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Editorial

Antiviral drugs and influenza prophylaxis

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Key words: avian influenza, neuraminidase inhibitors, pandemic, vaccination.

(Aust Prescr 2007;30:30–1)

Vaccination is the most effective form of protection against influenza. The primary role of neuraminidase inhibitors such as oseltamivir and zanamivir is the treatment of symptomatic infection as their prophylactic benefit is largely restricted to specific risk groups or settings.

Influenza A is a fragile but highly infectious RNA virus which continually re-enters the human population by one of two means. The first is by the mutation of strains that are already present in the human population. These altered strains survive by evading our adaptive immunity and cause seasonal epidemics which affect between 5% and 15% of the population every year. Most strains are not highly virulent but infections result in up to 2500 deaths in Australia each year. The majority of fatalities are in people over 65 years of age and those with significant respiratory, cardiac or renal impairment.

The second means of entry is from an animal reservoir. Migratory water birds such as ducks and geese can spread new influenza A genotypes to domestic fowl and other animals.

In this issue…

Autumn is a time for influenza immunisation. Although the vaccine is usually given to people who are vulnerable to the complications of influenza it may be requested by healthy people. Paul Dugdale examines whether or not immunising healthy people is beneficial. Despite the stockpiling of antiviral drugs to deal with avian influenza, David Siebert says that vaccines will offer more effective prophylaxis.

Anticoagulation is effective prophylaxis after deep vein thrombosis, but recurrent thrombosis can be difficult to diagnose. Harry Gibbs recommends a duplex ultrasound scan when warfarin therapy is completed.

Warfarin is one drug for which brand substitution is not recommended, however there are generic equivalents for many other drugs. Andrew McLachlan, Iqbal Ramzan and Robert Milne dispel some of the myths about bioequivalence and the risks of generic drugs.

An avian outbreak may produce variants that infect humans through contact with the faeces of sick birds. At least one major re-assortment (antigenic shift) of the genes for the viral surface proteins (H and N antigens) is required to produce forms virulent to non-immune humans. If these new variants have or acquire additional mutations that allow efficient human-to-human transmission, a global human epidemic (a pandemic) may ensue.

There have been three pandemics in the last 100 years. In 1918 the 'Spanish flu' killed approximately 2.5% of those it infected – more than 20 million people. This was up to fifty times more virulent than the subsequent pandemics in 1957 and 1968.

The influenza A epizootic H5N1, currently in wild and domestic fowl (bird flu), appears to be highly virulent. Half of the documented human cases have been fatal. Viral derivatives that establish human-to-human transmission may be less lethal if their virulence is sacrificed for transmission efficiency, but we cannot predict their virulence. Since 30–80% of current H5N1 isolates from infected patients are resistant to amantadine, neuraminidase inhibitors are both the first-line treatment and the first choice for prophylaxis in unvaccinated people exposed to the new virus.[1]

The efficacy of neuraminidase inhibitors in the treatment of severe H5N1 infections has been discouraging. This is often due to the long interval between the recognition and treatment of human infections. Early treatment appears to be beneficial.[2] The H5N1 virus can spread beyond the respiratory tree in some people. Shedding can occur at up to 10 times the rate of endemic viruses and may be prolonged for several days. This makes the duration of acute treatment difficult to gauge, but animal studies show that it may have to be for at least 10 days. Inhaled zanamivir is untried and may only be suited to prophylaxis.

In the prophylaxis of influenza, neuraminidase inhibitors are no more than 35–75% effective. The efficacy of oral oseltamivir 75 mg daily against symptomatic influenza is 61%, or 73% for 150 mg daily. This benefit is statistically independent of the dose used. Inhaled zanamivir 10 mg daily is 62% efficacious.[3] By contrast, vaccination against endemic human influenzas is 70–90% effective depending on the antigenic 'match' with the circulating strain.[4,5]

In institutional settings such as nursing homes oseltamivir is up to 92% effective as a prophylactic drug. It has also been shown to prevent lower respiratory tract complications in laboratory proven influenza cases.

Neither oseltamivir or zanamivir prevents asymptomatic infection nor do they have any prophylactic benefit in patients with 'influenza-like illnesses'. Viral resistance to both drugs is relatively uncommon so the lack of prophylactic efficacy appears to be due to other factors.[1] The most common adverse effect is dose-dependent nausea from oseltamivir.

Prophylactic drugs are inherently inferior to vaccines because of the continual need to re-supply, distribute and manage their use. In addition, viral characteristics, such as virulence, transmissibility and drug susceptibility, change in the face of the selection pressure caused by drug use. Judicious use of drug prophylaxis will not prevent pandemic spread, but it can buy time to manage the rate at which outbreaks take hold, allowing the scale-up of vaccine production. While vaccine production is technically difficult and will take a minimum of three months to activate, once there is an effective product, one or two doses will provide a high degree of protection.[6]

Due to the limited size of prophylactic drug stockpiles and their relatively low efficacy compared with vaccines, there are two drug strategies that make sense for managing a pandemic. First, confine the use of stockpiled drugs to the treatment of index cases and limited prophylactic courses for key personnel, including front-line healthcare workers and emergency service providers. Secondly, deploy drugs to interrupt early local transmission. 'Ring-fencing' and extinguishing minor outbreaks are possible, if the basic reproductive number (R_0*) is not high. This may be most valuable where a partially protective vaccine is available or partial immunity develops in the population.

Any strategy for the deployment of these drugs must be inferred from the known research and epidemiological data as prophylactic drug trials will be of limited power while the transmission rate remains low.[2,7]

Effective personal hygiene has a role in preventing the spread of disease, especially in hospital and occupational settings where hand washing and protective clothing are used. Although hygiene and public health measures are less effective in containing the spread of the virus in the general population they will be an important addition to prophylactic drug strategies.

Antivirals will be adjuncts to an effective vaccine, provided one becomes available soon after human-to-human transmission is identified. Unfortunately, only wealthy countries will have access to drug stockpiles and the capacity to expand the production of antiviral drugs and vaccines.

* In general population theory, R_0 describes the expected number of new infected hosts that one infected host will produce during his or her period of infectivity, in a large population that is fully susceptible.

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Further reading

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Conflict of interest: none declared

Letters

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

Fenofibrate–warfarin interaction

Editor, –The 'Medicinal mishap' about the fenofibrate–warfarin interaction (Aust Prescr 2006;29:166) perpetuates the myth that protein binding interactions are clinically relevant. Unless the clearance of unbound drug is saturable (not the case with fenofibrate), protein binding displacement interactions do not lead to sustained increases in steady-state concentrations of unbound drug if the drug has a low clearance (as is the case with warfarin).[1,2] It is the unbound concentrations of drug that correlate with the pharmacological effect. The only determinant of steady-state unbound concentration of drug, apart from the dose rate, is its clearance. This is generally dependent on hepatic metabolism or, in some cases, renal clearance or a combination of both.

Fenofibrate is an analogue of clofibrate, so information about clofibrate is relevant to the fenofibrate–warfarin interaction. Clofibrate potentiates the anticoagulant activity of warfarin but not because of displacement from plasma proteins. It causes a very small increase in the free fraction of warfarin but 'this pharmacokinetic interaction does not account for the clinical interaction between the two drugs, since free warfarin concentrations are unchanged'.[3] The mechanism of the interaction is unknown but is likely to be related to warfarin's effect on the synthesis of clotting factors. The metabolism of clofibrate is also a significant consideration. Clofibrate is hydrolysed to the active metabolite, clofibric acid, which is largely metabolised to its ester glucuronide. In a process known as 'futile cycling', ester glucuronides of clofibric acid and several other active drugs are retained in renal impairment. Their resultant hydrolysis yields higher than average plasma concentrations of the active drug. This futile cycling in renal failure with marked retention of clofibric acid has been reported in animal studies.[4]

The patient in the case had a very low creatinine clearance (17 mL/min). We suggest that there was 'futile cycling' of fenofibric acid, the active metabolite of fenofibrate, leading to high plasma concentrations and a substantial interaction with warfarin. Five other cases of a marked potentiation of warfarin by fenofibrate have been reported.[5,6] Unfortunately, the patients' renal function was not recorded but three were elderly with multiple diseases so they may have had substantial renal impairment.

The important point is that protein binding displacement interactions between any pair of highly bound drugs do not alter their unbound concentrations and, consequently, increased effects are most unlikely. This applies particularly to drugs with low clearances, such as warfarin.

We agree with the advice that closer monitoring of patients on warfarin is needed when starting fenofibrate to avoid excessive anticoagulation. Particular care is necessary if the patient has renal impairment.

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Dr RA Ghiculescu, author of the case, comments:

I concur that protein binding is usually of little clinical importance. Many so-called protein binding displacement interactions are reported but the weight of evidence shows this is not the mechanism to explain clinically relevant drug interactions. However, the reference I cited does report such a

phenomenon with fenofibrate itself and was therefore quoted as one of two possible mechanisms for this interaction. Apart from protein binding displacement the other mechanism was the probable inhibition of the CYP450 2C9 by fenofibrate.[1]

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Brand substitution was not the problem

Editor, –The title of the Medicinal mishap 'Brand confusion with digoxin' (Aust Prescr 2006;29:153) was misleading. It unfairly blames the 'proliferation of new brands' for the error that was made.

The patient's usual medications included warfarin and digoxin 62.5 microgram (Lanoxin PG) but he was given 250 microgram tablets (Sigmaxin). He consequently suffered digoxin toxicity.

Brand proliferation is a fact of life and is not new. It is the basis of substantial cost-savings for individuals and for governments. All of the brands must be of good quality and must be interchangeable. In Australia, the Therapeutic Goods Administration undertakes checks during the registration process. Given that Lanoxin PG and Sigmaxin PG are marked as interchangeable brands of digoxin in the Schedule of Pharmaceutical Benefits, there was no error in dispensing a different brand, provided that the patient had consented and the prescriber had not checked the box on the prescription that reads 'Brand substitution not permitted'. The error in this case was selection of the wrong strength: Sigmaxin rather than Sigmaxin PG.

A better target for our wrath is the case of the Coumadin and Marevan brands of warfarin. The product information for the two brands states 'Do not interchange Coumadin and Marevan. Bioequivalence between these two brands of warfarin has not been established'. Clinical reports suggest these brands are not bioequivalent.[1,2,3,4] A pharmacoeconomic analysis concluded that use of one brand only is 'economically attractive'[5] given the costs of morbid events.

The argument that 'to withdraw one brand would seriously disadvantage those patients who are stabilised on it'[6] has been advanced for years and serves to perpetuate the current unsatisfactory situation. It's time to bite the bullet and withdraw one of these inequivalent brands of warfarin, even if short-term inconvenience results for some patients and their prescribers in the form of monitoring the changeover.

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Injunction impedes independent information

Editor, –The editorial about the injunction (Aust Prescr 2006;29:120) noted that the judge felt the public interest would be best served by the regulatory authorities examining the evidence supporting the efficacy of *Ginkgo biloba*.

