of diabetic nephropathy. Only the RENAAL trial of losartan addressed death as part of its composite primary outcome.[3] There was no difference in deaths in the losartan group (158/751) compared to controls in the placebo group (155/762). In the other two studies there was no difference in the number of deaths between groups, but the studies were not designed with sufficient power to detect a difference in deaths as an outcome.[1,2]

In summary, I see no need to change the statement in my article that 'While AT_1 receptor antagonists may have the same benefits as ACE inhibitors, this has yet to be shown in clinical trials'.

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Missed doses

Editor, – I was fortunate to read the excellent article about missed doses (Aust Prescr 2002;25:16-8) but I did find myself questioning the advice given in the table 'Information for consumers' for progestogen-only contraceptives. This indicated that if a dose of the progestogen-only pill is delayed for more than three hours then back-up contraception is required for 14 days. This would seem contrary to the evidence that the cervical mucus protection afforded by this method begins after only about three hours and that the suppressive effect on the endometrium only takes a few days to occur. It is accepted practice in most family planning organisations worldwide that women are advised that should they be more than three hours late taking a dose of their progestogen-only pill they should use additional contraceptive cover for two days, not 14 as stated in the article. I agree that many of the recommendations around the use of progestogen-only contraceptives are 'fuzzy' to say the least! Perhaps at some stage in the future someone will have the energy to apply to the appropriate authorities to lift the restrictions on the use of progestogen-only contraceptives in women who are lactating or have thrombophilia. It is hard enough for the poor doctor just trying to do the right thing without having product information that is palpably inaccurate as well.

Terri Foran
Medical Director FPA Health
Ashfield, NSW

Dr Andrew Gilbert, one of the authors of 'I've missed a dose; what should I do?', comments:

We thank Dr Foran for her comments. Our article presented information as it is printed in the Consumer Medicine Information (CMI) sheet for levonorgestrel (Microval). The information in the CMI is required to be consistent with the Australian approved product information. It is clear from Dr Foran's comments that the product information, and therefore the CMI, does not reflect current clinical knowledge about the use of progestogen-only pills. With regard to missed doses, the product information for Microval states that in cases where a woman misses either one or two tablets 'she should use a mechanical method of contraception until 14 consecutive tablets have been taken'. The product information for the Micronor brand of norethisterone states even more strongly that if one dose is missed the pill 'should be discontinued immediately and a method of non-hormonal contraception should be used until menses have appeared or pregnancy has been excluded'.

We believe that it is extremely important that the product information and CMI reflect the evidence we have about the safe, effective and convenient use of these products in practice. We support strongly Dr Foran's contention that a mechanism needs to be found to require the pharmaceutical companies to update their product information in light of good practice-based evidence.

Influenza immunisation

Editor, – In an otherwise excellent article ('Influenza immunisation' Aust Prescr 2002;25:5-7) Dr Robert Hall dismisses antiviral drugs as 'conferring little public health benefit'. While this may be true under normal circumstances, it may not be so during an influenza pandemic which could strike with little warning and at any time of the year. The long lead time necessary for large-scale vaccine production against a pandemic influenza virus implies that at least in the initial stages we will have to rely on organisational strategies and antiviral drugs. A pandemic virus of high virulence would constitute a public health emergency with potentially severe

consequences including breakdown of social order. Selective antiviral prophylaxis then becomes a very important public health measure. To quote the World Health Organization influenza pandemic preparedness plan[1] 'it would be appropriate… to maintain a supply [of anti-influenza drugs] adequate for critical needs which might arise, such as protection of health care staff and laboratory workers'.

Peter Lake
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Drug promotion

Editor, – Dr Herxheimer rightly said in his editorial 'The importance of independent drug bulletins' (Aust Prescr 2002;25:3-4) that some over-enthusiastic colleagues talk about their preferred treatment. This is done not out of enthusiasm or devotion, but because of inducements offered by drug companies. There is now an unhealthy practice of drug companies hiring specialists to speak about their new products to select groups of medical practitioners especially invited to hill stations or costly hotels. How do medical associations and medical councils allow such a partisan practice by their members?

Wishvas Rane
Pune
India

CD review

Electronic Therapeutic Guidelines: complete (eTG complete). January 2002. Melbourne: Therapeutic Guidelines Limited.

Price: $220 subscription per year includes 3–4 updates. (Subsequent years approx. half any advertised initial subscription)*

John Fraser, Associate Professor and Director, New England Area Rural Training Unit, Tamworth, NSW

'eTG complete' is an interactive CD-ROM allowing easy access and searching of peer-reviewed Australian clinical guidelines produced by Therapeutic Guidelines Limited. Topics include analgesia, antibiotics, cardiovascular, respiratory, endocrinology, neurology, gastroenterology, dermatology, palliative care, psychotropics and drug prescribing in pregnancy and breastfeeding.

I have regularly subscribed to the paper-based versions of these guidelines for the last 10 years. They are an invaluable resource as an aid to clinical practice particularly in rural areas where access to specialist advice may be limited and some medical conditions are encountered infrequently. I now recommend these texts to my general practice registrars preparing for their examinations as a useful means of updating and revision. All versions are endorsed by the Royal Australian College of General Practitioners and other relevant discipline-specific specialist organisations and colleges. New versions are peer-reviewed, evidence-based and referenced.

Converting from a paper-based reference system to the electronic version, I found the software installed easily without difficulties. The software allows on-screen access to the familiar paper-based versions of guidelines. I found the pregnancy and breastfeeding guidelines to be a very useful addition allowing drugs to be searched alphabetically. The capacity to cross-reference and search topics which are discussed in more than one guideline is one of the main advantages of combining the guidelines into one electronic version.

A list of topics containing the search word are listed after each search. Alternatively, you can scroll down an index of topics. Consideration of bolding the main listing of the topic would be useful as some searches I conducted listed over 20 topics containing the word of interest. This would detract from its utility in checking details, when I am consulting, if I needed to scroll through multiple screens.

On average, 2–3 new editions of guidelines are developed each year. The subscription price of the CD compares with the paper version as it includes several updates to accommodate these new versions. After the first year, the price will be around $110 per year which equates with buying three new guidelines. My present versions of the guidelines include my own personal list of notes, writings and exceptions to 'rules' I have encountered in implementing them in practice. The CD-ROM version does not offer scope for you to add this same information. Consideration of a personal notes file on the C: drive linked to the CD-ROM may be considered to get around this problem. The 'eTG complete' is a useful addition to general practice, improving access to up-to-date peer-reviewed information in primary care.

Minimum system requirements
CD-ROM drive and mouse
32 MB of RAM, 60 MB free HDD space
Windows 95/98me/2000/XP: Pentium processor
Macintosh: Power Macintosh 7100/80 or equivalent
Unix/Linux/Posix: Pentium processor

* For more information contact Therapeutic Guidelines Limited 1800 061 260.

Interactions between complementary medicines and warfarin

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SYNOPSIS

Many complementary medicines have confirmed or potential interactions with warfarin. These interactions can increase or decrease the anticoagulant effect of warfarin and have the potential to cause serious adverse events. A number of herbs and foods alter the metabolism of warfarin by acting on cytochrome P450 enzymes. Other potentially interacting complementary medicines include those with possible effects on platelets and those containing natural coumarins. Warning both consumers and prescribers of warfarin about the potential for interactions with complementary medicines may reduce the risk of these interactions. Such warnings are appropriate for a drug that has a narrow therapeutic window and requires regular monitoring. In view of these interactions, prescribers should check the international normalised ratio within a week of a patient commencing or ceasing a complementary medicine.

Index words: anticoagulation, herbal medicines.

(Aust Prescr 2002;25:54–6)

Introduction

Interactions with warfarin can lead to either an increased or decreased anticoagulant effect. Those that increase the anticoagulant effect significantly increase the risk of serious haemorrhage. Interactions that decrease the anticoagulant effect significantly increase the risk of thromboembolic complications of the condition for which warfarin was prescribed.

Drug and dietary interactions with warfarin

Coumarins (mainly warfarin) are currently known to interact with approximately 250 different drugs. Interactions can increase or decrease the international normalised ratio (INR).

Haemostasis involves interaction between the vessel wall, platelets and coagulation factors. In addition to drug interactions that may alter the INR, medications may alter platelet activity and modify haemostasis resulting in prolonged bleeding time without affecting the INR. Antiplatelet agents will prolong bleeding time and may increase the risk of serious haemorrhage when taken with warfarin. As these drugs have a different action the INR may be unchanged despite the increased risk of bleeding.

Dietary factors may affect the action of warfarin and the resultant INR. Deficiency of vitamin K will increase the INR, while a diet high in vitamin K will decrease it. Dietary substances that inhibit or induce the cytochrome P450 pathway may alter warfarin's metabolism and increase or decrease its half-life.

While the anticoagulant effect of warfarin generally begins within 24 hours of taking the drug, the peak effect may take up to four days. As the effective half-life of warfarin is about 40 hours, and the anticoagulant effect is delayed, it takes several days after any dosing change before plasma concentrations and anticoagulant effects reach a steady state.

Interactions between warfarin and complementary medicines

A wide range of complementary medicines, both nutritional supplements and herbal preparations, have confirmed or potential interactions with warfarin.

Nutritional supplements that have documented interactions with warfarin include vitamin K, vitamin C and coenzyme Q_{10} which have been associated with a decrease in INR. Vitamin E has been associated with increases in INR, but there is conflicting evidence in the literature.[1]

A small number of herbal preparations have documented interactions with warfarin. The strength of the evidence to support these associations varies widely. Herbs with a documented increase in the anticoagulant effect include garlic[2] (*Allium sativum*), dong quai[3] (*Angelica sinensis*), danshen[4] (*Salvia miltiorrhiza*) and devil's claw[5] (*Harpagophytum procumbens*). Herbs with a documented decrease in the anticoagulant effect include Korean ginseng[6] (*Panax ginseng*) and green tea (*Camellia sinensis*).[7] The mechanism of these interactions is not always known and the majority of this literature is based on single cases.

In some cases the mechanism is understood. One medicinal plant and two foods have been shown to increase the metabolism of warfarin through their action on the cytochrome P450 pathways leading to the lowering of the INR. Substances known to induce P450 include St John's wort[8] (*Hypericum perforatum*), broccoli[9] and Brussels sprouts[10]. These interactions occurred with a standard dose of St John's wort extract (900 mg daily) and diets rich in broccoli and Brussels sprouts. Grapefruit juice, a known inhibitor of cytochrome P450, does not appear to alter warfarin metabolism.[11]

Potential interactions

A significant number of the substances cited in the literature as posing a risk should be defined as potential, rather than established, risks as the data on which the assessment has been made are an extrapolation from known chemical constituents within the substance or from *in vitro* studies. While these substances may indeed pose a risk, it remains theoretical until evidence exists from human cases or studies. Plants with potential risk include those with possible actions on platelets and those containing natural coumarins.

