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CONTENTS

Editorial

Variability in response to clopidogrel

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Key words: pharmacokinetics, platelet antagonists, proton pump inhibitors.

(Aust Prescr 2010;33:62–3)

The antiplatelet drug clopidogrel is effective when used in combination with aspirin for the prevention of coronary events in patients with coronary artery stents and acute coronary syndromes. However, there is growing evidence that despite this dual antiplatelet therapy some patients experience more atherothrombotic events than expected.[1] This therapeutic failure has been called 'clopidogrel resistance'. The possible factors contributing to variability in the response to clopidogrel include poor adherence, variable bioavailability, drug interactions, and genetic polymorphisms in drug metabolising enzymes or in platelet receptors.

Clopidogrel is a prodrug and its active metabolite irreversibly binds to and inhibits the adenosine diphosphate P2Y12 receptor on platelets. Approximately 85% of the dose is metabolised to an inactive metabolite (by plasma esterases) and 15% is activated by hepatic cytochrome P450 (CYP) isoenzymes in a two-step metabolic process involving CYP3A4 and CYP2C19.[2]

The impact of polymorphisms in the genes that control clopidogrel absorption, metabolic activation and pharmacological effect was examined in the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI). This study found that patients who were given clopidogrel after a myocardial infarction were more likely to have a recurrent cardiac event if they had an allelic variation of the CYP2C19 gene that led to reduced enzyme activity.[3] This finding was supported by another study which included healthy volunteers, and patients receiving clopidogrel for acute coronary syndrome (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction, TRITON-TIMI 38). The trial found that people with CYP2C19 variants encoding for reduced metabolic activity had lower concentrations of clopidogrel's active metabolite, reduced platelet inhibition and a higher rate of major adverse cardiovascular events.[4] Taken together these data suggest that the ability to generate adequate concentrations of the active metabolite is central to the variability in response to clopidogrel.

The possible impact of concomitant drug therapy on clopidogrel efficacy (via an effect on concentrations of the active metabolite) has also been investigated. Two retrospective studies, involving 13 000[5] and 8000[6] patients, have suggested a clinically significant reduction of efficacy, in terms of recurrent coronary events, in patients treated with clopidogrel if they were also receiving proton pump inhibitors. The effect was modest (approximately 25% increased risk in both studies) and of only borderline statistical significance, suggesting the need for caution in interpreting these results. Pantoprazole does not appear to attenuate clopidogrel's benefits. This has been attributed to its predominant effect on CYP2C9 inhibition and weaker effect on CYP2C19 activity.[5]

In this issue…

At the time of writing there is a moratorium on the use of seasonal influenza vaccine in children under five years of age. Questions are also being raised about the H1N1 immunisation campaign. It is hoped that these concerns do not detract from the overall benefits of immunisation against infectious diseases.

Preventing bacterial infections is important as antibiotic resistance is increasing. John Turnidge advises how to tackle the multiresistant organisms which are emerging in community practice. Preventing infection is critical in transfusions and Andrew Guirguis and Erica Wood tell us of the methods used to maximise the safety of plasma-derived products.

Prevention is the focus of the article by Jenny Reath and Ngiare Brown on the management of cardiovascular disease in Aboriginal and Torres Strait Islander people. Screening from the age of 18 years should help to reduce the high rates of cardiovascular morbidity and mortality.

Proton pump inhibitors are often prescribed to patients taking dual antiplatelet therapy to try and reduce the risk of gastrointestinal bleeding, so it is particularly relevant to know if they do reduce the efficacy of clopidogrel. A recent prospective randomised comparison of clopidogrel with prasugrel, a new thienopyridine antiplatelet drug, in which one-third of 14 000 patients were taking a proton pump inhibitor at study entry,[7] failed to confirm any clinically significant interaction during a 400-day follow-up period. There was no difference in the efficacy of either clopidogrel or prasugrel in preventing vascular events, between those patients who were taking proton pump inhibitors and those who were not. This appears to have been confirmed by the only randomised trial of omeprazole versus placebo in 3627 patients taking clopidogrel, the COGENT study, which was presented in September 2009 (21st annual Transcatheter Cardiovascular Therapeutics scientific symposium, California), but is not yet published. There were a total of 136 cardiovascular events over a mean follow-up of 133 days, and the Kaplan-Meier curves for the two groups were absolutely superimposed. While possibly not powered to detect very small differences, this result does seem to rule out any major reduction in the efficacy of clopidogrel caused by omeprazole. This is a reassuring finding as it has not been clear what could be done to avoid this problem. The use of H_2 antagonists (such as ranitidine) has been suggested, but there are doubts about their equivalent efficacy to proton pump inhibitors (and few data to support this recommendation).