In June 2006 a complaint about the promotion of Tebonin brand of *Ginkgo biloba* was sent to the:

- Therapeutic Goods Administration (TGA) which has jurisdiction over the pack and package insert
- Complaints Resolution Panel which deals with advertisements in printed media and the internet
- Complaints Resolution Committee of the Complementary Healthcare Council of Australia which investigates complaints about pharmacy posters, leaflets, fax and direct mail.

The TGA response was classified 'commercial-in-confidence'. However, the TGA did note that the indications for Tebonin changed in July 2006 from 'For the symptomatic relief of tinnitus' to 'May assist in the management of tinnitus'.

In October 2006 the Complaints Resolution Committee suggested that issues relating to the product's efficacy should be referred to the TGA.

In November 2006 the Complaints Resolution Panel determined that promotional statements about Tebonin made in print media and the internet breached the Therapeutic Goods Advertising Code. Schwabe Pharma Australia was requested to withdraw the advertisements from further publication and not use similar representations in the future.[1]

In December 2006 the Tebonin pack and insert continued to state that Tebonin was 'an effective treatment' for tinnitus. Print advertisements, although slightly changed, still claimed the product offered 'relief' from tinnitus without the TGA qualifier 'may'.[2] A number of Australian internet pharmacy sites also continued to promote Tebonin as an 'effective treatment' for tinnitus.

The Tebonin case suggests that confidence in Australian regulatory authorities may be misplaced.

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Drug dosing adjustment in people with reduced GFR

Editor, – The article 'Prescribing in renal disease' (Aust Prescr 2007;30:17–20) is a useful contribution to the complex issues currently facing prescribers. There is wide agreement that determining kidney function by measurement or assessment of glomerular filtration rate (GFR) is preferable to using the serum creatinine alone, for all clinical purposes (including drug dosing).

The vast majority of prescribing in Australian general practice occurs without knowledge of the patient's kidney function. When an assessment of kidney function is available it is now usually in the form of an automatically generated eGFR (estimated GFR) derived from the Modification of Diet in Renal Disease (MDRD) study. Few, if any, practitioners routinely calculate GFR by using the Cockcroft-Gault equation or measure creatinine clearance on all patients.

After considering these matters, a meeting of the Australian Creatinine Consensus Working Group agreed that the following recommendation should be promoted to Australian prescribers:

> Decision making in drug dose adjustment in people with chronic kidney disease is enhanced by an assessment of kidney function based on GFR rather than a serum creatinine concentration alone. In most out-of-hospital settings (particularly general practice) where an eGFR (MDRD) is on hand and no other measure of GFR is known or readily accessible, it is clinically appropriate to use eGFR to assist drug dosing decision making.
>
> However, for critical dose drugs, particularly in a hospital setting, it remains important to adhere to the published recommendations that usually involve the use of the Cockcroft-Gault equation to estimate GFR, or to measure creatinine clearance in order to amend dosing for renal function.

The product information guiding dose adjustment in patients with reduced GFR is often permeated with imprecise and undefined terminology (such as renal impairment, mild/moderate renal insufficiency) and is in need of a major overhaul with an emphasis on the recently introduced staging of chronic kidney disease by GFR reduction. There is also variability in the recommended use of the Cockcroft-Gault equation with regard to use of estimated ideal body weight from height and build, and there has been no update to the formula to account for re-standardisation of creatinine assays.

Automatically generated eGFR using the MDRD formula more closely correlates with true GFR than an estimate based on Cockcroft-Gault (particularly in the key clinical area of GFR reduction between 15 and 60 mL/min/1.73m^2) and both are better than a timed clearance. At the very least the eGFR alerts treating doctors to the possibility of reduced renal function prompting the use of other estimates if desired. In the future it is likely that eGFR will be the major basis for adjusting doses for people with reduced GFR. At present it appears reasonable and indeed preferable, in the absence of any other measure of kidney function, to use the eGFR (recognising its limitations) as a guide to prescribing particularly with non-critical dose drugs.

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Dr Randall Faull and Ms Lisa Lee, authors of the article, comment:

We are pleased there is agreement that prescribing of critical dose drugs should continue to follow published recommendations which usually use the Cockcroft-Gault equation to estimate GFR. We are however concerned about the message that body size is unimportant when considering the dosage of drugs. The automatically reported eGFR does not consider body size in its calculation, and so while it functions very well as a screening (and alert) device for renal impairment, it fails to differentiate between large and small people who will have markedly different absolute GFRs. From first principles it is the absolute GFR upon which the drug dosage should be based. The Cockcroft-Gault equation is accessible to general practitioners. Along with a calculator for ideal body weight, it is readily available on Medical Director, a computer program which is widely used by Australian general practitioners. The eGFR is an evolving tool and the MDRD equation can be adapted to consider body weight. In the future that may become the appropriate standard recommendation for calculating drug doses.

Influenza vaccination for healthy adults

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Summary

Seasonal influenza is a vaccine preventable disease that affects around 20% of the population each year. In healthy adults it is usually a brief illness, often resulting in a short amount of time off work. Influenza vaccination for healthy adults is recommended by the National Health and Medical Research Council, but is not universally funded through the National Immunisation Program. It is funded by a number of employers, particularly in health and aged care facilities. Healthy people who are not covered by the National Immunisation Program or their employers must pay for the vaccine themselves. Vaccination partially protects healthy adults from the disease with around six out of a hundred people vaccinated experiencing a benefit. It produces an additional benefit for those they care for, if they too have been vaccinated. The economic and perceived benefit of influenza vaccination for all healthy adults is related to the setting in which they live and work. This makes personal choice an important component of the decision to vaccinate, and reduces the strength of arguments to publicly fund vaccinations for healthy adults.

Key words: healthy adults, influenza vaccination, public funding.

(Aust Prescr 2007;30:35–7)

Introduction

The National Health and Medical Research Council's (NHMRC) Australian Immunisation Handbook[1] contains a general recommendation for annual vaccination against influenza for 'any person who wishes to reduce the likelihood of becoming ill with influenza', using the vaccine composition recommended by the World Health Organization (WHO) for the current southern hemisphere winter. The handbook goes on to make specific recommendations for vaccination of the following groups:

- everyone 65 years and older
- people with chronic illness
- residents of long-term care facilities
- contacts of people who have a high risk of developing complications from influenza, including household members, healthcare providers and staff of long-term care facilities.

These groups are among those who qualify for free vaccination under the National Immunisation Program.

The US Centers for Disease Control and Prevention currently recommend vaccination for similar population groups.[2] Ontario, Canada, is into its fifth year of a free influenza vaccination program for everyone aged six months or more. A review of this program has shown it is 'feasible, encourages vaccination in targeted and high-risk groups, and improves pandemic preparedness' and should lead to reductions in all measures associated with the burden of disease for influenza.[3] Clearly, there is argument about the merits of providing influenza vaccination to the healthy adult population.

Seasonal influenza

The family of influenza viruses includes many subtypes. The virus rapidly mutates and re-assorts to produce new variants. Influenza circulates endemically around the globe and the most successful subtypes produce seasonal epidemics. It is spread by respiratory droplets and fomites*. Previous exposure will protect against reinfection with the same subtype and may provide partial protection against different subtypes.

The case definition of 'influenza-like illness' is presentation with fever, cough and fatigue.[4] The disease itself is quite variable including asymptomatic (but contagious) infection, short-lived upper respiratory tract symptoms including coughing and sneezing, debilitating systemic effects such as fever, fatigue, generalised aches and pains that may last up to two weeks, through to primary viral pneumonia and secondary infections. Life-threatening complications are more common in people with chronic illness, the elderly and young children.

The effect of influenza on a population is measured by various means including the notifications of laboratory-confirmed influenza (recognising that only a small portion of cases have isolates tested), consultation rates for influenza-like illness, absenteeism from work and hospitalisation and mortality data. In 2005, Australia had 4575 cases of laboratory-confirmed influenza, with a peak rate of 40 influenza-like illness cases per 1000 general practice consultations in August 2005 (observed by a national network of 29 general practices). The 'all causes' weekly absenteeism rate, a non-specific index of

* objects or materials which are capable of transmitting infection

influenza activity, peaked in winter to 1.21%, up 0.4% from the annual average of 0.81% (based on Australia Post as a representative workforce).[4] In 2003–04, the national rate for hospital separations for influenza and pneumonia was 0.7 per 1000 population.[5] In 2004, 18 305 people died from influenza and pneumonia, which was the underlying cause in 2.6% of all deaths.[6] In summary, influenza epidemics occur every year in winter, often affecting 20–25% of the population.

Vaccination

The virological epidemiology of the different influenza strains is reasonably well understood. Effective vaccines with negligible serious adverse effects are made and available for circulating strains within months. This sets up the conditions for a public vaccination strategy.

The arguments against mass vaccination are that it is required annually, the attack rate varies widely from year to year and place to place, the vaccine does not protect against all cases of clinical influenza, and healthy adults that do get influenza rarely succumb to serious complications.

Influenza vaccination commonly causes local pain and swelling at the injection site (greater than 10%). It can also cause a mild influenza-like illness including fever and myalgia commencing a few hours after vaccination and lasting 1–2 days (1–10%). These adverse effects may put people off being vaccinated, especially if they have experienced them before. Treatment with paracetamol is effective.

For the southern hemisphere in 2007, the WHO recommended a vaccine composition that should protect against: A/New Caledonia/20/99(H1N1)-like virus, A/Wisconsin/67/2005(H3N2)-like virus and B/Malaysia/2506/2004-like virus.[7] This mix is available commercially from four pharmaceutical companies.

Currently, a live influenza vaccination delivered by nasal spray is undergoing phase III trials. If the trials are successful, it can be expected to have greater patient acceptability compared to vaccination by injection.

Evidence for vaccination

While the NHMRC has recommended that vaccination be provided to everyone who wishes to reduce their likelihood of becoming ill with influenza, it could not justify universal public vaccination programs for healthy adults. The reasoning for this is that the beneficial effect for the population group is relatively small. However, the benefit varies according to the setting that population members are within.

For healthy adults in the general community setting, a Cochrane review (of 25 studies involving almost 60 000 people) found that the recommended inactivated parenteral vaccines had a vaccine efficacy of 70% against the strains for which they were formulated. These vaccines have an efficacy of 25% against clinical influenza, resulting in a 6% reduction in people experiencing clinical influenza.[8]

This means that in a season where influenza will cause illness in say 24% of the unvaccinated population, vaccination will reduce the risk of influenza by 6% from 24% to 18% (6 is 25% of 24). Out of every 100 people vaccinated, 6 will benefit and 94 will not. Put another way, 17 people need to be vaccinated for one to benefit.