A wide range of herbal preparations have demonstrated **antiplatelet** activity *in vitro* and may potentially increase bleeding time.[12] These include a number of the most popular herbs on the Australian market: feverfew (*Tanecetum parthenium*), garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), ginger (*Zingiber officinale*), Korean ginseng (*Panax ginseng*), and liquorice (*Glycyrrhiza glabra*). Attributing *in vivo* activity based on laboratory investigation is inappropriate and in a number of cases clinical trials have failed to show similar effects in humans. For example, the role of garlic and ginger[13] as antiplatelet agents remains controversial. They may not possess antiplatelet activity, but if they do it may depend on specific formulations that concentrate an appropriate profile of active constituents.

Many herbs contain coumarins that may **potentiate the activity of warfarin**.[14] These include alfalfa (*Medicago sativa*), angelica (*Angelica archangelica*), aniseed (*Pimpinella anisum*), arnica (*Arnica montana*), asafoetida (*Ferula spp.*), celery (*Apium graveolens*), German chamomile (*Matricaria recutita*), Roman chamomile (*Anthemis nobilis*), fenugreek (*Trigonella foenum-graecum*), horse chestnut (*Aesculus hippocastanum*), prickly ash (*Zanthoxylum americana*, *Z. clava-herculis*), quassia (*Picrasma excelsa*), and red clover (*Trifolium pratense*).[12]

Concurrent use of complementary medicines and pharmaceutical drugs

United States data suggest that 18% of adults use prescription drugs concurrently with herbal or vitamin supplements[15]; 15 million people may be at risk of drug-supplement interactions. The review of Traditional Chinese Medicine (TCM) undertaken by the Victorian, New South Wales and Queensland Departments of Health in 1995 estimated from a sample of 274 patients that 39% took pharmaceutical drugs with their Chinese herbal medicine.[16] If this can be generalised to all users of complementary medicines and we apply this to the 1993 estimate of one in two Australians using at least one complementary medicine per year, then 19.5% of the Australian population use prescription drugs concurrently with complementary medicines. This suggests that 3.7 million Australians may be at risk of drug-supplement interactions.

Despite these figures, confirmed interactions are uncommon and reported adverse events are relatively sparse. Adverse reactions to complementary medicines probably remain under-reported[17], so the totals of adverse events and interactions are probably higher. However, it is unlikely that an epidemic of adverse events with complementary medicines remains undetected in Australia.

Strategic management of potential interactions

Two approaches are possible to limit the potential public health risk of drug interactions between complementary medicines and warfarin. The first is to place a warning label on all complementary medicines with any known interaction with warfarin where the causality has been demonstrated beyond a reasonable doubt. The second is to place a warning about the concurrent use of complementary medicines in the product information of warfarin and to educate warfarin prescribers to ask about complementary medicines use by their patients.

While these two approaches are not mutually exclusive, it can be argued that their risk management is substantially different. Labelling any medication with a warning statement can only be undertaken when there is clear evidence for such a warning. The number of complementary medicines with a potential to interact with warfarin is large, however, the number with clear evidence of such an interaction is small. Labelling the few medications where the evidence is clear will not reduce the risk of potential interactions with a large number of complementary medicines.

Given that the number of recognised drug interactions with warfarin has increased over time, it is appropriate to conclude that the number of interacting complementary medicines will also increase over time. We can safely assume that there are a number of currently unidentified interactions that will be found in the future.

Warning both consumers and prescribers of warfarin about the potential for interactions with all complementary medicines may reduce the risk of interactions, not only with preparations that have definitive and potential interactions, but also with those where the interaction is currently unidentified. Such a warning is in keeping with a drug that has a narrow therapeutic range and requires regular monitoring.

Warfarin prescribers need to be aware of complementary medicines usage and monitor the INR more frequently if this usage changes. As a precaution, patients on warfarin should have INR measurements about two and seven days after starting or changing any herbal treatment.[18] Prescribers need to alert patients to the clinical symptoms associated with minor and major bleeding and be prepared to cease both warfarin and the complementary medicine. In patients at special risk, such as the elderly and the debilitated, concurrent use of complementary medicines and warfarin should be undertaken with considerable caution. If the complementary medicine is necessary, it should be continued with the same care given to pharmaceutical drugs with a high risk of interaction.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 75)

1. Complementary medicines may increase the risk of bleeding in patients taking warfarin without affecting the international normalised ratio (INR).
2. Vitamin K supplements may decrease the effect of warfarin.

CD review

John Murtagh. The General Practice Series – Single User CD-ROM.

Price $195. 10% discount for *Australian Prescriber* readers.*

Ieva Ozolins, General Practitioner, Kangaroo Island Medical Clinic, Kingscote, SA

'The General Practice Series' is an interactive CD-ROM encompassing three books written by one of Australia's most eminent general practitioners and educators. It is presented as the 'on-screen' alternative to the print versions of Murtagh's 'General Practice', 'Practice Tips' and 'Patient Education'. After confirming with my practice manager that my office computer fulfilled the system requirements of the CD-ROM, I managed to install the software and subsequently use the program without expert assistance.

I found the program useful in providing patient education sheets in the office, as it allowed me to call up and print out single page information sheets and to discuss the information with the patient on the spot. The software also provided an easily accessible reference for the diagnosis and management of common and unusual patient presentations. The on-screen format of 'General Practice' mirrors that of the original 1994 textbook currently sitting on the bookshelves in my practice, with some additional chapters and content in many of the chapters. The font used in the text is appropriate for reading on screen, however I found that it is still easier to read longer entries from the print version, rather than scrolling through each page on the computer. The drop-down menu system is easy to operate, and the 'Help' icon will get you going if you are not confident when first opening the program. Generally I used the drop-down menu looking for specific conditions, although the package allows for searching through the individual texts by providing a contents page for each book, accessed from the home page.

As in the original print versions, information is presented in a clear, methodical manner. Professor Murtagh's approach is simple to follow whether looking at a symptom or symptom complex, or for a specific condition. Pointing to a reference number in the body of the text easily accessed key references. Unfortunately the text has not been updated to reflect some of the more recent changes faced in general practice, for example, in the childhood immunisation schedule and the availability of new forms of delivery of hormonal contraception and hormone replacement therapy. With this caution, 'The General Practice Series' software package should prove invaluable to medical students, registrars and many experienced general practitioners, just as the printed texts have in the past.

Minimum system requirements
Microsoft Windows 95, 98 or NT 4 operating system
PC with 486 MHz processor
16 MB RAM for Windows 95 or 98, or 32 MB for NT
Mouse or other pointing device
CD-ROM drive
SVGA colour monitor, 256 colours with 800 x 600 resolution (higher recommended)
100 MB hard disk space for full installation

* Contact McGraw-Hill (02) 9415 9888, quote code MUR0502.

Contraception, hormone replacement therapy and thrombosis

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SYNOPSIS

The combined oral contraceptive pill and hormone replacement therapy increase the risk of venous thrombosis. Women should be checked for other factors predisposing them to thrombosis before these drugs are prescribed. The increased risk is usually attributed to oestrogen. Case-control studies of patients taking contraceptives containing the progestogens desogestrel, gestodene or norgestimate, suggest these drugs may also increase risk. However, confounding factors in these studies make interpretation difficult. The increased risks associated with hormone replacement therapy may be offset by its benefits in relieving menopausal symptoms.

Index words: desogestrel, gestodene.

(Aust Prescr 2002;25:57–9)

Introduction

In healthy young women the estimated incidence of venous thromboembolism is one per 10 000 woman years of follow-up. The association of combined oral contraceptives with an increased risk of venous thromboembolism has been documented since the 1960s. There are no reliable data suggesting that progestogen-only methods carry an increased risk of venous thromboembolism, but some studies suggest the newer progestogens used in combined pills may increase the risks. Women taking hormone replacement therapy (HRT) also have an increased risk of thromboembolism.

Risk factors for venous thromboembolism

Venous thromboembolic disease manifested either as a deep vein thrombosis or a pulmonary embolus is rare amongst young women but increases with age. Other factors associated with an increase in venous thromboembolism include obesity, smoking and inherited thrombophilia. The risk of venous thromboembolism increases following surgery, trauma, immobilisation, during and immediately following pregnancy, in cancer patients, during long-distance air travel and with the use of combined oral contraceptives (Table 1). Other conditions which are associated with an increased risk of venous thromboembolism are autoimmune diseases such as systemic lupus erythematosus, inflammatory bowel disease, hypothyroidism and renal disease.

Venous thromboembolism and combined oral contraceptives

A number of changes occur in the complex pathways of coagulation and fibrinolysis in women using combined oral contraceptives. These include a significant increase in fibrinogen and vitamin K-dependent coagulation factors, but there is also a significant increase in fibrinolysis which may balance any potential thrombotic risk in women without other risk factors for venous thromboembolism.

The risk appears to be related to the oestrogen dose. As the oestrogen dose has been reduced, the incidence of venous thromboembolism has declined from 9–10/10 000 woman years for high-dose oestrogen pills (≥ 50 microgram) to 3–4/10 000 woman years for low-dose (≤ 35 microgram) pills.

The progestogen question

In 1995 the British Committee on Safety of Medicines (CSM) issued a warning about a reported increased risk of venous thromboembolism in women taking combined oral contraceptives containing the ('third generation') progestogens desogestrel, gestodene or norgestimate compared to those containing levonorgestrel or norethisterone ('second generation').[1] As a result a large number of women taking third generation pills either changed to other formulations or discontinued use of oral contraceptives. There was a subsequent increase in unplanned pregnancies and induced abortions.[2]

Table 1

Risk of thromboembolism in women taking oral contraceptives according to personal characteristics

Characteristic	*No combined oral contraceptive*	*Taking second generation oral contraceptive*	*Taking third generation oral contraceptive*
Non-smoking, no risk factors	5–11/100 000	9–19/100 000	30/100 000
Hereditary thrombophilia	67/100 000	215/100 000	431/100 000
Current smoking	14/100 000	N/A	N/A
BMI > 30	20/100 000	N/A	N/A

Attributable risk factors for venous thromboembolism with obesity and smoking in women taking second and third generation pills are not available. In women taking a combined oral contraceptive, those with a BMI > 25 have an odds ratio of 6.4 for venous thromboembolism compared to women with BMI < 20. Attributable risk also increases with age.