In November 2009, however, the US Food and Drug Administration (FDA) announced changes to the product information, based on studies suggesting reduced efficacy in terms of platelet function. The new recommendations are to avoid prescribing omeprazole or esomeprazole concurrently with clopidogrel. The FDA states that there are insufficient data to make a recommendation regarding other proton pump inhibitors, but it also recommends that patients on clopidogrel avoid cimetidine (but not other H_2 antagonists), fluconazole, ketoconazole, voriconazole, etravirine, fluoxetine, fluvoxamine and ticlopidine.[8] Understandably this recommendation has caused confusion in the cardiological community, who believe that clinical outcomes are more important than platelet function studies.

Suggestions to overcome so-called clopidogrel resistance include the assessment of adherence to clopidogrel therapy, increasing the clopidogrel dose (to increase the amount of active metabolite), screening patients to identify CYP2C19 variants, and avoiding drug interactions with proton pump inhibitors. Well-designed trials to evaluate the effectiveness of these strategies are lacking, but a recent case series suggested minimal benefits from increasing the clopidogrel dose to as high as 300 mg daily.[9] Routine testing of CYP2C19 allelic variations is not common practice and the risk of adverse effects from increasing the clopidogrel dose requires further investigation. Assessing patient adherence to clopidogrel therapy and avoiding possible drug interactions currently appear to be the most practical strategies. Lastly, it remains unclear whether the interaction between proton pump inhibitors and clopidogrel is of clinical significance.

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Further reading

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Professor McLachlan was a member of a clopidogrel advisory board sponsored by Sanofi Aventis in 2008.

Professor Campbell: none declared

Letters

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. Letters are usually published together with their responses or comments in the same issue. The Editorial Executive Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

H1N1 immunisation

Editor, – Having just read the interesting editorial 'H1N1 immunisation: too much too soon?' (Aust Prescr 2010;33:30–1) by Peter Collignon, it would be evident that considerable waste took place in the delivery of the vaccine to the patient. Not only in the use of multidose vials, but in the waste of the unused vials which now have to be discarded with the introduction of the new 2010 trivalent influenza vaccine. I wonder if details of the wastage and relevant costs are available.

I understand that CSL developed the swine flu vaccine and delivered the vials to the Commonwealth Health Department. Was CSL paid by the Government for the vaccines or did CSL bear the loss?

As Deputy Chair of the Return Unwanted Medicines Project, I would also be interested to know how the unused vaccine vials are to be destroyed – I hope it is in an environmentally responsible manner!

Ken Bickle
Pharmacist
Greenwich, NSW

Professor Peter Collignon, author of the editorial, comments:

I agree with Ken Bickle that considerable waste was associated with the H1N1 immunisation program. Full details are not readily available because of 'commercial in confidence' agreements. From media reports it appears that CSL received about $120 million from our Federal Government for 21 million vaccine doses.[1] An added potential cost to the Government is the indemnity CSL received for any serious adverse events resulting from the vaccine.

Only a quarter of these doses were distributed[1] and the vaccine was presented in multidose vials. Multidose vials result in much higher vaccine wastage compared to single-use preloaded syringes.[2] I suspect that 30% of the distributed vaccine doses were never administered. Additionally, most of the vaccine given was to those over 65 years.[3] This age group already had high levels of pre-existing immunity to H1N1 (swine flu) and thus vaccination was not likely to have been much benefit for them.