Vaccination of healthy adults caring for people at risk of complications from influenza aims to reduce the exposure of those they care for to influenza. However, a Cochrane review of this strategy in aged-care settings found staff vaccination was only associated with reduced influenza-like illness in patients when the patients were vaccinated too.[9]

We can surmise that in the residential care setting, vaccination of staff reduces the patient's **chance of being exposed** to the influenza virus, but vaccination of patients, which reduces the exposed patient's **chance of becoming infected**, is also required to synergistically reduce patient infection rates.

Should healthy adults be vaccinated?

The upshot of the available evidence and expert recommendations is that at a personal level, it is quite reasonable for healthy adults not to be vaccinated against influenza, with the expectation that if they do contract influenza it will be a brief illness from which they will fully recover. Of course, many healthy adults will have views on how much they wish to avoid influenza and this may be influenced by forthcoming events such as international travel, weddings, exams and conferences.

However, when healthy adults are in the setting of caring for people who have a high risk of complications from influenza, the duty of care makes for a clear-cut recommendation to vaccinate.

While such a 'settings' approach to clinical decision-making is intuitively sensible, it is often not given the prominence it deserves in public health thinking. Nevertheless, it is central to understanding the difference between the NHMRC recommendation that all adults who wish to lower their risk of influenza should consider vaccination, and the lack of coverage of healthy adults (without caring responsibilities) in the free National Immunisation Program.

Funding for vaccination

For healthy adults who work, vaccination is reasonably cost-effective, and may even be cost saving if more than two and a half days of work are lost for every episode of influenza.[10] This makes it reasonable for employers to offer influenza vaccination to their staff, as many employers now do. Self-employed and casually-employed people who do not receive sickness benefits may be particularly attracted to vaccination.

One reason for public funding of health care for those who can afford it, is that individuals are not readily able to decide for themselves what health care is in their best interests. Where individuals can decide for themselves, the arguments for

public funding for this group become significantly weaker. For healthy consenting adults, their individual judgement about the importance of avoiding influenza is central to determining the value to them of being vaccinated. This increases the likelihood that adults with the means, or their employers, will pay for vaccination, and reduces the imperative for governments to take over the responsibility of funding vaccination for this group.

Future directions

Influenza vaccination policy, like the influenza virus, evolves at a relatively rapid rate. Emerging evidence from the Ontario experience of universal vaccination will be closely assessed by policy makers, including the NHMRC in its review of the National Immunisation Handbook and the US Advisory Committee on Immunization Practices, which is currently considering universal influenza vaccination. If this is recommended, vaccine production will need to be increased considerably.

A key issue is whether indirect costs of illness (for example, days off work) will be considered in cost-effectiveness calculations used to develop the case for public funding. If these costs are included, it is likely that cost-effectiveness ratios will improve significantly. Making public funding available on this basis will amount to a slight increase in taxation funding and a slight increase in health expenditure, and should result in slightly improved national productivity. Whether our governments are ready to accept arguments that preventive health expenditure is a useful public investment that drives productivity growth, remains to be seen.

Acknowledgement: Meagan Morrison provided research assistance in the preparation of this article.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 55)

1. The influenza vaccine protects 90% of healthy adults against clinical infection with influenza.
2. Vaccinating staff working in aged care facilities reduces influenza-like illness in unimmunised residents.

Dental notes

Prepared by Dr M McCullough of the Australian Dental Association

Influenza vaccination for healthy adults

Very few dentists fall into the groups eligible for free vaccination under the National Immunisation Program. However, it is likely that all dentists working in both private and public practice are routinely having an annual vaccination against influenza. This decision to be vaccinated and the discussion about it, is likely to strongly influence work colleagues, dental nurses, oral hygienists and therapists, as well as patients.

The diagnosis of recurrent deep venous thrombosis

Harry Gibbs, Associate Professor of Medicine, University of Queensland, and Director, Department of Vascular Medicine, Princess Alexandra Hospital, Brisbane

Summary

Duplex ultrasound is the preferred investigation for the diagnosis of initial and recurrent deep venous thrombosis. The contralateral leg should be scanned when thrombosis is diagnosed as it is bilateral in 30% of cases. At the completion of anticoagulant therapy a venous duplex scan should be performed to establish a new baseline. Recurrent deep venous thrombosis can subsequently be diagnosed if there is a 5 cm increase in the extent of residual thrombus or an increase in the compressed thrombus diameter of more than 2 mm. If there is any doubt about the presence of a recurrent thrombosis serial ultrasound should be used.

Key words: d-dimer, ultrasound, venography.

(Aust Prescr 2007;30:38–40)

Introduction

Deep venous thrombosis (DVT) is a common cause of mortality and morbidity with an annual incidence of about 1/1000. It may be complicated by pulmonary embolism and the post-thrombotic syndrome.

About 30% of patients with a proximal thrombosis (involving the popliteal or more proximal veins) who do not receive anticoagulant therapy will develop symptomatic pulmonary embolism within 30 days. Symptomatic pulmonary embolism is dangerous as 25% of cases are fatal. Post-thrombotic syndrome is characterised by pain and swelling of the affected limb and occurs in 50–60% of patients with symptomatic DVT. Graduated compression stockings relieve the symptoms in many cases. However, about 10% of patients will have symptoms that impair their quality of life in spite of compression stockings and about 4% will develop venous ulcers.

Anticoagulation is highly effective in preventing death from pulmonary embolism in patients with DVT. It is indicated for all proximal DVTs and for most cases of symptomatic distal DVT. Therapy begins with low molecular weight or unfractionated heparin followed by long-term treatment with a vitamin K antagonist such as warfarin.

The problem of recurrence

Anticoagulation is highly effective in preventing recurrent DVT, but is associated with a risk of major bleeding of about 3% per year. It is therefore usual to stop anticoagulation six months after a first episode of DVT. Thereafter, DVT is often a chronic and relapsing condition with recurrences in about 30% of patients within eight years. Recurrent DVT is important as it increases the likelihood of post-thrombotic syndrome and is associated with pulmonary embolism.

Risk factors for recurrence

Several risk factors predict the recurrence of DVT. The most powerful of these is whether or not the first thrombosis was provoked by a transient risk factor such as surgery. The annual recurrence rate is 1–3% in patients whose DVTs were provoked by transient risk factors, compared with 8% in patients whose DVTs were unprovoked. Certain clinical, laboratory and imaging factors are also important predictors of recurrence.

Clinical predictors of recurrence include male gender, increasing age and body mass index, active malignancy and neurological disease with paresis of the extremities. Laboratory abnormalities that predict recurrence include thrombophilias such as antiphospholipid antibodies, deficiency of protein C, S or antithrombin and the Factor V Leiden or prothrombin gene mutations. The commonest of these abnormalities are the Factor V Leiden and prothrombin gene mutations but these have only a very weak influence on recurrence. Extensive residual thrombus on imaging studies is also a risk for recurrence.

At present, indefinite anticoagulation is usually recommended after an otherwise unprovoked first DVT in patients with active malignancy or with certain rare thrombophilias (including the presence of antiphospholipid antibodies, homozygosity for the Factor V Leiden and prothrombin gene mutations and multiple thrombophilias). These conditions have particularly high recurrence rates. Although other patients usually stop after six months, studies of the role of longer-term anticoagulation in other sub-groups are ongoing.

Diagnosis of first DVT

The clinical diagnosis of DVT is inaccurate as other clinical conditions may mimic it. Anticoagulant therapy is potentially dangerous as it causes major bleeding in about 5% of cases

of acute DVT within the first three months and 3% per year thereafter. Objective testing is thus required to establish or refute the diagnosis of DVT before treatment. Anticoagulation should not be commenced for suspected DVT without confirmatory objective testing, except in extreme circumstances.

Imaging

Contrast venography was regarded as the gold standard for the diagnosis of DVT, but requires intravenous contrast media and exposes the patient to ionizing radiation. As duplex ultrasound is readily available, safe and accurate it has essentially replaced venography as the first and definitive diagnostic test. For proximal DVT the sensitivity and specificity of duplex ultrasound are greater than 90%.

Duplex ultrasound is the first-line investigation for the vast majority of patients with suspected DVT. The diagnostic criterion for DVT is incompressibility of the vein when applying gentle pressure with the overlying ultrasound transducer. Additional findings with DVT include the presence of echogenic material within the vein lumen, incomplete filling of the vein with colour Doppler, and lack of the usual variation of the venous flow with respiration.

Perform a comprehensive duplex ultrasound scan when anticoagulation is ceased

Duplex ultrasound is operator dependent. Ideally the scan should be performed by a sonographer accredited by the Australasian Sonographer Accreditation Registry who is supervised by a clinician experienced in reporting vascular ultrasound. A comprehensive duplex ultrasound should examine the veins continuously from the inguinal ligament to the ankle. This is effective for excluding DVT so it is safe to withhold anticoagulation if the scan is negative. A positive result is adequately specific for DVT to indicate anticoagulant therapy.

Duplex ultrasound of the contralateral leg should be performed in all confirmed cases as DVT is bilateral in about 30% of patients. This helps avoid diagnostic confusion at a later stage if symptoms then develop in the other leg.

Computerised tomography and magnetic resonance venography are expensive. They offer no tangible advantage over duplex ultrasound.

Laboratory tests

D-dimer is a thrombus breakdown product that is almost always detected in the blood of patients with DVT. Sensitive d-dimer assays (using whole blood or ELISA methods) have been used to exclude DVT and reduce the need for imaging. Patients who have a low probability of DVT, as assessed by a standardised clinical scoring system such as the Wells score[1] (Table 1), and who also have a negative d-dimer test can safely have anticoagulation withheld. D-dimer is not able to exclude DVT in patients with a high Wells score so those patients require diagnostic imaging.

There are many causes of a positive d-dimer including infection, malignancy, acute coronary syndromes, recent surgery, pregnancy and severe peripheral artery disease. A positive d-dimer is therefore of no diagnostic value. Overall, about 30% of patients in whom DVT is initially suspected will have it excluded by a low Wells score and negative d-dimer testing. In practice, however, d-dimer testing is often performed inappropriately and without reference to the Wells score. For these reasons and because duplex ultrasound is safe, inexpensive and usually accessible, I favour it over d-dimer as the initial test in all patients with suspected DVT.

Diagnosis of recurrent DVT

Duplex ultrasound is the first-line investigation but the diagnosis of recurrent DVT can be difficult. The diagnostic criteria for recurrent DVT include incompressibility of a previously normal segment of vein or an increase in the compressed diameter of a segment of vein with previously documented thrombus. Both of these criteria require knowledge of the extent of residual thrombus that is present at the completion of anticoagulant therapy. It is therefore critical to perform a comprehensive duplex ultrasound scan when anticoagulation is ceased, to establish a new baseline against which further scans can be compared. The extent of residual thrombus should be recorded by reference to anatomical landmarks such as the upper border of the patella and the

Table 1

Wells score for clinical assessment of deep venous thrombosis (DVT) [1]

Clinical feature	Score
Active cancer	1
Paralysis, paresis or plaster immobilisation of the lower extremities	1
Bedridden for three days or major surgery, within four weeks	1
Localised tenderness along the deep venous system	1
Entire leg swollen	1
Calf diameter more than 3 cm larger on the symptomatic side	1
Pitting oedema greater on symptomatic side	1
Collateral nonvaricose superficial veins	1
Alternative diagnosis more probable than DVT	–2

Probability of DVT:

low	0
moderate	1 or 2
high	3 or more

saphenofemoral junction. For example, residual thrombus might be reported to extend from 5 cm below the upper border of the patella to 3 cm below the saphenofemoral junction. The compressed diameter of the vein should also be recorded at a number of points. This detailed information is required to interpret the results of subsequent scans and should be provided in the ultrasound report. A detailed diagram of the extent of residual DVT provides a rapid visual assessment of the required information and is particularly useful for subsequent comparison.