Assessing the evidence

The CSM's advice was based on case-control studies published in 1995–96 which suggested that the odds ratios for venous thromboembolism in women taking combined oral contraceptives containing desogestrel, gestodene or norgestimate were 1.5–2.3 compared to combined oral contraceptives containing levonorgestrel and norethisterone.[3,4,5] Publication of these studies was followed by a number of articles pointing out possible sources of bias[6], the lack of a plausible biological explanation for the findings and a number of confounders that were not identified or taken into account in the original studies.

Prescribing bias

Bias occurs when a drug is prescribed more commonly to women with a medical condition that could be a contributory cause to the condition under scrutiny. Analysis of the studies showed that second and third generation combined oral contraceptives tended to be used in different populations of women. As third generation progestogens were less androgenic and considered to carry even less cardiovascular risk than low-dose second generation pills they tended to be prescribed more commonly for women with cardiovascular risk factors.[7]

Healthy user effect

This refers to how the duration of use influences the characteristics of the user population. Venous thromboembolism usually occurs in the first year of taking a combined oral contraceptive particularly in women with risk factors. As second generation pills have been marketed for much longer (than third generation pills) women with venous thromboembolism would have already stopped using them, leaving a group of continuing users who were at lower risk of venous thromboembolism. The early studies of users of second generation pills showed a risk ratio of 3.9 whereas the 1995–96 studies of the same pills showed the highest risk ratio to be 1.6 compared to non-users. In addition to having taken their pills for a shorter duration, prescribing bias added to the risk because third generation pills were more likely to be prescribed for women with cardiovascular risk factors. (There were preliminary data to suggest that women taking third generation pills were less likely than women taking second generation pills to have a myocardial infarction.[8]) The risk factors of the two groups were therefore not comparable.[7]

Confounders

A confounder is a characteristic of the user, which distorts the risk associated with exposure to a particular therapy because in itself it could increase the risk of the condition under scrutiny. The three original studies adjusted for possible confounders such as body mass and age but not for duration of use.[3,4,5] When first-year users of third generation pills were compared with first-year instead of long-term users of second generation pills, there was no significant difference in the incidence of venous thromboembolism (odds ratio 1.4, 95% confidence interval (CI) 0.8–2.5).[9]

In 1998 two further case-control studies used separate general practice populations and tried to avoid some of the deficiencies and address some of the criticisms of the earlier studies. They found no significant difference in the risk of venous thromboembolism between second and third generation combined oral contraceptives[10], while a third study appeared to confirm the risk, adding to the debate and confusion.[11]

What does the evidence mean?

Until the CSM's warning no previous association had been demonstrated between progestogen potency and venous thromboembolism. Furthermore a review of all 17 comparative studies on the haemostatic effects of desogestrel, gestodene and levonorgestrel-containing combined oral contraceptives found no difference in the established risk markers for venous thromboembolism between the third and second generation products.[12]

In 1998 the World Health Organization reported that combined oral contraceptives containing desogestrel and gestodene probably carry a small risk of venous thromboembolism beyond that of combined oral contraceptives containing levonorgestrel. However, thromboembolism is so rare that their increased risk contributes very little to the mortality or long-term disability of oral contraceptive users.[13]

Although the debate about the differential risks of second and third generation combined oral contraceptives continues, the absolute risk of deep vein thrombosis in young women without risk factors for venous thromboembolism is extremely low. However, a low risk of venous thromboembolism may outweigh any advantages third generation pills have over second generation pills.

Prescribing steroidal contraception

When prescribing contraception a careful medical history must be taken to exclude either a personal or strong family history of thromboembolic disease and risk factors for venous thromboembolism. Women with no risk factors for venous thromboembolism may be prescribed any combined oral contraceptive containing 35 microgram or less of ethinyloestradiol. However, they should be informed of the controversy surrounding third generation progestogens and given a choice of pill formulation based on an assessment of their individual benefits and risks.[14] Pills containing ethinyloestradiol 50 microgram should only be used if cycle control is an ongoing problem with lower doses.

Women with a confirmed history of a venous thromboembolic episode should never be prescribed the combined oral contraceptive. Those with a strong family history of venous thromboembolism should undergo screening to exclude thrombophilia before starting a combined oral contraceptive. Women with thrombophilia or multiple risk factors for venous thromboembolism should not use combined oral contraceptives. They can use progestogen-only methods, for example the progestogen-only pill, the injectable contraceptive formulation of medroxyprogesterone acetate, the sub-dermal etonogestrel implant, or the levonorgestrel-releasing intrauterine system. Alternatively they could consider use of a copper-bearing intrauterine device or barrier methods.

Danish population studies have shown that non-smoking women over 40 years old have a 10-fold increase in the risk of developing a venous thromboembolism compared to women in their 20s. Obesity further increases the risk. A BMI greater than 30 is associated with an independent risk ratio of 2.27 (CI 1.80–4.11) and current smoking with a risk of 1.42 (CI 1.12–1.79). The more risk factors for thromboembolism the greater the risk of developing a thrombosis while taking combined oral contraceptives.

To minimise the risk of venous thromboembolism, women undergoing pelvic surgery or procedures requiring extensive immobilisation, including wearing a long leg plaster, should, wherever possible, stop combined oral contraceptives two to four weeks before the procedure. They should not resume their pill until two weeks after achieving complete mobilisation. Alternative methods of contraception should be used during this period and should be started as soon as the pill is discontinued. In women who are not breastfeeding the combined oral contraceptive should not be started until three weeks postpartum.

Hormone replacement therapy and thromboembolism

Hormone replacement therapy appears to be related to an increased risk of venous thromboembolism in the first 12 months of use. The estimated incidence of idiopathic thromboembolism in postmenopausal women not using HRT is estimated to be 13/100 000 women, while in women using HRT it is 20–30/100 000. A large population-based study has found the adjusted odds ratio in HRT users compared with non-users was 4.6 (CI 2.5–8.4) in the first six months of use and 3.0 (CI 1.4–6.5) 6–12 months after starting treatment.[15] No major differences in risk were observed between users of high and low oestrogen doses, unopposed or opposed oestrogen treatment, and oral or transdermal therapy. Among current users of HRT, idiopathic venous thromboembolism occurs at two to three times the rate in non-users accounting for one to two additional cases per 10 000 women, per year.

Given the benefits of HRT in relation to relief of menopausal symptoms, a small increase in the risks of venous thromboembolism may be an acceptable trade-off for many women. However, it is important that women are informed of the slightly increased risk of venous thromboembolism to enable them to make an informed decision about taking HRT.

Conclusion

All women should be given information about the (low) risk of venous thromboembolism with combined oral contraceptive use and advised under what conditions to stop the pill and switch to alternative methods of contraception. The benefits of HRT on menopausal symptoms also greatly outweigh the risk of venous thromboembolism for women without risk factors.

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FURTHER READING

Venous thromboembolism with third generation oral contraceptives and cyproterone. Aust Adv Drug React Bull 2002;21:7.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 75)

3. As the risk of thrombosis is low, women do not have to stop taking the combined oral contraceptive pill before elective surgery.
4. The low dose of oestrogen used in hormone replacement therapy is not associated with an increased risk of venous thromboembolism.

The evidence-relevance gap – the example of hormone replacement therapy

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SYNOPSIS

Bridging the gap between scientific evidence and what is relevant for each patient is challenging. The 'evidence-relevance' gap is particularly apparent with the plethora of public information available about hormone replacement therapy, and where the patient expects concise and practical advice from a professional she knows and trusts. We need to recognise the limitations of clinical trials and consider the outcomes in absolute terms, then interpret the relevance to the patient. The relief of symptoms should be pursued on its own merits. The long-term benefits still need clarification with more research evidence.

Index words: evidence-based medicine, consumers, drug information.

(Aust Prescr 2002;25:60–2)

Introduction

'Should I take HRT?' is a common question in general practice. What we actually tell our patients about hormone replacement therapy (HRT) is dependent upon many factors. A key factor is the evidence about benefits and harm, but equally important are the patient's symptoms, current knowledge, expectations and attitude to medical interventions. The challenge for the clinician is to bridge the gap between scientific evidence and what is relevant to the individual seeking advice.

There are two key perspectives when considering HRT:

- relief of menopausal symptoms
- long-term benefits.

Symptom relief

The advice about HRT should be relatively simple. A trial for 2–3 months will ascertain whether the flushes, vaginal dryness, fatigue or other symptoms are relieved. The patient can decide herself if she feels better or worse, and whether the effort and any adverse effects are acceptable or not. Having reflected on the phenomena of coincidence and placebos, the clinician can decide with the patient whether or not to continue. The duration of further treatment can be decided over the course of time, with some consideration of the long-term benefits and adverse effects.

Long-term benefits

A totally different approach is needed when considering the long-term benefits. An *Australian Prescriber* editorial said, '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 [further trials] are available it is not possible to make general recommendations for the duration of treatment'.[1] I would suggest that even when these major trials are completed the challenge of turning the evidence into relevant advice would remain.

Interpreting the relevance of clinical trials

The word 'significant'

Statistical significance refers to a mathematical variable, a 'p' number, e.g. $p < 0.05$. This is a measure of the unlikelihood of an observation being due to co-incidence or wishful thinking. There is a frequent double play on this word in medical literature. A 'highly significant' result from a research trial should not be used to imply clinical significance.

Clinical relevance

Real-life outcomes determine relevance, not surrogate end-points such as bone mineral density or serum cholesterol. What is important to the patient is the reasonable likelihood of relieving or preventing some suffering. Surrogate end-points may have some relationship to morbidity in other contexts, but it is important for any medical intervention to be justified on the basis of human suffering prevented or relieved.

The dilution to irrelevance effect

Researchers have the habit of looking to a bigger trial for answers to difficult or previously unanswered questions. To seek statistical significance with larger sample sizes is in fact an implication of irrelevance for each individual. If you cannot show an effect in 1000 people, how relevant is a trial that needs 20 000 to achieve statistical significance? The pooling of data from multiple trials by meta-analysis has a similar goal, and therefore a similar weakness.

Consumer factors

When advising our patient about HRT we have to consider their views as well as the evidence.