A recent study has questioned the reproducibility of duplex ultrasound examinations and has suggested that a change of thrombus length of more than 9 cm is required to accurately diagnose recurrent DVT.[2] This observation has not been tested in clinical outcome studies and requires replication. Currently, it is my practice to diagnose a recurrence if there is an increase in the length of thrombus of more than 5 cm in a duplex ultrasound scan performed by an experienced sonographer. An increase in the diameter of the vein by more than 2 mm when compressed by the ultrasound transducer also suggests recurrence. Finally, acute DVT tends to have a less echogenic appearance than chronic thrombus although this observation is subjective and has not been studied in comparative or outcome trials. If there is any doubt as to whether there is recurrent DVT then I perform two more scans over the next two weeks. If there is no change in these, then I withhold anticoagulation and only arrange further investigations if there is a significant clinical change. As duplex ultrasound is safe and inexpensive, I have a low threshold to undertake this surveillance program.

Venography may be difficult to interpret in recurrent DVT. Computerised tomography and magnetic resonance venography have no established role.

A negative d-dimer may be of value in excluding recurrent DVT, but is less well-tested than for a first thrombosis. A positive d-dimer test neither confirms nor refutes the diagnosis of recurrent DVT, but necessitates further imaging investigations.

Additional tests

If the patient was thoroughly investigated at the time of their first deep venous thrombosis, there is no need to repeat all the specialist tests. The need for additional tests is guided by the history, examination and basic investigations. If the platelet count is persistently elevated, a myeloproliferative disorder may need to be excluded. A recurrent thrombosis that occurs during anticoagulation could be related to an undetected malignancy.

Conclusion

Recurrent deep venous thromboses can be difficult to diagnose. Identifying a recurrence is easier if the patient had a duplex ultrasound scan when they completed the anticoagulant therapy for their first thrombosis. Although its accuracy depends on the skill of the operator, duplex ultrasound is safe and relatively inexpensive. It should be the first-line investigation for recurrent deep venous thrombosis.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false

(answers on page 55)

3. Magnetic resonance venography is now the gold standard test for the diagnosis of recurrent deep vein thrombosis.
4. After anticoagulant therapy for deep vein thrombosis is completed, the venous system should be assessed by duplex ultrasound.

Frequently asked questions about generic medicines

Andrew J McLachlan, Professor of Pharmacy (Aged Care), Centre for Education and Research on Ageing, Concord Repatriation General Hospital and Faculty of Pharmacy, University of Sydney; Iqbal Ramzan, Professor of Pharmaceutics, Faculty of Pharmacy, University of Sydney; and Robert W Milne, Associate Professor, Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide

Summary

In Australia, generic products must be bioequivalent to the innovator brand name product, or the market leader, before they are approved. Australia has rigorous scientifically-based evaluation procedures for generic medicines based on the internationally accepted principle of bioequivalence. Under the Pharmaceutical Benefits Scheme, generic substitution is only permitted if two products are bioequivalent. Consumers should be encouraged to know and record the name of the active ingredient in the medicines they are receiving to avoid confusion between different brands of medicines. Healthcare professionals have a key role in helping consumers understand any real or perceived differences (or lack thereof) between different brands of medicines. Prescribing generics helps to contain health costs.

Key words: bioequivalence, pharmacokinetics.

(Aust Prescr 2007;30:41–3)

Introduction

When the patent of an innovator drug expires, other manufacturers can make generic versions. A generic drug contains the same active ingredient as another product, but is marketed under a different name. In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) recognises the interchangeability of different brands containing the same active ingredient, providing these brands are proven to be bioequivalent.[1,2,3,4]

What is bioequivalence?

Two products are bioequivalent when they produce such similar plasma concentrations of the active ingredient that their clinical effects can be expected to be the same.

In a standard bioequivalence test both products are administered on separate occasions to healthy volunteers. Bioequivalence is then determined by comparing the peak plasma concentration (C_{max}), time to achieve a maximal concentration (T_{max}) and the extent of absorption (area under the concentration-time curve, AUC) of the products (Fig. 1).

These studies are well suited to identifying potentially significant differences in the delivery characteristics of the active substance of different products. The same bioequivalence principles apply to new drugs when different formulations of an active ingredient are compared.

Bioequivalent products are marked with a superscript a or b in the Schedule of Pharmaceutical Benefits.[5]

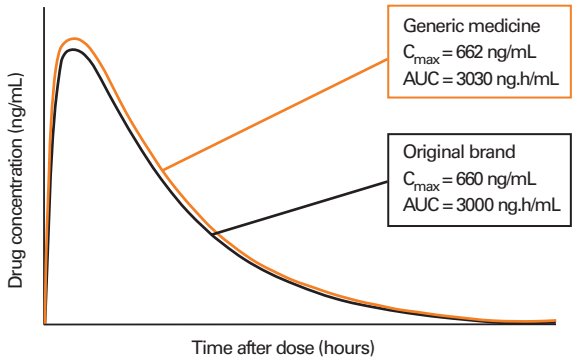
Is bioequivalence clinically important?

Yes, only those products that have been **proven to be bioequivalent** should be used interchangeably. On **scientific** grounds there is no reason to be concerned about substituting a generic product for a branded product that is flagged as being bioequivalent.[5]

Fig. 1

Bioequivalence analysis – a hypothetical bioequivalence study

Mean concentration–time curves for two brands of a drug after single oral doses



The original brand:generic medicine ratio for AUC is 0.99 (90% CI 0.91 to 1.04) and for C_{max} is 0.99 (90% CI 0.92 to 1.07).

C_{max}	peak plasma concentration
AUC	area under the concentration–time curve
CI	confidence interval

Reprinted with permission from NPS News 2006;44:3.

Switching inequivalent products may lead to lower or higher blood concentrations of a drug in a patient. This may increase the risk of therapeutic failure or drug-related toxicity.

The precise extent to which inequivalence between two formulations will affect the clinical response depends on their pharmacological and/or therapeutic properties. It depends specifically on which part of the drug concentration-effect curve is affected by any concentration difference.[4] For example, if the drug is usually dosed close to the upper flat part of the dose-response curve, then large changes in plasma concentration will result in only small changes in therapeutic response or adverse effects. Theoretically, this is a greater concern for drugs with a narrow therapeutic index, such as carbamazepine, digoxin and sodium valproate. However, this is not as problematic as may be predicted because patients taking these drugs are generally closely monitored (either by measuring concentrations or effects). For drugs with wider safety margins, there should be no concerns about a change in response when switching from one bioequivalent brand to another.

Which medicines should not be substituted?

Products that are not bioequivalent should not be substituted for each other. For example, metoprolol is available as both an intermediate release and a modified release tablet. These dose forms are not bioequivalent and should not be substituted.

There are two innovator brands of warfarin available in Australia. These have not been proven to be bioequivalent and so it is recommended that warfarin products should not be substituted.

There has been considerable debate regarding the bioequivalence of drugs with a narrow therapeutic index, that is, drugs for which a small change in blood drug concentration leads to significant change in therapeutic response or toxicity.[6] These drugs generally display relatively minor variability within a patient from day to day but often display considerable variability between patients.[4,6] Taken together this implies that the dose required to achieve the same concentration in the body, and therefore the same pharmacological effect, might be quite different **between** different patients. However, **within** a patient the dose requirements are unlikely to vary greatly over time and between doses while the patient is clinically stable. Bioequivalence principles and criteria equally apply to medicines with a narrow safety margin.[6,7]

Can people have a reaction to the excipients in different products?

Yes, although adverse reactions to excipients are rare. Pharmaceutical products contain the active pharmacological ingredient and a range of excipients that are designed to deliver the active drug optimally in a reliable and reproducible manner. These excipients can be diluents, binders, fillers, surfactants, lubricants, coatings and dyes. Excipients are generally considered 'inactive', but there is some evidence to suggest that excipients can have an impact on patient tolerability.[8] The main risk is allergy or intolerance to a specific ingredient such as lactose. The range of excipients used pharmaceutically is small, and the type used in individual products must be carefully chosen so that bioequivalence is achieved. The quality and safety of all excipients are carefully reviewed by the Therapeutic Goods Administration (TGA) and excipients can only be used if they are safe and non-toxic. It may not be possible to determine which ingredients in either generic or branded products may cause an allergic reaction given that formulations are likely to be similar. Patients who are aware of their allergies can refer to the ingredients listed in the Consumer Medicines Information that accompanies the product.

How can patients avoid being confused by the brand name of generic products?

Patients should be encouraged to know and record the name of the active ingredient in the medicine they are taking rather than the product brand name. In this way a patient will understand that the same medicine may be available in different brands. This has implications for the way medicines are labelled. Ideally, the active ingredient in the product should be displayed with greater or equal prominence to the brand name on the packaging as recommended by the TGA in the 'Best practice guideline on prescription medicine labelling'.[9]

Public hospitals are likely to only have one or two brands of a medicine and these are often generic products. As patients move in and out of hospital it is likely that generic substitution will occur to a greater extent. This reinforces the need for patients to be aware of and carry a list of the name of the active ingredient or generic name of their medicines to maintain effective management of their condition.[10]

When deciding whether to substitute a generic product for a branded product, one must always consider the patient's understanding of their medicines and the risk of medication misadventure. Discuss this with the patient and provide appropriate information.[3]

If there is potential for confusion on the part of the patient and there is a risk of dose duplication, then generic substitution may need to be avoided (independent of the drug involved) unless the patient or carer fully understands the difference between the various brands of the same medicine. Clearly elderly patients, those with cognitive impairment and patients taking multiple medicines for serious chronic illness are at greatest risk of misadventure from their drugs.

Do community pharmacists make a bigger profit if they substitute a generic drug?

Not necessarily. Under the Brand Premium Policy of the Pharmaceutical Benefits Scheme (PBS), pharmacists are allowed to substitute a generic product when a branded product is prescribed, unless the prescriber directs otherwise.

The PBS provides a subsidy up to the price of the cheapest brand of a drug in a particular therapeutic area. This often creates

a price difference between generic and branded products.

The pharmacist's profit margin varies from drug to drug and product to product. In the past, cost savings for community pharmacists arose when they purchased bulk orders of generic drugs directly from manufacturers. This issue was not unique to generic products because some manufacturers of branded medicines also sold their products directly to community pharmacies under price-volume agreements. This is one of the many economic issues that community pharmacists have to deal with in the efficient running of their businesses. Recent PBS reforms have created different remuneration schedules for generic and branded medicines resulting in these cost savings now being retained within the PBS.

Can the bioavailability of bioequivalent products differ by up to 40%?

No, for two drugs to be bioequivalent, the 90% confidence intervals (90% CI) for the ratio of each pharmacokinetic parameter, C_{max} and AUC, must lie within the range 0.8–1.25 (sometimes also expressed as 80–125%).

The 90% CI of 0.8–1.25 is a numerical index and not a direct measure of the difference in systemic concentrations of the active ingredient resulting from administration of the two products. It does not mean that the C_{max} and AUC ratios estimated for each formulation can vary by –20 to +25%. In reality, for a product to fit within these relatively tight confidence limits the mean AUC and C_{max} must be very close, and any difference in bioavailability is certainly less than 10%.[4]

Conclusion

The bioequivalence criteria used in Australia have been defined and refined over many years and are internationally recognised as the acceptable criteria for assessing bioequivalence.[1] There is persuasive evidence that the current internationally accepted limits and approaches to bioequivalence can accommodate all medicines.[6,7]

Only drugs that are marked as bioequivalent should be substituted for each other. Likewise, drugs that are not bioequivalent should not be exchanged.

To avoid confusion, healthcare professionals should, where possible, reinforce the name of the active ingredient in the medicine, when prescribing, dispensing and administering medicines to patients.

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Each author has acted as a paid consultant to the pharmaceutical industry (including companies that manufacture innovator branded and generic medicines). Professors Ramzan and McLachlan are also members of the Pharmaceutical Subcommittee, Australian Drug Evaluation Committee.

Dental notes

Prepared by Dr M McCullough of the Australian Dental Association

Frequently asked questions about generic medicines

Habits formed in the early years after graduation often remain with us during our working life. Despite continuing professional development, when pressed for time or perhaps in a difficult clinical situation, we often revert to practices established early in our professional career. Prescribing drugs by brand name may be done out of habit, but this may not be in the best financial interest of our patients. We need to continually assess our prescribing habits and consider cost in our choice of drugs. There is usually no reason to be concerned about substituting a bioequivalent generic product for a branded product. To avoid confusion, always tell the patient the active ingredient of the medicine prescribed. When we write a prescription, we are recommending that our patients use a drug, not necessarily a brand.

Long-term management of people with psychotic disorders in the community

Nicholas A Keks, Professor, and Judy Hope, Psychiatrist, Monash University and Delmont Private Hospital, Melbourne

Summary

Psychoses affect up to 4% of the population. These conditions usually require long-term treatment with antipsychotic drugs, mood stabilisers or both. The availability of effective treatment means that most people with psychoses can live in the community. Psychosocial treatments and the provision of community services are critical, but are often inadequate. Long-term adverse effects can be a problem and adherence to treatment can be difficult for almost all patients. Depot antipsychotics have been widely used to improve adherence to maintenance treatment, but extrapyramidal adverse effects have been a major problem.

Key words: antipsychotics, depot formulations.

(Aust Prescr 2007;30:44–6)

Introduction

Psychoses include schizophrenia, schizoaffective disorder, psychotic depression and bipolar mania. The diagnostic boundaries between these disorders can be unclear, but together they have a lifetime prevalence in the population of about 4%. Antipsychotic drugs treat positive symptoms (delusions, hallucinations and thought disorder) across the diagnostic spectrum. Atypical antipsychotics are also helpful for mania and psychotic depression. Mood stabilisers are also used in psychoses to treat mania and depression, usually in addition to antipsychotic drugs.[1]

While up to 30% of patients do not experience any relapse after their first psychotic episode, the remainder will develop long-term problems. Some patients will manifest a remitting-relapsing pattern of illness, while others will develop chronic illness, including negative symptoms (flat affect, poverty of thought, amotivation, social withdrawal and poor concentration). Negative symptoms tend to be associated with poor insight into the presence of illness and the need for treatment. Adherence to treatment can therefore be particularly problematic.

Chronic or relapsing illness is associated with impaired function and lower quality of life. These patients require active rehabilitation and integration into the community.

Long-term management in the community

Although many people with psychoses have a favourable outcome, others suffer unemployment, social and family dislocation and housing problems. Many patients with psychosis may require a comprehensive mix of services, which can be challenging to co-ordinate. Community psychiatric services may offer case management to assist with management planning and organisation. Specialist services provide specific psychological interventions (such as cognitive behavioural therapy for refractory psychoses) and vocational rehabilitation aimed toward functional recovery. Assertive community management (which involves proactive home visits, medication support and personal assistance) is recommended.

Almost all patients with psychoses living in the community will see a general practitioner; 81% do so in any given year. Often working together with specialist psychiatric services and social agencies, general practitioners can provide a number of key interventions.[2]

The physical care of patients with psychoses is a central role for general practitioners. These patients are at greater risk of physical illness, particularly cardiorespiratory and metabolic disorders. General practitioners can regularly monitor patients' physical state, undertaking a number of relevant investigations every 6–12 months depending on individual requirements (Table 1).

Good communication between the general practitioner and specialists is imperative

In addition to monitoring the mental state for evidence of deterioration or relapse, general practitioners can provide supportive psychotherapy and counselling, monitor and encourage adherence to treatment, check for adverse effects and adjust the dose and type of medication in collaboration with a psychiatrist. They also liaise with family and carers, provide education about the illness, and recognise and address problems associated with substance abuse. Good communication between the general practitioner and specialists is imperative.

Antipsychotic medications

Following the first psychotic episode, antipsychotic medication is usually stopped by the patient after 1–2 years, although

Table 1

Monitoring the physical health of patients with psychosis *

Assessment	Checks for:
History and examination, including: – cardiovascular – neurological – funduscopic exam through undilated pupils	 – evidence of arrhythmias and ischaemic heart disease – tardive dyskinesia, akathisia and tremor – lens opacities and retinal pigmentation
Weight: calculate body mass index (weight/height^2)	changes in weight
Random blood glucose	diabetes (increased risk with some atypical antipsychotics)
Cholesterol and triglycerides	cardiovascular disorders (increased risk)
Vitamin B_{12} and folate	nutritional deficiency
Calcium, phosphate	drug effects
Full blood exam, erythrocyte sedimentation rate	infection, nutritional deficiency, anaemia
Liver function	alcohol and other drug effects
ECG	drug effects, cardiovascular disease
Drug screen	illicit drug use
Other investigations as appropriate, e.g. – thyroid function – therapeutic drug monitoring – echocardiography – cervical smear	 – effects of lithium – effects of lithium – cardiomyopathy (clozapine)

* suggested monitoring at initial examination and repeated at 6–12 month intervals depending on risk

long-term therapy is the rule for patients with recurrent illness. Antipsychotics prevent relapse in patients with remitted positive and mood symptoms, and maintenance treatment helps to reduce symptoms in patients with chronic illness. These drugs enable many patients who previously would have been institutionalised to live in the community.

The most commonly used conventional antipsychotics in the long-term treatment of psychoses are high-potency oral antipsychotics, such as haloperidol and trifluoperazine or depot formulations, such as flupenthixol. The major drawback with conventional antipsychotics is their tendency to produce extrapyramidal adverse effects at effective doses. These include dystonias, parkinsonism, akathisia and tardive dyskinesia, a disfiguring, stigmatising and often irreversible neurological disorder.

Atypical antipsychotics are a diverse group of drugs with a lower risk of extrapyramidal adverse effects at therapeutically effective doses. Some atypicals may be more effective than conventional antipsychotics in long-term treatment. Clozapine is particularly effective for treatment resistant cases. While its toxicity restricts initiation of treatment to specialist centres, increasingly general practitioners are involved in long-term care and monitoring of patients on clozapine therapy. Risperidone has shown superior efficacy to haloperidol in long-term prevention of relapse.[3] Recently, high-dose olanzapine was shown to have greater effectiveness than conventional and other atypical antipsychotics (apart from clozapine) in terms of discontinuation rates over an 18-month period.[4]

While reducing problems with extrapyramidal adverse effects, atypicals have caused other problems such as postural hypotension, weight gain and hyperglycaemia. Each drug seems to have adverse effects which are particular problems, for example, clozapine can cause neutropenia, agranulocytosis and myocarditis. Olanzapine frequently causes considerable weight gain and increases glucose and lipids which can lead to hyperlipidaemia and diabetes.[4] Although weight gain is less of a problem with risperidone, it may cause sexual dysfunction and amenorrhoea due to hyperprolactinaemia. Quetiapine may cause mild weight gain, while amisulpride and aripiprazole are generally well tolerated in long-term treatment (although aripiprazole can initially cause troubling nausea and restlessness).

Addressing adherence to treatment

Education, cognitive behaviour therapy, social skills training, treatment of substance abuse, personal assistance and assertive community support are probably the most important measures in aiding adherence when medication is not fully effective in

re-establishing the patient's insight.[5] Depot formulations are widely used when psychosocial measures have been inadequate to ensure adherence to daily oral doses.

Depot antipsychotics take a long time to reach steady state, so oral supplementation is usually required in the first few months of treatment. Depending on the drug, the interval between injections can be extended to four weeks. Many patients receiving conventional depot antipsychotics experience extrapyramidal adverse effects, including a high prevalence of tardive dyskinesia.[6]

Risperidone is available in a long-acting injectable formulation. Initial findings and clinical experience suggest that injectable risperidone is effective for maintenance treatment of schizophrenia-related psychoses and causes relatively few adverse effects. The incidence of new cases of tardive dyskinesia has been low to date, but weight gain, amenorrhoea and sexual dysfunction do occur.

Conclusion

The long-term treatment of psychosis is challenging. General practitioners have a key role, particularly in the ongoing physical care of patients and in monitoring medication and the patient's mental state. Adherence to treatment is a frequent problem, which can be addressed with intensive psychosocial assistance. More often than not, services are less than adequate, and other measures such as long-acting injectable antipsychotic drugs may be required to ensure that patients continue their medication.

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Professor Keks has received research funding from, or has been a consultant to, all pharmaceutical companies marketing atypical antipsychotic drugs in Australia.

Self-test questions

The following statements are either true or false (answers on page 55)

5. Atypical antipsychotics do not cause tardive dyskinesia.
6. Up to 30% of patients have no relapses after their first psychotic episode.

Book review

Therapeutic Guidelines: Gastrointestinal. Version 4.

Melbourne: Therapeutic Guidelines Limited; 2006. 272 pages. Price $39, students $30, plus postage

Aniello Iannuzzi, Visiting Medical Officer, Coonabarabran Hospital, NSW

Therapeutic Guidelines: Gastrointestinal highlights that this series is about **therapeutic** guidelines, rather than just medication guidelines. It is suitable for all health professionals. Students and junior clinicians will find more than they need to pass exams and survive on the wards. The succinct and up-to-date information in this book will appeal to senior clinicians.