Consumer effort

The 'effort and bother of it all' is largely unmeasured in clinical trials, where individuals are enrolled for the cause of research, and ongoing participation is encouraged and supported by the whole process of a trial. General practitioners who know their patients well, will understand the 'effort and bother' of starting any long-term medical intervention. The daily consumption of medication, the monthly visit to the pharmacy, and the six-monthly visit to the doctor are all burdens which can be substantial for some patients. Similarly, the so-called minor adverse effects such as weight gain and breast soreness are quite real for the sufferer. Furthermore, concern can arise that any new symptom might be related to the treatment, and this leads to further monitoring or investigation. The effort involved is well illustrated by the not infrequent plea, 'Do I really have to take these tablets, Doctor?' Finally, a general practitioner can sometimes anticipate that the compliance required is beyond the likely effort of the patient, especially when the goal is prevention rather than symptom relief.

Consumer attitude to risk

It is presumed that the consumer wants to worry about risk. Some will and some will not. An Australian study which assessed patients' attitudes to HRT, thrombolysis and coronary artery bypass surgery concluded, 'Patients do not view favourably the risk:benefit ratio of three surveyed medical interventions'.[2] This conclusion shows a difference between evidence-based medicine and consumer attitude. Similarly consumer attitude is often related to fear and preconceptions and every clinician knows how easy it is to induce anxiety.

Facts of life

Cancer, heart attack, or dementia will get us all one day. How hard should we try to avoid one to score another? Similarly with significant comorbidity or reduced life expectancy (e.g. multiple sclerosis or dementia), how relevant is long-term drug therapy that simply changes the odds of an unlikely event?

What advice can we give about long-term HRT?

I believe it is fruitful to examine data from the perspective of actual outcomes. Although the data may change a little when future trials are completed, the question will remain – how relevant will the change in outcome be to the patient?

While every woman is different, there are two main answers to questions about HRT.

Patient: 'Should I take HRT, Doctor?'
Doctor: 'Do you have symptoms?'
Patient: 'Yes.'
Doctor: 'You will probably feel better. Give it a go.'

Patient: 'Should I take HRT, Doctor?'
Doctor: 'Do you have symptoms?'
Patient: 'No.'
Doctor: 'Do you want to be as well as possible in 20 years, and do not mind 20 years of medication, and understand there may be both benefits and harms?'
If yes: 'Give it a go.'
If no: 'Leave well alone.'

Table 1

The outcome for 100 60-year-old women over 10 years

New event	*No treatment*	*With HRT*	*Events per 100 treated*		*Notes*
			Prevented	*Caused*	
Heart disease (angina, acute myocardial infarction, cardiovascular death)	10	7	3		Cholesterol 6.0, HDL 1.1, blood pressure 130/80, non-smoker, no pre-existing ischaemic heart disease[3] If pre-existing ischaemic heart disease – no benefit at all[4]
Symptomatic fracture	3.2	1.6	1.6		Bone density loss is slowed by HRT, but is only a modest predictor of fracture[5] Many trials measure vertebral fracture, 2/3 of which are radiographic and asymptomatic[6]
Breast cancer	2.5	3.2		0.7	Incidence not mortality[7]
Venous thromboembolism	2.3	6.2		3.9	The impact on deep vein thrombosis/pulmonary embolism is very certain[8]

Notes

- The improved outcome in heart disease and fracture are optimistic estimates of relative risk reduction.
- To extrapolate beyond 10 years may show more benefit, but equally plausible is more harm.

In Table 1 I have collated some data from major clinical trials. It presents the approximate outcome data for 100 60-year-old women over a period of 10 years.

The pertinent observation here is that the actual number of patients whose outcome is changed is actually rather small. The pertinent question is how relevant are these harms and benefits, considering the effort involved, to the patient seeking my advice?

There is a case to dismiss the long-term benefits of HRT, not because of lack of evidence, but because they might just be irrelevant. If a woman seeks advice about the benefits and risks of long-term HRT, the absolute long-term outcome data should be considered. Some women wanting detailed information about HRT could be presented with the absolute data; many others will trust their doctor explicitly. What we tell them will depend on our understanding of the evidence and our knowledge of the patient. Unfortunately it is not as simple as saying, 'There is significant (statistical) evidence of benefit', or worse, 'All women should take HRT'.

Conclusion

The advice to patients about hormone replacement therapy needs to be carefully considered. As discussed in the previous *Australian Prescriber* editorial, the clinical trials have limitations.[1] There are also limitations in translating the evidence from trials to advice given and the 'real world'. The benefit of relieving symptoms speaks for itself. The change in long-term outcome, both beneficial and harmful, is relatively small, and considering consumer factors, may well be irrelevant for many.

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Drugs and the QT_c interval

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SYNOPSIS

Many commonly used drugs can prolong the QT_c interval, especially if used in combination with other substances which affect their metabolism. Prolongation of the QT_c interval can cause life-threatening polymorphic ventricular tachycardia also known as torsade de pointes. Women and certain susceptible people are more prone to prolongation of the QT_c interval. This predisposition could be congenital or due to conditions such as hypokalaemia, hypomagnesaemia, renal failure or cardiac failure. Susceptible patients need an electrocardiogram before and after starting drugs that can prolong the QT_c interval. If a drug prolongs the QT_c interval beyond normal limits, the benefits of continuing the drug should be weighed against the relatively rare risk of potentially life-threatening arrhythmias.

Index words: torsade de pointes, antiarrhythmic drugs.

(Aust Prescr 2002;25:63–5)

Introduction

Many drugs can prolong the QT interval of the electrocardiogram (ECG). This effect is important as it is associated with polymorphic ventricular tachycardia and possible sudden cardiac death. Prescribers need to be aware of the drugs that have been implicated, particularly if the patient is already taking a drug which prolongs the QT interval or has a condition associated with QT prolongation.

QT and QT_c interval

The QT interval is the time between the start of the QRS complex and the end of the T wave in the ECG (Fig. 1). It represents the duration between the onset of depolarisation and the completion of repolarisation of the myocardium. There is commonly a variation in the QT interval measured in the various leads of the ECG. This 'T wave dispersion' occurs when the terminal portion of the T wave is isoelectric in some leads. When multiple leads are used the longest QT interval is considered to be the true QT interval.

The QT interval is dependent on heart rate, age and gender. A diurnal variation of the QT interval associated with the variations in sympathetic tone has also been described. The observed QT (QT_o) interval can be corrected (QT_c) for heart rate by using the following formula where RR is the interval in seconds between two successive R waves on the ECG.

$$QT_c = QT_o (\sqrt{RR})$$

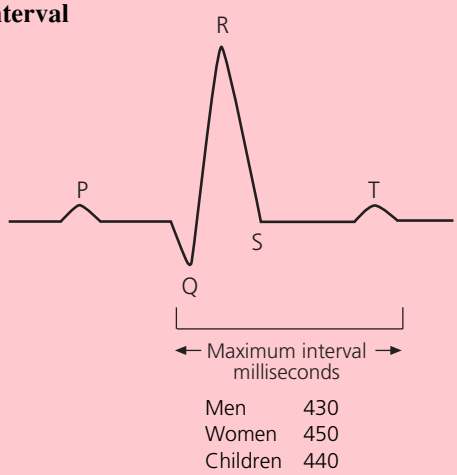
A QT_c interval of 430 milliseconds (ms) is accepted as the upper limit of normal for men and 450 ms as the upper limit of normal for women. In children up to the age of 15, the upper limit of normal is 440 ms.[1]

Long QT_c interval and arrhythmia

Prolongation of the QT_c interval is either acquired or due to a congenital long QT_c syndrome (Table 1). Drugs are by far the commonest cause for an acquired long QT_c interval. Grapefruit juice can increase the risk of drug-induced QT_c prolongation by inhibiting the metabolism of amiodarone.[2] Women are more

Fig. 1

QT interval



The QT interval is the time between the initiation of the QRS complex and the termination of the T wave in the electrocardiogram.

Table 1

Causes of long QT_c interval

Congenital (at least six genetic mutations identified)

- Romano-Ward syndrome (autosomal dominant)
- Jervell and Lange-Nielsen syndrome (cardiac abnormality–autosomal dominant & associated deafness–autosomal recessive)

Acquired

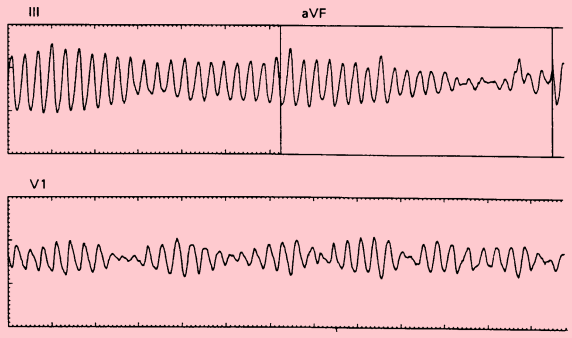
- drugs
- cardiac pathology (heart failure, ischaemia, myocarditis)
- electrolyte abnormality (hypokalaemia, hypomagnesaemia)
- cerebrovascular disease (subarachnoid haemmorhage, ischaemic stroke)
- severe bradycardia (especially complete heart block)
- hyperthyroidism/hypothyroidism

susceptible than men to drug-induced QT_c prolongation. Renal failure, cardiac failure and hepatic failure are also risk factors.

Prolongation of the QT_c interval is a sign of prolonged repolarisation of the ventricular myocardium. This leads to the phenomenon of early afterdepolarisation which can trigger polymorphic ventricular tachycardia, also known as torsade de pointes.[3] This abnormal rhythm is characterised by alternating electric polarity, periodic twisting of the points of the QRS complex around the isoelectric line and heart rates of 200–250 (Fig. 2). Each cycle of uniform morphology and axis lasts for 5–20 complexes. The arrhythmia is usually self-terminating, but can degenerate into ventricular fibrillation or rarely sustained ventricular tachycardia. It may result in dizziness, syncope, cardiac arrest and occasionally death.[4]

Fig. 2

Rhythm strips showing torsade de pointes



There is alternating electrical polarity and periodic twisting of the points of the QRS complex around the isoelectric line.

Drugs that cause QT_c prolongation

The mechanism of drug-induced QT_c prolongation is believed to be usually due to blockade of cardiac potassium channels. A long QT interval is most frequently seen with class I and class III antiarrhythmic drugs. Other classes of drugs that cause QT_c prolongation include antihistamines, antidepressants, antibiotics, antifungal drugs and antipsychotics (Table 2). The prolongation of the QT_c interval by these drugs is usually seen within several days of starting them. The class Ia antiarrhythmic drugs (quinidine, procainamide) and class III drugs (sotalol, amiodarone) prolong the repolarisation phase of the cardiac action potential.

Sotalol and amiodarone are often used to treat atrial or ventricular tachyarrhythmias. Doses of 160 mg or more of sotalol commonly cause QT_c prolongation; this effect has a clear dose-dependent relationship. Amiodarone is unique in that even though it prolongs the QT_c interval, it rarely leads to polymorphic ventricular tachycardia. This is believed to be due to its ability to block calcium channels and beta adrenergic receptors.