Many of the therapies described in this guide are non-prescription, making it a useful resource for pharmacists and dietitians. It is a wake-up call for medical practitioners, reminding us that prescribing drugs is not the only way to solve clinical problems.

Basic day-to-day problems are dealt with comprehensively, namely constipation, nausea, vomiting and diarrhoea. All clinicians, irrespective of their specialties, will find useful information in these chapters.

The first section, 'Getting to know your drugs', is a 25-page pharmacology revision of all the gastrointestinal drugs of importance. The only oversight was dexamethasone, which is subsequently referred to a lot in the nausea and vomiting chapter.

The other chapters deal with all the important non-surgical conditions of the gastrointestinal tract. These include viral hepatitis, *Helicobacter pylori*, diverticular disease, irritable bowel syndrome, as well as disorders of vitamin and mineral metabolism. There are also useful sections dealing with enteral nutrition and stoma management. This book contains many practical tables as well as appendices relating to pregnancy, ostomy appliances and support groups.

It is a handy pocket-sized book which is also available in an electronic format with the other guidelines in the series. I strongly recommend this book to all clinicians.

Evidence, risk and the patient

Paul Neeskens, General Practitioner, Pialba, Queensland

Summary

Drugs are often assessed by their effect on surrogate outcomes, such as blood pressure or cholesterol, rather than clinical end points such as death. This results in risk factors being treated to prevent possible future events. Patients must be willing to take drugs for many years in the hope that they will obtain the same benefit as the patients in clinical trials. Patients in clinical trials are, however, often different from the patients seen in practice. It is therefore important to consider the whole patient and not just prescribe a drug to treat a risk factor in isolation. When deciding to prescribe, the absolute benefit of treatment should be discussed with the patient.

Key words: clinical trials.

(Aust Prescr 2007;30:47–50)

Introduction

Prescribing drugs to treat risk factors is a daily routine activity for most Australian general practitioners. Underpinning the pharmacotherapy of risk factors is evidence from clinical trials that is widely accepted to validate the merit of this treatment. However, many people may need to have their risk factors treated to prevent an adverse outcome for one person. Considering the whole patient is integral to the art of medicine, so we should consider the individual and not just their risk factors.

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.[1] To apply this principle we have to assess what the evidence from clinical trials means.

Assessing evidence – the scientific dimension

The anatomical and pathophysiological mechanisms of disease, though important to understand, are not the evidence that underpins the validity of medical treatment. Medicine is essentially an observational science and clinical trials endeavour to determine significant differences between the natural history of disease and the effect of treatment. Some basic understanding of statistics is needed – especially when assessing risk factor modification.

Significance

A result is statistically significant when the 'p' value is less than 0.05. This arbitrarily chosen value means that there is a 95% likelihood that an observation is not due to chance. The p value is a measure of the reliability of an observation, but it does not quantify any effect.

The word 'significant' is frequently used inconsistently. A statistically significant result from a trial is sometimes erroneously interpreted as having a high clinical significance.

Reporting risk reductions

Trials look at the incidence of outcomes with and without intervention. Absolute risk reduction is the difference between the outcome in the control group and the outcome in the intervention group in a specified time period.

The relative risk reduction is the absolute risk reduction as a proportion of the baseline rate. A relative risk reduction often seems impressive, but it may only represent a small difference. For example, if the event rate is 0.2% in the control group and 0.1% in the intervention group the relative risk reduction is 50%, but the absolute risk reduction is only 0.1%.

One must always know whether a quoted risk change is relative or absolute. Benefits of treatment are often presented in relative terms, but harms and adverse effects are usually presented in absolute terms (Table 1).

Number needed to treat or harm

The number needed to treat is the number of patients who must be treated for a period of time to prevent one having

Table 1

Absolute and relative risk

Event rate control	Event rate intervention	Relative risk reduction	Absolute risk reduction	Number needed to treat	p value
20%	10%	50%	10%	10	< 0.05
4%	2%	50%	2%	50	< 0.05
0.2%	0.1%	50%	0.1%	1000	< 0.05

The p value measures the reliability of the observation, not the quantum of effect.
If the effect is small, a small p value can still be achieved with a large sample size.

the outcome of interest. It is the inverse of the absolute risk reduction (1/ARR). For example, if the absolute risk reduction after five years is 2%, then the number needed to treat is 50 (1/0.02). Fifty people need to be treated for five years to prevent one adverse outcome. This means that the outcome of interest will be unchanged for the 49 other people who took the treatment for five years. Some of these 49 people may come to harm as a result of adverse effects of treatment.

The number needed to harm is a less frequently published number. It is essentially the inverse of the absolute rate of adverse effects. Over 10 years, if 4% of women suffer venous thromboembolism while on hormone replacement therapy and 2% without hormone replacement therapy, the absolute harm rate of the therapy is 2% and the number needed to harm is 50. That is, for every 50 women treated one will develop a thrombosis that would not have otherwise occurred.[2]

Outcome

Trial end points are varied and one must have a clear understanding of the outcomes measured. Death, disability and morbidity are clinical end points, while others such as blood pressure, cholesterol or bone density are surrogate or intermediate markers. Surrogate end points may have merit as indicators of potential benefit, but they rely on other evidence providing a causal link to clinical outcomes. In the end all interventions must be justifiable by an improvement in patient well-being, that is, by clinical end points.

Assessing evidence – patient factors

Many trials exclude pregnant women, children, older people and patients with significant comorbidity. The benefit or harm in 'real world' patients may not be equivalent. Similarly, some treatments have only been studied in particular groups or after patients intolerant to test doses have been excluded (for example, the HOPE trial where 10% of the initial cohort were excluded after the run-in phase).[3]

Health professionals interact with individuals, not trial cohorts or populations. The characteristics of the individual patient are therefore an important consideration when deciding whether to treat a risk factor.

Patient attitude

Everyone has a different attitude to risk. The sedentary smoker who drinks a bottle of wine per day clearly has a different life attitude to a teetotal non-smoker who walks for an hour every day.

Patient anxiety

The label of 'risk' can cause some patients to become significantly anxious. The effect of labelling has been well documented to impair quality of life. This is particularly pertinent in the context of a symptomless risk factor and should be considered before introducing the issue of risk with patients.

Patient effort

Harm from treatment includes more than potential drug adverse effects. Treatment involves visits to the doctor, prescriptions, blood tests, possibly diagnostic imaging, cost and the daily consumption of drugs. When the benefit of treatment is a trust that the odds of some future event are reduced rather than an immediately experienced improvement in well-being, the effort to adhere to treatment can be significant.

Comorbidity

The outcome being prevented must be relevant to the patient. A critical phenomenon here is significant other disease. The quality of life gained is more important than the raw quantum. In patients with significant comorbidity, a physician needs to consider and discuss whether the benefit gained is worth the additional intervention. An example here is hypercholesterolaemia in a patient with advancing dementia. One may be able to reduce the risk of a cardiovascular event, but is this relevant to this patient?

Risky realities

The association of an observation with a negative outcome does not necessarily mean treating the observation improves the outcome. The transverse ear lobe crease has been associated with a higher risk of coronary artery disease.[4] Excision of the ear lobe is unlikely to change things. For many years it was stated that hormone replacement therapy reduced the risk of heart disease on the basis of plausible pathophysiological models. The Women's Health Initiative trial suggests the actual outcome was different.[2]

Risk is never zero and is never reduced to zero. At any age there is a risk of disease and even death. Drug therapy for cardiovascular risk reduces a baseline level of risk at best by a relative 50%. For example, in a person with known ischaemic heart disease whose absolute risk of another event may be 30% in five years, maximal risk factor reduction reduces that to 15% in five years. It is not reduced to zero, and in that time that individual still has various risks for injury or other illness. Prevention by drug therapy of risk factors is never absolute, contrary to prevention in other contexts such as immunisation, where a serious infectious disease prevented is one that will probably never occur.

There are quite distinct principles underlying treatment and prevention. All interventions have a risk of harm, but a person's willingness to accept the risk will depend on their situation. The rate of adverse reactions to chemotherapy may be acceptable to a cancer patient with a poor prognosis. However, a similar rate of adverse effects would not be acceptable for a vaccine given to many healthy individuals to prevent disease in a few. Similarly, the effort of treatment for symptomatic disease can be readily justified by the improvement in the symptoms, whereas

in risk factor modification the effort is now, for all, but the benefit is later, for some.

Who to treat?

Drugs are approved by the Therapeutic Goods Administration (TGA) if they are relatively safe and have reasonable evidence of efficacy. If the drug is cost-effective in a particular condition it will be listed on the Pharmaceutical Benefits Scheme (PBS). Similarly, treatment guidelines are expert interpretations of the evidence on how to achieve the best outcomes for a particular disease. However, the health professional's role is a step further beyond the TGA, PBS and guidelines to a focus on the outcome for the whole patient rather than just their disease. Specific consideration must be given to the individual relevance of the outcome being sought, and what information is suitable for a patient to make an informed decision.

Informing patients about risk

Patients should understand the benefits and harm of the treatment being offered, especially when this could be lifelong drug therapy. Relative risk reductions do not really quantify the merit of a treatment. Absolute data can be presented in several ways. Some authors recommend the Visual Rx analogue diagrams with a number of people represented as stick figures and the control and intervention groups marked in different colours or shades.[5] Other authors have shown that patients and physicians more readily understand outcomes by using natural frequencies[6] (such as, for 100 similar persons an event will occur in 10 without treatment and 7 with treatment) rather than percentages or odds ratios. Another technique is to ask the patient to imagine a room full of 100 similar people and compare the various outcomes for a number of those in that room.

Using natural frequencies and absolute risk data, a patient can be in a better position to assess the merit of a treatment in the context of their own attitudes, preferences, expectations and other morbidity. Absolute outcome data and number needed to treat have been published for many drugs.

Here are two examples of using absolute outcome data to assist with decision-making about preventive pharmacotherapy.

Sixty-year-old female with hypercholesterolaemia

The readily available New Zealand cardiovascular risk calculator[7] can quantify absolute risk. With a blood pressure of 130/80, total cholesterol of 7.5 mmol/L, and an HDL cholesterol of 1.1 mmol/L, a non-smoking non-diabetic female has a five-year cardiovascular event risk of 7%. It is generally agreed that statins will reduce risk by a third. With treatment the five-year risk is thus about 5%.

When discussing the merit of treatment against the effort and potential adverse effects, consider the absolute risk reduction. About seven in 100 people will have an event in five years with no treatment, but if 100 take the statin for five years, five will have an event.