The combined administration of certain drugs can increase the risk of developing cardiac arrhythmias associated with long QT_c syndrome. Any substance that inhibits the metabolism of an implicated drug can enhance its effect on QT_c prolongation. Risk of sudden death due to fatal cardiac arrhythmias when erythromycin was taken with terfenadine attracted considerable attention before terfenadine was withdrawn.

Table 2

Some drugs associated with QT_c prolongation

Antibiotics
azithromycin
clarithromycin
erythromycin
roxithromycin
metronidazole (with alcohol)
moxifloxacin

Antifungals
fluconazole (in cirrhosis)
ketoconazole

Antivirals
nelfinavir

Antimalarials
chloroquine
mefloquine

Anaesthetics
halothane

Antiarrhythmics
disopyramide
procainamide
quinidine
amiodarone
sotalol

Antidepressants
amitriptyline
clomipramine
imipramine
dothiepin
doxepin

Antipsychotics
risperidone
fluphenazine
haloperidol
clozapine
thioridiazine
ziprasidone
pimozide
droperidol

Antihistamines
terfenadine*
astemizole*

Other
probucol
cisapride

* no longer marketed in Australia

Safe prescription of drugs which prolong the QT_c interval

Drug-induced QT_c prolongation is not a universal phenomenon. Why some individuals are susceptible to this condition and others are not, is still unclear. They may possibly have a subclinical genetic mutation that is only revealed when they are exposed to certain drugs. Before prescribing a drug that is known to cause QT_c prolongation, it is important to enquire about any past history of syncope or cardiac arrest. Also obtain a detailed family history of syncope, sudden death at a younger age or congenital deafness[5] (a feature of Jervell and Lange-Nielsen syndrome). Any suspicion of a congenital long QT_c syndrome should be confirmed with a 12 lead ECG. If the ECG shows prolongation of the QT_c interval, drugs which could make it worse should be avoided.

Co-administration of two or more implicated drugs or an offending drug with a substance capable of inhibiting its hepatic metabolism should be avoided. It is important to question the patient about the consumption of non-prescription medications (such as terfenadine and astemizole) before prescribing a drug which can prolong the QT_c interval. An association with a medication that prolongs the QT_c interval should be sought in patients who present with syncope or cardiac arrest. Such a relationship should particularly be looked for in patients with no cardiac history or relevant family history.

When an implicated drug is prescribed to a high-risk patient (Table 1), it is advisable to perform a 12 lead ECG within the first few days of treatment to look for QT_c prolongation beyond normal limits. If QT_c prolongation is observed, it is advisable to stop the offending drug or switch to an alternative drug that has no such effect.

Management of torsade de pointes due to long QT syndrome

Brief episodes of self-terminating polymorphic ventricular tachycardia do not require any specific treatment apart from withdrawal of the suspect drug and correction of metabolic abnormalities. If torsade de pointes has haemodynamic consequences it requires prompt termination. Electrical defibrillation is usually effective. Infusion of magnesium or acceleration of the heart rate with rapid pacing or isoprenaline infusion can be useful as stabilisation therapy in the acute setting. To prevent a recurrence the offending drug is withdrawn and any electrolyte abnormality is corrected. Patients with proven congenital or idiopathic long QT_c syndrome who have a history of cardiac arrest, syncope, documented torsade de pointes or a family history of sudden death at a young age are usually treated with an implantable cardiac defibrillator.

Conclusion

Accurate identification of the patients at risk of QT_c prolongation and torsade de pointes is a difficult task. It is important to assess each patient before prescribing an implicated drug and then closely monitor them afterwards. Clinicians should be alert to the increasing list of drugs causing QT_c prolongation and to the presence of predisposing conditions.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 75)

5. Grapefruit juice prolongs the QT interval.
6. Women are more susceptible than men to drug-induced prolongation of the QT_c interval.

Book review

Dartnell, J. Understanding, influencing and evaluating drug use.

Melbourne: Therapeutic Guidelines Limited; 2001. 98 pages.
Price: $33, students $25.30, plus postage.*

Peter McManus, former secretary, Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee

It is appropriate that a review of Jonathan Dartnell's book appears in the pages of *Australian Prescriber*, as the subject matter encompasses a common heartland – that of working towards the more rational use of medicines in society.

There are essentially three core sections in the book, beginning with the complex environment in which prescribing decisions are made, involving such influences as attitudes, time pressures, patient expectations and commercial incentives. It also outlines the current regulatory and funding processes, although mention in Figure 1 of the technical advice from the Pharmaceutical Evaluation Section going to the Pricing Authority should more correctly be from the Economics Sub-Committee to the Pharmaceutical Benefits Advisory Committee.

The following chapter moves on to the specific strategies that can be used to improve drug use. It considers the range of interventions that have proved effective and the settings in which they have been applied. It rightly highlights the importance of skilled personnel and adequate and sustained resources.

Chapter 4 on the methods for monitoring and evaluating these strategies is particularly well researched and written. It highlights the iterative quality assurance cycle that is at the centre of drug use evaluation. The two main phases in the cycle are: firstly investigative (defining drug use, identifying problems and measuring the impact of interventions), while the second is interventional (problem solving, consensus building and activity implementation towards improving drug use).

This is not a 'how-to-do' manual but rather a detailed review of developments in the discipline of drug usage evaluation over time. It also sets the likely directions and challenges for the future in an area, given the inexorable pressure of rising drug expenditure within the health budget, whose importance will only grow.

Although this review is set in an international context, it is obvious that Australia has had a proud history of activity in this field, and this book adds to the recognition that drug use evaluation is an essential service for assuring and improving the way medicines are used.

It is a valuable resource for health professionals and students interested in drug usage evaluation. But it will also be of interest to wider groups such as epidemiologists, social scientists, health economists and administrators, whose disciplines either make significant contributions towards or could gain valuable insights from, a field that is working towards ensuring the best possible health outcomes from the medicines we use.

* For more information contact Therapeutic Guidelines Limited 1800 061 260.

Malaria prevention in the expatriate and long-term traveller

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SYNOPSIS

The prevention of malaria in expatriates and long-term travellers is complex. The traveller's doctor needs to consider the destination, the nature of the travel, the effectiveness and potential adverse effects of antimalarial medication, and the general health of the traveller. A preventative regimen can be devised combining several strategies including mosquito avoidance measures, chemoprophylaxis, emergency standby treatment and rapid self-diagnosis of malaria.

Index words: chemoprophylaxis, chloroquine, doxycycline, mefloquine.

(Aust Prescr 2002;25:66–9)

Introduction

In 1999, 3.2 million Australians travelled abroad, and travel to countries where malaria is endemic is becoming increasingly common. Each year an estimated 30 000 cases of malaria occur in non-immune travellers worldwide.[1] Many people, including aid workers, missionaries, students and healthcare workers, are travelling to work and live in rural and remote malarial regions. The estimated mortality rate for falciparum malaria in non-immune adults is up to 5%, so the medical practitioner entrusted with providing safe and suitable travel health advice will need to carefully consider the need for antimalarial prophylaxis. When the traveller's stay in an endemic area exceeds six months the issues can become quite complex.

Issues to consider

There is no perfect choice of antimalarial regimen for long-term travellers and expatriates. Prevention involves careful consideration of a number of factors, which include:

- the prevalent endemic malarial species – prophylaxis needs to be seriously considered for travel to areas with significant levels of *Plasmodium falciparum* because of its associated mortality
- the susceptibility of malarial parasites to commonly used drugs – endemic chloroquine-resistant *P. falciparum* reduces the effectiveness of chloroquine-based regimens
- the intensity of malaria transmission – the higher the intensity, the greater the need for antimalarial prophylaxis
- the risk of exposure – includes issues such as urban or rural residence, the type of accommodation and the proximity of mosquito breeding grounds
- the duration of stay – the longer one stays the greater the cumulative risk of contracting malaria, but also the greater the problems of compliance and adverse effects
- the seasonal pattern – if transmission is seasonal, prophylaxis may only be required during the malarial season
- the availability of reliable diagnostic tests and medical care for malaria – if these are lacking malaria poses a greater health risk and so there is a greater need for prophylaxis
- the potential adverse effects of the prophylactic medications – may affect their suitability for the individual traveller
- compliance issues – these need to be considered as the traveller may be better served by a less effective regimen that can be adhered to, than a more effective regimen that cannot
- the traveller's characteristics – factors such as age, pregnancy, comorbidities and drug allergies all have a significant bearing on the choice of prophylaxis
- the traveller's preference – this needs to be strongly considered as it has a vital bearing on the ultimate success of any prophylactic regimen.

These issues need to be discussed openly with the traveller. A mutually acceptable plan for malaria prevention can then be developed.

Malarial protective measures

Protection against malaria in the long-term traveller can include some or all of the following:

- mosquito avoidance measures
- chemoprophylaxis
- emergency standby treatment
- self-diagnosis kits.

Mosquito avoidance measures

These measures are the mainstay of any long-term antimalarial prophylaxis regimen. They are important in reducing the risk of contracting malaria in any traveller, but because of the many difficulties and limitations of chemoprophylaxis they are vital in long-term travellers. Adequate time must be spent with the patient to educate them about measures to reduce:

- exposure to the female Anopheles mosquito (minimise outdoors activities during its feeding time from dusk to dawn, and protect living quarters from mosquitoes)

- attracting the mosquito (avoid dark clothing, aftershaves, perfumes)
- bites (covering exposed skin areas with clothes or diethyltoluamide (DEET)-containing repellents, use of mosquito nets, permethrin impregnated clothes and nets, and using insecticides or repellents inside dwellings).

Chemoprophylaxis

The currently available medications we feel should be considered are summarised in Table 1.

Doxycycline

Doxycycline is very effective prophylaxis for chloroquine-resistant *P. falciparum*. There are no known serious adverse events from its long-term use, however daily dosing is a disadvantage and may lead to poor compliance. Vaginal thrush and photosensitivity may be troublesome adverse effects. It should be swallowed with food or an adequate quantity of water to avoid oesophagitis. An advantage of doxycycline is that it may provide some protection against infectious diarrhoea, tick-borne infections, scrub typhus, leptospirosis and some sexually transmitted diseases such as chlamydia. It is contraindicated in pregnant or breastfeeding women and children under eight years of age.

Mefloquine

Mefloquine has been extensively used and is very effective prophylaxis for people living in areas where chloroquine-resistant *P. falciparum* is endemic. Weekly administration helps compliance, and there has been no increase in adverse events with long-term use.[2] In prophylactic doses it is generally well tolerated with studies showing no significant differences in adverse events compared to other antimalarial regimens apart from atovaquone/proguanil.[2] Although severe neuropsychiatric adverse events are rare (estimated 1:10 000 users), it is not recommended for those who have underlying neuropsychological problems (e.g. epilepsy, depression). Some people experience mild neuropsychological effects such as headache, dizziness, mood changes, insomnia and vivid nightmares. As most adverse effects will occur within the first month of use, a trial of mefloquine for 3–4 weeks before departure to test its tolerability in long-term travellers is often worthwhile. We do not recommend mefloquine in the first trimester of pregnancy unless there is a significant risk of chloroquine-resistant *P. falciparum* malaria, although there is mounting evidence to support its safety. It is also not recommended for children less than 5 kg in weight.

Atovaquone/proguanil hydrochloride

This combination is highly effective prophylaxis for chloroquine-resistant falciparum malaria. Although gastrointestinal symptoms can occur it is well tolerated, and comparative studies show it to be better tolerated than mefloquine, doxycycline and chloroquine/proguanil for prophylaxis.[1] The use of the combination by long-term travellers is limited by its expense, a lack of long-term safety data and concerns about the development of resistance. We therefore currently do not routinely recommend its use for prophylaxis.

Chloroquine

Chloroquine has the advantage of improved compliance because it is taken weekly. It can be used by pregnant women and young children and is generally well tolerated. The main adverse effects are gastrointestinal upsets and a bitter taste. Long-term use is safe, however regular retinal screening is recommended after five years of continuous use as there is a potential risk of cumulative retinal toxicity. Chloroquine reduces the effectiveness of intradermal rabies vaccine necessitating vaccination by the intramuscular route.

The use of chloroquine is limited by the resistance of *P. falciparum* parasites. It may still have a role, taken alone or combined with proguanil, in areas with low resistance rates or low transmission risk (e.g. India) or where medical care is readily accessible. Chloroquine may also be used if the patient is intolerant of or reluctant to take other regimens or will have problems with compliance.

Proguanil

The use of proguanil is limited by the widespread resistance of *P. falciparum* parasites, and lack of compliance with its daily dosing. It is mainly used in combination with chloroquine.

Table 1

Characteristics of recommended antimalarial prophylactic medications

Medication	*Resistance**	*Dose*	*Frequency*	*Pregnancy*	*Children*	*Time prior to entering a malarial endemic area*	*Time after leaving a malarial endemic area*
Chloroquine	Yes	300 mg	weekly	Yes	Yes	1 week	4 weeks
Doxycycline	No	100 mg	daily	No	≥ 8 years	2 days	4 weeks
Mefloquine	Yes †	250 mg	weekly	No ‡	> 5 kg	2 weeks	4 weeks
Proguanil	Yes	200 mg	daily	Yes	Yes	1 day	4 weeks
Atovaquone/ proguanil	No	250 mg/ 100 mg	daily	No	> 11 kg	1 day	1 week

* for falciparum malaria
† resistance reported in Northern Thailand, Cambodia and Myanmar
‡ may be used in 2nd and 3rd trimesters

Long-term use is safe, but there is a low incidence of adverse effects (mouth ulcers). It can be used in pregnancy and childhood.

Emergency standby treatment (Table 2)

Long-term travellers may choose not to take chemoprophylaxis, but instead rely on mosquito avoidance measures and the use of a reliable treatment if they become infected. If symptoms suggestive of malaria develop, they either seek urgent medical attention, if available within 24 hours, or take an emergency self-treatment course effective for the local malarial resistance patterns, preferably after using a self-diagnosis malarial kit. For standby treatment to be an option, the traveller needs to be well educated about the various symptoms that suggest malarial infection, and be precisely instructed on how to take the treatment. Self-treatment should always be followed by a medical consultation as soon as possible.

Atovaquone/proguanil hydrochloride

This regimen is highly effective for all forms of malaria, there is no reported resistance and adverse effects are minimal. The combination can be used after any of the chemoprophylactic drugs. Its major disadvantage is that it is significantly more expensive than other regimens.

Mefloquine

This is an effective treatment in areas without reported resistance. A disadvantage is the high risk of adverse reactions (28–59%) associated with a treatment course.[3] There are rare reports of severe neurological disturbances such as depression, psychosis and seizures.[4] Emergency treatment with mefloquine is not recommended for people taking mefloquine for prophylaxis as there is an increased risk of adverse events.

Sulphadoxine-pyrimethamine

This offers a simple, inexpensive and well-tolerated regimen. However, it is no longer recommended in Africa, South America and South-East Asia because of increasing resistance. Uncommon, but serious, complications such as Stevens-Johnson syndrome and agranulocytosis, further limit its use.

Quinine

This is highly effective against chloroquine-resistant malaria. However, its use is limited by a high incidence of adverse effects, and a complex, prolonged regimen requiring combination with another drug.

Halofantrine

This is an effective treatment which is active against chloroquine-resistant *P. falciparum*. It is available via the Special Access Scheme, however, we do not recommend it because of its potential for fatal cardiac arryhthmias (especially in those on mefloquine chemoprophylaxis) and the availability of safer, effective alternative drugs.

Self-diagnosis kits

Relatively inexpensive kits (e.g. ICT, Parasight F, RAPIMAL) have been developed which allow the rapid self-diagnosis of malaria. They are immunochromatographic card tests that use a drop of blood to detect malarial antigens. These tests have been shown in numerous laboratory studies to be very sensitive and specific for falciparum malaria. As such they are well suited to long-term travellers who may not be taking prophylaxis, or who are taking a less effective prophylactic regimen, especially in those who are living without close access to medical care. They are easy to carry, simple to use, and give a quick result. However, studies have shown that many travellers have difficulty using them accurately in the field. These kits should therefore only be prescribed after appropriate instruction and training in their use.[5]

Table 2

Malarial standby treatment regimens

Medication	*Resistance*	*Adult dose*	*Reduce dose for children*
Atovaquone/ proguanil	No	four tablets (250 mg/100 mg) daily for three days	< 40 kg
Mefloquine	Yes *	500 mg immediately, repeated eight hours later †	< 50 kg
Sulphadoxine-pyrimethamine	Yes	three tablets (500 mg/25 mg)	< 13 years
Quinine	No	600 mg three times daily for seven days ‡	< 50 kg

* Resistance has been reported in Thailand, Cambodia and Myanmar

† If < 60 kg use 250 mg for second dose

‡ Combined with sulphadoxine-pyrimethamine (in sensitive areas, three tablets) or doxycycline (100 mg twice daily for seven days)

Summary

There is no ready solution to antimalarial prophylaxis for the long-term traveller or expatriate. Their doctor needs to be familiar with malarial epidemiology and drug resistance patterns in the area to be visited, the pros and cons of the various prophylaxis and treatment options, and the medical history and personality of the traveller involved. With this in mind, and with the provision of sufficient time for discussion with, and education of, the traveller, a suitable and safe regimen can usually be devised.

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FURTHER READING

See resources on the following web sites:

US Centers for Disease Control and Prevention www.cdc.gov/travel

World Health Organization www.who.int/ith/

Health Canada www.travelhealth.gc.ca

Department of Public Health and Travel Medicine, James Cook University www.jcu.edu.au/school/phtm/PHTM/putravel.htm

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 75)

7. Doxycycline is unsuitable for malaria chemoprophylaxis in pregnant women.
8. Mefloquine should not be used for self-treatment by someone who has been taking it for malaria chemoprophylaxis.

Dental notes

Prepared by Associate Professor R.G. Woods and Associate Professor N. Savage of the Australian Dental Association

Managing dental patients receiving warfarin therapy

Warfarin is an anticoagulant which inhibits synthesis of the vitamin K-dependent coagulation factors II, VII, IX and X. Indications for anticoagulation are increasing, and dentists will be consulted by patients taking warfarin.

The activity of warfarin is expressed using the international normalised ratio (INR).[1] A normal coagulation profile has an INR of 1.0. The desirable INR range for patients depends on the condition being treated. Patients receiving treatment for deep vein thrombosis have a lower target range than those with prosthetic heart valves.[2] The risk of bleeding increases exponentially as the INR rises. Gingival bleeding can indicate a raised INR. Oral surgery can be completed safely with an INR from 1.5 to 2.5.[3] A small study has suggested that with appropriate local measures to reduce bleeding, teeth may be removed by simple extraction with an INR of 2–4.[4] However dentists should still be cautious before they remove teeth where the INR exceeds 3.

The possibility of postoperative bleeding in patients taking warfarin concerns dentists. However, before deciding if warfarin therapy should be interrupted the risk of perioperative or postoperative bleeding must be balanced against the risk of thromboembolism.[2]

Before dental treatment a thorough medical history should be obtained including details of any condition likely to be treated with warfarin. The dentist should also consider possible drug interactions with warfarin.[5] Medications including antibiotics such as metronidazole, herbal remedies and alcohol may unpredictably alter the INR. If an interaction is considered likely or if the effect of any prescribed medication is not known, the dentist should consult the doctor supervising the patient's anticoagulant therapy. The INR should be checked before surgery.

For routine conservative dental treatment including scaling, changing an established warfarin regimen is not justified.[6] In most cases of dento-alveolar/oral surgery, including simple extraction of teeth, bleeding can be controlled in a reasonable time by minimising the extent of surgery to one site or quadrant, and using firm sutures or firm postoperative packs over the wound. Preferably surgery should be performed in the morning to facilitate postoperative observation. For extensive surgery the assistance of the physician supervising coagulation therapy is required to assist in determining whether a change of coagulation therapy is indicated.

Where the operative site is infected the use of antibiotics should be restricted to a preoperative prophylactic dose and postoperative antibiotics should be discontinued as soon as reasonable. Prolonged use of broad spectrum antibiotics should be avoided as it may change the effectiveness of warfarin by altering gut microflora compromising availability of vitamin K. Aspirin and non-steroidal anti-inflammatory drugs may also increase the risk of bleeding.

Local anaesthetics should be given cautiously avoiding venepuncture. To avoid the needles becoming barbed and tearing tissues, they should be used once only for each mucosal or skin puncture. Local vasoconstriction may be encouraged by infiltrating a small amount of local anaesthetic solution with 1:100 000 or 1:200 000 adrenaline close to the surgery site.