Overweight patient taking metformin for type 2 diabetes

The United Kingdom Prospective Diabetes Study (UKPDS)[8] showed a difference in diabetic end points over 10 years between 'conventional' treatment (fasting glucose < 15 mmol/L, and no hyperglycaemic symptoms) and 'intensive' treatment (glucose < 6 mmol/L). With conventional treatment macrovascular complications occurred in 31% of patients and microvascular in 9.2%. With intensive treatment including metformin, the rates were 23% and 6.7%.[3] The prescriber and patient should discuss the downside of intensive treatment with respect to hypoglycaemia, metformin adverse effects such as diarrhoea, and the patient effort required to achieve a fasting glucose < 6 mmol/L.

Conclusion

Risk factor pharmacotherapy is underpinned by population-based research. In contrast, the primary care physician has to decide what to recommend or do with each individual patient. An understanding of the limitations of epidemiological evidence, a familiarity with using absolute outcome data, an acknowledgement of the ethical perspectives and a focus on the whole patient should ensure that pharmacotherapy for risk factors is useful and relevant to the patient.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 55)

7. A reduction of greater than 50% in relative risk confirms a clinically significant intervention.
8. Treating risk factors reduces adverse outcomes but cannot prevent them completely.

New drugs

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

Dasatinib

Sprycel (Bristol-Myers Squibb)

20 mg, 50 mg and 70 mg tablets

Approved indication: chronic myeloid leukaemia and acute lymphoblastic leukaemia

Australian Medicines Handbook section 14.3.5

Most patients with chronic myeloid leukaemia have a chromosomal translocation that produces the Philadelphia chromosome (Ph). This results in an abnormal tyrosine kinase which causes cells to become malignant. This translocation can also occur in patients with acute lymphoblastic leukaemia.

Imatinib (see New drugs, Aust Prescr 2001;24:129–31) is an inhibitor of this abnormal tyrosine kinase and is effective in many patients with newly diagnosed chronic myeloid leukaemia. However, some patients are resistant to imatinib when they start therapy or develop resistance during therapy due to mutations in the abnormal tyrosine kinase gene. These mutations interfere with imatinib binding.

Dasatinib is a new tyrosine kinase inhibitor that binds to a broader range of kinases compared to imatinib. *In vitro*, dasatinib has been shown to have inhibitory activity against imatinib-resistant leukaemia cell lines.

After oral administration of dasatinib, maximum plasma concentrations are observed within 0.5–3 hours and it has an overall mean terminal half-life of 5–6 hours. Dasatinib is extensively metabolised, mainly by cytochrome P450 3A4, and is predominantly eliminated in the faeces as metabolites.

Other drugs that inhibit cytochrome P450 3A4, such as erythromycin and other macrolides, may increase exposure to dasatinib and should be avoided. Likewise, inducers of cytochrome P450 3A4, such as dexamethasone, rifampicin, carbamazepine and St John's wort may reduce the concentrations of dasatinib and are not recommended. Dasatinib increases the risk of toxicity from other cytochrome P450 3A4 substrates that have a narrow therapeutic index, such as quinidine and ergot alkaloids. H_2 blockers and proton pump inhibitors are likely to reduce the oral bioavailability of dasatinib and are not recommended. If antacids are used, they should be given two hours before or after taking dasatinib.

The efficacy of dasatinib was first assessed in a phase I dose-escalation study in 84 patients with chronic myeloid leukaemia or Ph-positive acute lymphoblastic leukaemia who could not tolerate or were resistant to imatinib. Patients received 15–240 mg of dasatinib orally per day. Following treatment, 68 (81%) patients had a major haematological response (assessed by counting white blood cells, platelets, blasts and myelocytes and metamyelocytes in peripheral blood), and 37 (44%) patients had a major cytogenetic response (based on the percentage of Ph-positive cells in metaphase in bone marrow). Responses were maintained in 95% of patients with chronic-phase disease (median follow-up of 12 months) and 82% of patients with accelerated disease (median follow-up of 5 months). Most patients with lymphoid blast crisis or Ph-positive acute lymphoblastic leukaemia relapsed within six months.[1]

An open-label phase II trial studied the efficacy of dasatinib (70 mg taken twice a day) in 186 patients with imatinib-resistant or -intolerant chronic-phase chronic myeloid leukaemia. After eight months, 168 (90%) patients achieved complete haematologic responses and 97 (52%) achieved major cytogenetic responses. Sixteen patients developed progressive disease or died.[2]

Another study assessed the efficacy of dasatinib (70 mg taken twice a day) from combined data of open-label phase II trials in patients (resistant or intolerant to imatinib) with chronic myeloid leukaemia in blast crisis. Of these patients, 74 had myeloid blast crisis and 42 had lymphoid blast crisis. After 8 months,

dasatinib had induced major haematologic responses in 31–34% of patients. Major cytogenetic responses were observed in 31% of patients with myeloid blast crisis and 50% of patients with lymphoid blast crisis.[3]

In the phase II trials, response rates to dasatinib were similar in patients with imatanib-resistant tyrosine kinase mutations compared to patients without mutations. However, one particular mutation (T3151) conferred resistance to both dasatinib and imatinib treatment in the phase I and II trials.[1,2,3]

Myelosuppression was a common adverse effect of dasatinib treatment. In the phase I trial of 84 patients, about 60% of them had their treatment interrupted because of myelosuppression and 25% had their dose reduced. Other common adverse events included pleural effusions (18% patients), diarrhoea (23% patients), peripheral oedema (19% patients), nausea (10% patients), dyspnoea or pulmonary oedema (12%), rash (11%), headache (10%) and gastrointestinal haemorrhage (8%).[1] These adverse events were also common in the phase II trials.[2,3] There have been reports of intracranial haemorrhage, which have been fatal in some patients.

As myelosuppression is common with dasatinib treatment, patients should have regular complete blood counts. Dasatinib should be administered with caution in patients who have or are likely to develop a prolonged QT_c interval.

Dasatinib provides a second-line treatment for patients with imatinib-resistant chronic myeloid leukaemia or Ph-positive acute lymphoblastic leukaemia. However, resistance to dasatinib has been observed in some patients. The effect of this drug on long-term patient survival is unknown.

T T T manufacturer provided clinical evaluation

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Dienogest/ethinyloestradiol

Valette (Bayer Schering Pharma)

2 mg dienogest/30 microgram ethinyloestradiol tablets

(Valette contains 21 active tablets and 7 placebo tablets)

Approved indication: contraception

Australian Medicines Handbook section 17.1.1

Dienogest adds to the choice of progestogens available in combined fixed dose contraceptive pills. The combination with ethinyloestradiol has been available in Europe for several years and has been assessed in published postmarketing studies.

In one study there were 11 unplanned pregnancies during 92 146 treatment cycles with the combination. Although irregular bleeding occurred in the first few cycles, 2% of women per cycle reported no withdrawal bleeds. Approximately 4% stopped treatment because of menstrual irregularities. Adverse reactions, including breast pain, weight gain and headache resulted in 3% of the women stopping treatment.[1]

Other adverse events include thrombosis, hypertension and alopecia. The contraindications resemble those of other oral combined contraceptive pills.

Open studies confirm that the combination is an effective contraceptive, but it is difficult to judge if it has any advantages over other combined pills. Dienogest has an antiandrogenic action, so it may have a beneficial effect on the skin of some women with acne.

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Factor VIII inhibitor bypassing fraction

FEIBA-NF (Baxter Healthcare)

vials containing 500 or 1000 units of powder for reconstitution

Approved indication: haemophilia A or B in patients with inhibitors

Australian Medicines Handbook section 7.4

Patients with haemophilia A (factor VIII deficiency) or B (factor IX deficiency) are unable to form a functional tenase complex (calcium, factors VIII, IX and X) which converts factor X to factor Xa and allows normal clotting to occur. Management of these patients usually involves giving a recombinant form of the missing factor. However, patients can develop inhibitory antibodies which neutralise the activity of these clotting factors. Currently in Australia the action of these inhibitors is bypassed by giving patients recombinant factor VIIa to activate the extrinsic clotting cascade (see New drugs, Aust Prescr 1999;22:95–8).

If factor VIIa therapy fails or is contraindicated, these patients can be treated with factor VIII inhibitor bypassing fraction. This contains prothrombin, factors IX and X (mainly non-activated), and factor VII (mainly activated).

Factor VIII inhibitor bypassing fraction is administered intravenously. The timing interval of subsequent doses depends on the site and severity of the bleed. As there is a risk of thrombosis, single doses of factor VIII inhibitor bypassing fraction should not exceed 100 units per kg of body weight and

the infusion rate should not be greater than 2 units per kg of body weight per minute. The maximum daily dose should be less than 200 units per kg of body weight.

An open-label trial compared intravenous factor VIII inhibitor bypassing fraction and recombinant factor VIIa in 48 patients with haemophilia A. Each patient was started on one treatment after their first bleeding episode, then crossed over to the alternative treatment for the second bleeding episode. Both products were found to be effective in about 80% of patients six hours after treatment.[1] Similar levels of efficacy have been observed in other trials.

With blood-derived products such as factor VIII inhibitor bypassing fraction, there is always a risk that it may contain infectious agents. A French study collected information about 433 bleeding episodes in 60 patients treated with factor VIII inhibitor bypassing fraction between 1978 and 1993. Of patients who were regularly evaluated, 1 of 52 became positive for human immunodeficiency virus (HIV) and 41 patients became positive for hepatitis C virus.[2] Plasma from which this product is derived now undergoes viral serologic testing for hepatitis B, hepatitis C and HIV-1 and HIV-2 antibodies. In an effort to remove viruses, the product also undergoes vapour heat treatment and nanofiltration. However, despite the plasma screening and viral removal procedures, there is still a theoretical risk that viruses such as parvovirus B19 and hepatitis A could be transmitted via this product.

In the French study, 17 of 54 evaluable patients had increased inhibitor levels (by more than 50%) after infusion of factor VIII inhibitor bypassing fraction. However, this did not affect the response of these patients to therapy.[2]

Thrombosis is a recognised complication of factor VIII inhibitor bypassing fraction. In a pharmacovigilance study from 1999 to 2002, the incidence of thrombotic adverse events in patients treated with factor VIII inhibitor bypassing fraction was found to be 8.24 per 100 000 infusions. The most common event was myocardial infarction which occurred five times. Cerebrovascular thrombosis, pulmonary embolism and disseminated intravascular coagulation were also reported.[3]

Doctors should be aware that tests used to determine clotting time such as activated partial thromboplastin time (APTT) do not correlate with clinical improvement in patients being treated with factor VIII inhibitor bypassing fraction. Therefore clinical outcomes rather than results of these tests should be used to monitor the efficacy of this drug.

Factor VIII inhibitor bypassing fraction provides a second-line therapy for patients who fail to respond to factor VIIa therapy or for whom factor VIIa is contraindicated. However, prescribers should be aware that this product is derived from human plasma and can potentially transmit infectious agents.

T T T manufacturer provided clinical evaluation

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Human protein C

Ceprotin (Baxter)

vials containing 500 IU or 1000 IU as powder for reconstitution

Approved indication: congenital protein C deficiency

Australian Medicines Handbook section 7.4

Protein C is a circulating glycoprotein. When it is activated, protein C has an anticoagulant effect on the clotting system. Patients who have a deficiency of protein C are therefore prone to thrombosis. These patients may need to take warfarin for life.

Starting warfarin in a patient with a severe congenital deficiency of protein C can result in skin necrosis. This is thought to be caused by an imbalance of coagulant and anticoagulant activity which results in capillary thrombosis.

Another presentation of severe protein C deficiency is purpura fulminans. This occurs in babies who are homozygous for the deficient gene. Capillary thrombosis within a few hours of birth results in ecchymoses and skin necrosis. The child may die or require an amputation if gangrene sets in.

It is hoped that concentrates of protein C will help to manage purpura fulminans and coumarin-induced skin necrosis. This product is manufactured from pooled human plasma. One international unit contains the same protein C activity as 1 mL of plasma. An initial dose of 60–80 IU/kg is recommended to restore protein C activity. The half-life is variable and may be shortened in patients with purpura fulminans or skin necrosis so several doses may be needed to maintain the activity of protein C. In acute cases the protein C activity should be checked every six hours.

Although concentrates have been used to treat patients with protein C deficiency due to severe sepsis, a recombinant product (drotrecogin alfa) is already available. As the severe congenital cases of protein C deficiency are rare, clinical trial data are limited. Intravenous injection of the concentrate will help some patients, but it may not prevent death.

As the product is a protein patients can develop hypersensitivity reactions. Its anticoagulant action can also cause bleeding.

T manufacturer provided only the product information

Note: †

Ivabradine

Coralan (Servier)

5 mg and 7.5 mg tablets

Approved indication: angina

Australian Medicines Handbook section 6.2

Atherosclerotic coronary disease can result in the myocardium not receiving all the oxygenated blood it needs. This inadequate perfusion can present as angina. One approach to managing angina is to reduce myocardial oxygen demand by slowing the heart rate. This is one of the actions of beta blockers.

Ivabradine slows the heart rate by its action on the pacemaker activity of the sinoatrial node. It inhibits a current known as the I_f current (F for funny as the current has unusual properties). The I_f current contributes to diastolic depolarisation, so blocking it reduces heart rate and therefore increases diastolic filling time and myocardial perfusion.

Although ivabradine is well absorbed its bioavailability is reduced to 40% by first-pass metabolism. Food delays absorption but increases bioavailability so the twice-daily doses should be taken with food. The metabolism of ivabradine involves cytochrome P450 3A4, so the concurrent use of potent inhibitors of this enzyme, such as macrolide antibiotics and azole antifungals, is contraindicated. Dose adjustment may be needed with less potent inhibitors, or inducers of CYP3A4. The metabolites of ivabradine are excreted in the urine and faeces.

A phase II study randomised 360 patients with chronic stable angina to take 2.5 mg, 5 mg or 10 mg ivabradine or a placebo twice daily for two weeks. This was followed by an open-label extension during which all patients took 10 mg ivabradine twice daily for two or three months and then a randomised withdrawal of treatment for one week. The heart rate reduced in proportion to the dose of ivabradine. After the first two weeks of treatment patients taking ivabradine could exercise for longer before the onset of ECG changes or angina. Exercise tolerance diminished in patients who were randomised to take a placebo during the withdrawal phase.[1]

The efficacy of ivabradine has been compared with atenolol in a double-blind trial. After taking the recommended starting dose of 5 mg twice daily, 315 patients had their dose of ivabradine increased to 7.5 mg twice daily and 317 increased to 10 mg twice daily for 12 weeks. The beta blocker group increased their dose from 50 mg to 100 mg atenolol daily. All groups experienced an increase in the time they could exercise for during exercise tolerance tests. The mean number of angina attacks per week decreased by 2.2 with ivabradine 7.5 mg, 2.3 with ivabradine 10 mg and 2.7 with atenolol 100 mg. Overall ivabradine was not inferior to atenolol.[2]

Ivabradine has also been compared with the calcium channel blocker amlodipine in a trial lasting three months. Again all patients had an increase in total exercise duration at the end of the study. Another study added ivabradine or a placebo to treatment with amlodipine. After three months, exercise tests, at the peak of ivabradine activity, showed that the patients taking the drug could exercise for longer than those who added a placebo.

In the placebo-controlled trial the main difference in adverse effects was visual disturbances in the patients taking ivabradine.[1] These effects also appeared in the other trials. More than 14% of patients described transient increases in brightness in parts of their visual fields. Most of these 'phosphenes' resolved during treatment. Blurred vision is also common.

Some patients will develop bradycardia so ivabradine is contraindicated in patients with a heart rate less than 60 beats per minute. Heart block can also occur so ivabradine should not be used in patients with atrioventricular block (3rd degree). Other contraindications include sino-atrial block, sick sinus syndrome and heart failure (class III–IV). Ivabradine should not be used to treat arrhythmias or unstable angina. Prescribing it with drugs that prolong the QT_c interval is not recommended as is concurrent treatment with calcium channel blockers, such as verapamil and diltiazem, which can slow the heart rate.

Compared with placebo, ivabradine significantly delays the onset of angina during exercise testing, but the difference is a matter of seconds. For example, after the first two weeks of the placebo-controlled study, patients who had taken ivabradine 5 mg twice daily could exercise for approximately 14 seconds longer than the placebo group before the onset of angina.[1] In the study where it was added to amlodipine, ivabradine had no statistical advantage over placebo if the exercise tolerance test was done at the time of trough drug activity.

It is too early to say if ivabradine will reduce deaths from ischaemic heart disease. The data are limited, but the estimated incidence of death in the trial population is 3.1 per 100 patient years with placebo, 2.4 with ivabradine, 2.1 with amlodipine and 0.5 with atenolol.

As ivabradine appears to have no clear advantage, it seems appropriate to limit its indication to patients with chronic stable angina who are in sinus rhythm and have a contraindication or an intolerance of beta blockers. Unfortunately the main trials of ivabradine were not specifically in people who cannot take beta blockers and the 10 mg twice-daily dose used in some trials exceeds the dose recommended by the product information.

T T manufacturer provided additional useful information

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Ziprasidone hydrochloride

Zeldox (Pfizer)

20 mg, 40 mg, 60 mg and 80 mg capsules

Approved indication: schizophrenia and bipolar I disorder

Australian Medicines Handbook section 18.2

Ziprasidone is one of several atypical antipsychotic drugs now available in Australia.[1,2] It binds to dopamine and serotonin receptors in the brain. At D_2, $5HT_{2A}$ and $5HT_{1D}$ receptors it acts as an antagonist while at $5HT_{1A}$ receptors it acts as an agonist. The mechanism of action of ziprasidone in schizophrenia and bipolar disorder is unknown.

The recommended dose range for both indications is 80–160 mg a day. It should be taken twice daily with food as this increases its bioavailability. It is eliminated by metabolism with most of the metabolites being excreted in the faeces. The half-life of 6–10 hours is prolonged if the patient has impaired liver function.

Short-term trials (4–6 weeks) of ziprasidone in a variety of doses for schizophrenia have had conflicting results, but in most the drug has been better than placebo. A longer study (52 weeks) of 294 inpatients with stable symptoms of schizophrenia found that those given ziprasidone had a lower rate of relapse and a longer time to relapse than those given a placebo. Its efficacy is probably similar to that of haloperidol.[3]

Ziprasidone has also been approved for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder. Two short-term (3 weeks) double-blind phase III studies (of around 200 patients each) compared ziprasidone (80–160 mg a day) to placebo in a 2:1 ratio. In both trials, ziprasidone improved mania-related symptoms.[4,5]

A trial of 437 patients compared ziprasidone to haloperidol (a typical antipsychotic) or placebo. Both drugs improved the symptoms of mania in patients compared to placebo, although haloperidol seemed to be more effective. This was reflected in the observation that less haloperidol-treated patients discontinued because of 'lack of efficacy' than ziprasidone-treated patients (8.8% vs 20.2%).

In another bipolar disorder trial, ziprasidone was compared to placebo as an additional treatment in 204 patients taking lithium. There seemed to be no obvious extra benefit of taking ziprasidone as well as lithium in terms of recovery from a manic episode.

The number of dropouts in trials of patients with bipolar disorder was generally high. One of the main reasons for discontinuation was 'lack of efficacy', which accounted for 12.9–20.2% of ziprasidone-treated patients, 8.8% of haloperidol-treated patients, 6.9% of ziprasidone plus lithium-treated patients and 13.6% of patients taking lithium alone. In patients treated with placebo, the dropout rate due to 'lack of efficacy' varied from 28.8% to 36.4%.

In terms of safety, the most common ziprasidone-related adverse events in patients with bipolar disorder included somnolence and movement disorders such as extrapyramidal syndrome. However, extrapyramidal effects were less common in ziprasidone-treated patients compared to haloperidol-treated patients.

Severe drug-related adverse events were observed in the trial of patients taking ziprasidone and lithium. These included seizure, neuroleptic malignant syndrome and a higher rate of extrapyramidal syndrome (22 of 101 patients) compared to patients taking lithium alone (3 of 103 patients).

For schizophrenia, somnolence was reported in 14% of patients. Ziprasidone caused fewer extrapyramidal adverse effects than haloperidol, but more nausea and vomiting.[3] In the longer-term trial 7–10% of patients discontinued ziprasidone because of adverse effects. Ziprasidone may cause less weight gain than other atypical antipsychotic drugs.[3]

Some of the adverse effects of ziprasidone may be explained by its action at receptors. Antagonism of $alpha_1$ adrenergic receptors can produce postural hypotension while antagonism of histamine H_1 receptors may contribute to somnolence. As somnolence is a common adverse event, patients should be cautioned about driving and operating machinery while taking this drug.

There has been concern that ziprasidone prolongs the QT_c interval on the ECG. This has been observed in patients with schizophrenia and patients with bipolar disorder, although these changes were clinically significant in only a few patients. For this reason, ziprasidone should be avoided in patients with a history of cardiac illness and should not be used with other drugs that increase the QT_c interval. Patients may need to have an ECG at baseline and after they have started treatment.

Atypical antipsychotic drugs may have more effect than older drugs on the negative symptoms of schizophrenia, such as apathy. There is little evidence to suggest that ziprasidone is any better than other new drugs for schizophrenia. It appeared to be as effective as risperidone at improving psychotic symptoms in patients with schizophrenia.[6] A Cochrane review concluded that 'well planned, conducted and reported long-term randomised trials are needed if ziprasidone is to be accepted into everyday use'.[3]

Prescribers should be aware that ziprasidone should only be used as a short-term treatment for acute bipolar manic and mixed episodes and not for long-term maintenance. It is intended as a monotherapy and so should not be used in combination with other drugs prescribed for the treatment of bipolar disorder.

T T T manufacturer provided clinical evaluation

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The T-score (T) is explained in 'Two-way transparency', Aust Prescr 2007;30:26-7.

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

Answers to self-test questions

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

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