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The management of the heavy drinker in primary care

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SYNOPSIS

More than 55 000 Australians drink alcohol at levels that could endanger their long-term health. Each year, around 3700 die due to complications of alcohol use. In 1992, alcohol abuse was estimated to cost Australian society $145 million in direct health costs and $767 million in road accident costs. General practitioners are well placed to identify patients who drink heavily. They can treat them with the help of some of the many community services.

Index words: alcohol dependence, acamprosate, naltrexone, disulfiram.

(Aust Prescr 2002;25:70–2)

Introduction

Approximately 1 in 6 Australians who consult general practitioners are drinking above the limits recommended by the National Health and Medical Research Council (NHMRC). Many of these heavy drinkers are not identified. There are many barriers to their recognition and some practitioners may lack confidence in asking about the problem and in their ability to deal with it. Some doctors, perhaps because they saw many individuals with end-stage liver disease during their training, believe that it is pointless to try and persuade the patient to change their drinking habits or co-operate with treatment. Quite frequently the issue of alcohol is hidden among many other physical, social and psychological problems. The patient may not link these problems with their drinking.

Problem drinking and alcohol dependence

The NHMRC recommends that alcohol consumption should not exceed 28 standard drinks per week for men and 14 standard drinks per week for women. A standard drink contains approximately 10 g of alcohol (approximately the amount of alcohol in 200 mL of beer, 100 mL of wine, 60 mL of fortified wine, 30 mL of spirits). Consumption of more than 28 standard drinks per week for men or 14 standard drinks for women is considered hazardous. More than 42 standard drinks per week for men or 28 standard drinks for women is considered harmful.

Problem drinking includes:

- alcohol consumption at levels that are harmful or potentially so
- binge drinking (six or more standard drinks for a male, four or more for a female in one drinking session) which increases the risk of trauma (e.g. motor vehicle accidents or work-related accidents), interacts with medication, and leads to poor decision-making in social circumstances
- long-term risky consumption (28 or more standard drinks per week for women, 42 or more for men) which increases the risk of chronic organ damage, such as liver disease, brain damage, cardiomyopathy).

Alcohol dependence is diagnosed when three or more of the following have been present at some time during the previous year:

- a strong desire or compulsion to drink
- difficulty controlling drinking
- a physiological withdrawal state on stopping or reducing alcohol use
- evidence of tolerance
- progressive neglect of other pleasures or interests or persisting use of alcohol despite clear evidence of harm.

In 1997, 4.1% of Australians (6.1% of men and 2.3% of women) met the criteria for alcohol dependence. Among 18–24 year olds the prevalence of alcohol dependence was 9.3%.[1]

Clinical presentation

Clinical presentations that should alert the doctor to possible harmful drinking include:

- physical illness, for example liver disease, pancreatitis, peripheral neuropathy, frequent unexplained falls and fractures, hypertension, hypertriglyceridaemia
- psychological disorders, for example anxiety, depression, sleep problems
- features suggestive of alcohol abuse or dependence, for example, smell of alcohol on breath, sweating, tremor, agitation, nausea, unexplained seizures
- social problems such as family or marital conflict, work problems, motor vehicle accidents and missed appointments.

Screening and assessment

Many general practitioners ask screening questions when seeing a new patient. This provides an opportunity to include some simple alcohol screening questionnaires, such as the CAGE[2] (see Box 1) or the AUDIT[3]. AUDIT * is a 10-item questionnaire which has very few false positives or negatives. It is recommended for detecting problem drinkers in primary care. A positive response on any item on the CAGE questionnaire or a score of 8 out of 40 on the AUDIT warrants a detailed assessment.

* The full version of AUDIT is available in the electronic version of this article on the *Australian Prescriber* web site (www.australianprescriber.com).

The detailed assessment includes taking an alcohol history; the frequency of drinking, quantity, pattern and duration of consumption should be accurately recorded. It is often helpful to go through a typical drinking day from the first drink to the last to ascertain the pattern of consumption or to use the seven day recall (starting from today) in a patient who gives unclear answers. A check for physical, social and emotional problems related to alcohol consumption, as well as for dependence, is needed. This is followed by a physical examination looking for evidence of liver disease or other disorders associated with long-term alcohol use.

Laboratory tests are rarely definitive, but can often support the diagnosis. An elevated gamma glutamyl transpeptidase and an increased mean corpuscular volume are informative results. Negative tests do not exclude the diagnosis.

Brief interventions

Several large randomised control trials in primary care found that brief interventions will often reduce alcohol consumption for a proportion of patients drinking at dangerous levels.[4] The general practitioner should expect some 10–30% of their patients to change their drinking behaviours as a result of brief interventions. These consist of an assessment of alcohol intake, the feedback of information on levels of drinking and levels of harm that apply to the individual (including any physical findings and laboratory abnormalities) with clear advice to cut down or to stop drinking. These approaches can be accompanied by a leaflet such as those produced by the Australian Drug Foundation or the provision of other self-help materials.

For individuals with more serious problems, particularly significant alcohol dependence, assistance should be sought from clinicians who specialise in this field. Many general practitioners may also refer these patients to a drug and alcohol counsellor for ongoing support.

Motivating change over time

Some individuals find it difficult to respond to brief advice. A significant number will not be ready to change their behaviour. The offer of follow-up visits, the monitoring of their health status and sensitive discussion of the benefits and harms of drinking can allow the patient to be involved in decisions about drinking. It is helpful to place the emphasis on personal choice, responsibility and to give assistance in removing any barriers to change. Support of the family can help considerably in this regard. If reduced (controlled) drinking is the goal, an agreed target should be set and the patient asked to keep a daily record of consumption. Follow-up is essential. If an individual has evidence of severe dependence and particularly of organ damage, or when controlled drinking has failed, abstinence must be the clear goal and the patient may need assistance to commence this in the form of withdrawal support (detoxification).

Withdrawal can be supported by general practitioners, providing the patient has adequate support at home and when withdrawal is likely to be mild or moderate (see Box 2). Many programs have a home-based withdrawal nurse available to assist with supervising medication and monitoring the patient. Such an approach is more likely to succeed if you give:

- information about what is likely to happen during withdrawal
- a written plan to the patient and family
- an appointment for regular follow-up.

Medication is often required to modify the signs and symptoms of alcohol withdrawal and reduce the risk of seizures.[5] Diazepam in a dose of 5–10 mg, 3–4 times per day is usually adequate. The patient needs to take time off work and not drive a motor vehicle while under treatment. Vitamin B supplements in the form of thiamine 100 mg daily and other B and C vitamins for 5–6 days can be given because many patients are poorly nourished.

If the withdrawal symptoms are expected to be severe, it is preferable that withdrawal is undertaken in a residential facility with adequate nursing and medical supervision. The severity of withdrawal can be predicted by:

- a previous history of severe withdrawal (withdrawal seizures or hallucinations)
- the level of alcohol consumption over the last month. The higher the consumption the more likely that withdrawal will be severe (consumption of over 15 standard drinks daily is a reasonable guide to severe withdrawal)
- the presence of intercurrent disorders such as significant liver disease, pancreatitis, malnutrition, infection.

Box 1

The **CAGE** test consists of four questions, the letters of the acronym being the initial letters of a key word in each question:

1. Have you ever felt the need to CUT down on your drinking?
2. Have you ever felt ANNOYED by others asking you about your drinking?
3. Do you feel GUILTY about your drinking?
4. Do you ever have an EYE-OPENER in the morning?

A score of two 'yes' answers on the CAGE test indicates that drinking problems are likely.

Box 2

Management of alcohol withdrawal

- Assess the likely severity of withdrawal symptoms
- Assess psychosocial supports
- If mild to moderate withdrawal is expected, and psychosocial supports are adequate, then prescribe diazepam up to 10 mg four times daily in the first 24 hours
- Reduce dose by 10 mg daily over the next 3–4 days
- Give symptomatic medication for nausea, headache, and diarrhoea
- Manage in residential service if severe withdrawal is present or expected and if psychosocial supports are poor
- Severe withdrawal should be managed by an experienced medical practitioner or with specialist advice

Relapse and its prevention

Alcohol dependence is a chronic relapsing disorder similar to asthma, arthritis, and diabetes. Withdrawal treatment is unlikely to have any long-term benefits, but is merely the entry into treatment. Therapy and lifestyle changes should be as successful as they are in other medical disorders. Lifestyle changes include:

- avoidance of high-risk situations (places, companions, social functions) where heavy alcohol use is likely to occur
- drinking more slowly, replacing alcoholic drinks with non-alcoholic drinks
- attention to nutrition
- taking up substitute activities such as exercise, meditation and intellectual pursuits.

The patients are able to learn from lapses and relapses and recognise with hindsight what would trigger them to drink again. Negative emotional states are by far the most common triggers for relapse. Psychological and social support, and adequate treatment of anxiety and depression will help considerably in preventing relapse. Pharmacotherapy can be used as an adjuvant treatment.

Medications

Drug treatment can be used as an adjunct to other management strategies. There are three medications that may help to reduce relapse, however there is not good randomised control trial evidence to guide us in matching the medication to the patient.

Acamprosate

This drug is believed to work by modifying the effects of excitatory and inhibitory neurotransmitters on the brain, diminishing the craving for alcohol after withdrawal.[6] It is therefore usually started soon after detoxification. The recommended dose is two 330 mg tablets three times a day with meals. If the patient weighs less than 60 kg then four tablets per day is usually adequate. After one year's treatment 18% of patients will have remained abstinent compared with only 7% of patients given a placebo.[6]

Acamprosate does not interact with alcohol or benzodiazepines. Its few adverse effects include headaches, diarrhoea and less commonly, pruritis. Acamprosate is not metabolised to any extent in the liver but requires good renal function for excretion. It is not usually recommended in patients with severe renal impairment or severe liver disease and it is contraindicated during pregnancy.

Acamprosate is subsidised by the Pharmaceutical Benefits Scheme (PBS). An authority prescription is needed.

Naltrexone

This oral long-acting drug may influence drinking and craving by blocking the effects of endogenous opioids, which are part of the reward system activated by alcohol. Naltrexone reduces alcohol consumption in some patients and maintains abstinence in others. The recommended dose is one tablet (50 mg) daily commenced soon after alcohol cessation. In combination with psychosocial support it can be expected to halve relapse rates in dependent drinkers. However, after 13 weeks the rate of relapse with naltrexone (38%) is not significantly less than the rate with placebo (44%).[7]

Naltrexone does not interact with alcohol or benzodiazepines. The adverse effects include nausea which may be prominent, headache and dysphoria. Naltrexone should be avoided in patients with a known sensitivity to the drug or those with acute hepatitis or cirrhosis, as it is metabolised in the liver. It is not recommended for use in pregnancy. As naltrexone may precipitate opioid withdrawal, it is contraindicated in patients who are using opioids.

Naltrexone is available on the PBS. It requires an authority prescription.

Disulfiram

Disulfiram blocks the action of aldehyde dehydrogenase leading to an accumulation of acetaldehyde. If the patient drinks, this metabolite causes unpleasant effects such as headache, flushing, nausea, vomiting, and palpitations. Most patients require one tablet (200 mg) daily, some require more than this. It is usually restricted to individuals who have a desire for abstinence, who have failed other medications and whose medications can be supervised to ensure compliance.

Rare severe adverse effects of disulfiram include hepatoxicity and psychotic reactions. Liver function tests should be checked before and at regular intervals during treatment. Disulfiram should be stopped if a rise in liver enzymes occurs. It is also not recommended for patients with known or incipient vascular disease such as stroke, heart disease, hypertension or diabetes. It should not be given during pregnancy.

Choice of drugs

Individuals who regularly take medication 2–3 times a day and have a reasonably stable lifestyle will often do well on acamprosate. Likewise, if individuals need to take an opiate (e.g. codeine) for chronic pain, this drug is to be preferred over naltrexone.

Naltrexone is preferred if once a day medication is likely to lead to better compliance (e.g. in an individual with a disorganised work schedule), however this medication is not recommended for individuals for whom nausea and vomiting is a major problem.

Most binge drinkers do not do well on acamprosate or naltrexone (but it does not contraindicate their use). These individuals often do better on disulfiram. However, this drug is likely to be of benefit only if it can be supervised, to ensure compliance.

Conclusion

General practitioners and other primary care workers play an important role in helping the heavy drinker to change. This requires a high index of suspicion, the capacity to make a diagnosis and to support the individual in a sensitive way. Referral to specialist services may be required in those with complex problems.

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Useful sources of information and support for health professionals and patients are listed in the electronic version of this article on the *Australian Prescriber* web site (www.australianprescriber.com).

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 75)

9. Patients should start acamprosate the day before they commence detoxification.
10. Patients taking disulfiram need regular tests of liver function.

Medicinal mishaps

Carbamazepine toxicity

Prepared by Mahesan Anpalahan, Consultant Physician, Western Hospital, Melbourne

Case

A man in his forties was referred by his general practitioner for investigation of high fever associated with leucopenia, neutropenia, lymphopenia, thrombocytopenia and abnormal liver function. He had been off colour for two weeks with intermittent fevers, headaches and severe constitutional symptoms. According to the patient and his doctor's letter he had previously been well, did not smoke, consumed alcohol in moderation and was not receiving any long-term medications. He had not been overseas recently and did not have risk factors for hepatitis or HIV infections. He said his only medication was a recent prescription for cyproheptadine for poor appetite.

On examination, the patient was unwell, with a temperature of 39.8°C and there were a few petechiae on the trunk. The rest of the physical examination was unremarkable.

The patient was managed symptomatically and investigations excluded bacterial and viral infections, and haematological malignancies. Initial investigations revealed the following abnormal results:

- white blood cells 2.3 x 10^9/L (neutrophils 0.4 x 10^9/L, lymphocytes 0.5 x 10^9/L)
- platelets 28 x 10^9/L
- gamma-glutamyl transferase 789 IU/L
- alanine aminotransferase 285 IU/L
- aspartate aminotransferase 121 IU/L
- alkaline phosphatase 334 IU/L
- bilirubin 24 micromol/L.

Three days after admission during a ward round it was noticed that he had been prescribed carbamazepine 400 mg daily and his drug chart showed he had received one dose. His wife had informed the medical team about this medication two days after admission. The patient was then prescribed carbamazepine as it was felt that he was missing out on one of his usual medications.

Further enquiry revealed that the patient was prescribed carbamazepine 18 days before admission by his psychiatrist for a mood disorder. He was initially advised to take 200 mg daily and the dose was increased to 400 mg five days before admission. Before starting carbamazepine his blood tests had been normal apart from mild thrombocytopenia (platelets 121 x 10^9/L) and a low normal total white blood cell count (4.1 x 10^9/L).

With this new information it was realised that carbamazepine could have been the cause of the patient's illness. The carbamazepine was stopped and the fever settled after day four. The haematological and liver function abnormalities resolved completely over the following weeks. The bone marrow showed normal cellularity with granulomatous changes.

Comment

Febrile illness, leucopenia, neutropenia, lymphopenia, thrombocytopenia and liver function abnormalities are recognised features of carbamazepine toxicity. However, manifestation of all of these in one patient is rare. The temporal relationship, the doses of the drug used and the clinical syndrome would probably suggest that our patient had an idiosyncratic reaction. The normal cellularity of the bone marrow suggests a peripheral, probably immune-mediated, mechanism for the cytopenia.

Conclusion

This case illustrates how unwittingly breached basic medical principles may adversely affect patients. Had the full drug history been available to the treating team or if the team had been efficient in obtaining this vital information at the time of admission, the delay in diagnosis and many unnecessary investigations would have been avoided. There are many reasons why drug histories are not available, and the way a hospital

'system' operates may be responsible. When an additional drug is identified it should not be administered before its possible relevance to the patient's condition is considered.

This case once again emphasises that traditional dictum that diagnosis begins with obtaining a detailed medical history, including the drug history. It also shows that patients need to be told what symptoms to watch for if they are taking a drug with potentially serious adverse effects.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Sulesomab

LeukoScan (Australian Radioisotopes)

3 mL vials containing 0.31 mg powder for reconstitution

Approved indication: diagnosis of osteomyelitis

Prompt treatment of osteomyelitis may prevent bone necrosis. Early diagnosis is therefore important, but the infection may not show up on a plain X-ray. A technetium (^{99m}Tc) bone scan will detect most cases, but sometimes cannot distinguish infection from other causes of inflammation. Using sulesomab may overcome this problem.

Sulesomab is a monoclonal antibody which binds to antigens on the surface of neutrophils. If it is labelled with ^{99m}Tc it will reveal areas where there is intense inflammation. *In vitro* studies suggest that labelled sulesomab binds more avidly to activated granulocytes.

After the sulesomab and the ^{99m}Tc are mixed they are given by intravenous injection. Imaging can take place between one and eight hours after the injection. Most of the dose is renally excreted, with 41% of the radioactivity appearing in the urine within 24 hours of the dose.

Sulesomab has been studied in 122 patients with diabetes who were thought to have osteomyelitis secondary to foot ulcers. The performance of the scan was assessed by bone biopsy. The scan detected 74 of the 81 patients with osteomyelitis and excluded it in 23 of the 41 patients who did not have osteomyelitis. Sulesomab therefore has a sensitivity of 91% and a specificity of 56%. The sensitivity compares favourably with the technique of using radiolabelled white blood cells, which has a sensitivity of 79%. Sulesomab imaging has slightly greater accuracy (81% versus 75%) and the results are likely to influence the patients' management.[1]

Leucocyte numbers fall after the injection, but usually recover within 10 days. Other reported adverse effects include eosinophilia and rashes. The production of sulesomab involves mice, but no anti-mouse antibody reactions occurred in the trial.

Sulesomab is safer and easier to use than radiolabelled white blood cells, so it is being studied in other conditions, such as inflammatory bowel disease, where the detection of inflammation is important.

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Tegaserod

Zelmac (Novartis)

6 mg tablets

Approved indication: irritable bowel syndrome in women

Australian Medicines Handbook Section 12.2.1

The cause of irritable bowel syndrome is uncertain. As there are several possible mechanisms a variety of drugs have been used in treatment. There has been interest in drugs acting on 5-HT receptors because of the effects of serotonin in the gastrointestinal tract.

Tegaserod is a partial agonist of the 5-HT_4 receptor. It stimulates the peristaltic reflex and accelerates gastrointestinal transit. Tegaserod may therefore have a role in patients with irritable bowel syndrome who are predominantly troubled by constipation.

A double-blind trial randomised 881 patients with constipation-predominant irritable bowel syndrome to take tegaserod or a placebo for 12 weeks. Tegaserod produced statistically significant subjective improvements in bowel movements and abdominal discomfort. There was a non-significant improvement in bloating.[1]

Patients take tegaserod twice a day before meals. Its bioavailability is only 10% and this is reduced by food. Most of the dose is excreted unchanged in the faeces, but a metabolite is produced which is excreted in the urine. Liver impairment increases the plasma concentrations of tegaserod.

Adverse reactions to tegaserod most frequently involve the gastrointestinal tract. The effect of the drug will result in approximately 9% of patients developing diarrhoea. Other adverse events occur with a frequency similar to that of placebo.

There is a large placebo response in patients with irritable bowel syndrome. In the largest study of tegaserod 43.5% of patients responded, but so did 38.8% of the patients given a placebo. The therapeutic advantage of tegaserod appears to decline with time so it should be discontinued if there has been no response after one month of treatment. In patients who respond, the maximum duration of treatment should be 12 weeks. As the number of men in the clinical trails was limited, tegaserod is only approved for women with constipation-predominant irritable bowel syndrome.

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Travoprost

Travatan (Alcon)

0.004% solution in 2.5 mL dispenser

Approved indication: raised intraocular pressure

Australian Medicines Handbook Section 11.2.5

Travoprost adds to the choice of prostaglandin analogues available to treat conditions such as glaucoma. Latanoprost is already widely used for this indication (see 'New drugs for glaucoma' Aust Prescr. In press 2002).

As travoprost is an analogue of prostaglandin $F_{2\alpha}$, it reduces intraocular pressure by increasing the outflow of aqueous humour. Only a single daily dose is required as the effect lasts for at least 24 hours.

A clinical trial compared 801 patients treated with travoprost, latanoprost or timolol for a year.[1] Intraocular pressure was reduced by 30% or to below 17 mmHg in 54.7% of the patients using travoprost, 50% of those using latanoprost and 39% of those using timolol. The mean intraocular pressure with travoprost was 0.8 mmHg less than with latanoprost. Another study confirmed that travoprost has a significantly greater effect than timolol on intraocular pressure.[2]

More than 37% of patients may experience ocular hyperaemia while taking travoprost. This occurs more frequently than in patients using latanoprost or timolol. Other ocular adverse effects include itching, discomfort and changes in the eyelashes. Travoprost can also cause a slow discolouration of the iris which may be permanent.

In addition to monotherapy, travoprost can also be used as adjunctive therapy with timolol. If the patient is using two drugs they should be instilled at least five minutes apart.

While the efficacy of travoprost is similar to that of latanoprost, its local adverse effects may reduce its acceptability to patients.

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Answers to self-test questions

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

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