The World Health Organization has documented the major infection problems associated with unsafe injection practices.[4] This results in millions of viral and bacterial infections every year, especially in developing countries.[5] Multidose vials and immunisation practices may only be a small component of this problem, but this risk can be virtually eliminated with the use of preloaded single-use syringes for vaccination (which we use for seasonal flu vaccinations here). Using single-use preloaded syringes also results in considerably less wastage of vaccine.[2] This reduced wastage will usually more than compensate for their small additional cost (about 14 cents).[2]

Multidose vials may sometimes have a place for the delivery of inexpensive vaccines in countries with low resources and poor infrastructure.[2] They have no place in a country such as Australia.

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Editor, – I was disappointed to read the editorial on H1N1 vaccination (Aust Prescr 2010;33:30–1), especially when the National Prescribing Service states that the publication is evidence-based and peer reviewed.

In particular, the article states: 'In the past, many infections, such as *Staphylococcus aureus*, hepatitis B and HIV, have been caused by vaccination programs using multidose vials.[2]' From my limited research, I am not aware of **any** past documented infections associated with general practice vaccination programs in Australia (as we are predominately using for H1N1 vaccination), nor any documentation of hepatitis B or HIV infections from any vaccination programs. Reference two in the editorial does not back up his claim – it in fact refers to the author's own article which has no comment on transmission of disease from multidose vials.

In addition, I question the balance of the author when discussing influenza vaccination. He quoted only one

study that 'showed that the decrease in all-cause mortality attributable to seasonal influenza vaccine was 4.6%', without noting the limitations of this study, nor referring to the wide body of international evidence supporting influenza vaccination, including those referenced in the 9th edition of the Australian Immunisation Handbook.

Although it is fair to comment that we would benefit from more effective influenza vaccines, and that policy makers must carefully review pandemic planning, including the role of multidose vials, I do not believe that the debate is assisted by claims that are not correctly referenced, nor highlighting of single studies. I would also question whether this editorial is consistent with the National Prescribing Service's claim to 'provide accurate, balanced, evidence-based information'.

Greg Rowles
General practitioner
Riddell Country Practice
Riddells Creek, Vic.

Professor Peter Collignon, author of the editorial, comments:

I agree with Dr Rowles that we need more effective influenza vaccines and a review of pandemic planning. I accept that it is best to reference primary sources rather than reviews. Unfortunately word and reference limitations in invited editorials make that difficult to do at times.

On the issue of efficacy, most studies on influenza vaccines have major biases.[1] Generally vaccination rates are lower in people who are most at risk of death and thus the benefits from influenza vaccination are likely overstated.[1,2] Morbidity and mortality are often lower in vaccinees, even before the start of the flu season, compared to controls. One of the few studies that have tried to untangle these biases was the one I quoted. This very large Californian study found a benefit for vaccination, but it was 10-fold less than previously attributed for influenza vaccination.[2]

Infection control guidelines recommend as best practice that single-dose vials are used wherever possible. There is extensive documentation on the transmission of many different viral and bacterial infections when multidose vials are used. This includes vaccination programs using multidose vials.[3–7]

In Australia we had the Bundaberg disaster in 1928. Diphtheria vaccine contaminated with *Staphylococcus aureus* from multidose vials caused the deaths of 12 children and resulted in a Royal Commission.[4] In Geelong in the late 1960s, two factory workers died from *Streptococcus pyogenes* following workplace flu vaccinations from multidose vials. The coroner subsequently recommended against the use of multidose vials.[5,6] More extensive references on this international problem have been discussed previously.[7]

Multidose vials are involved in the transmission of infectious organisms. I believe they should not be used in mass vaccination campaigns in Australia.

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Radiographic contrast media and metformin

Editor, – I write regarding the article dealing with radiographic contrast media (Aust Prescr 2010;33:19–22).

I have recently authored a systematic review relating to the safety of iodinated contrast in patients receiving metformin.[1] The review found no evidence to substantiate beliefs about the need to cease metformin in individuals with stable, normal renal function who were to have a 'normal' amount of intravenous iodinated contrast for an examination such as a CT scan. Despite a number of international guidelines having disparate recommendations about cessation of metformin, the Royal Australian and New Zealand College of Radiologists (RANZCR), the Royal College of Radiologists (RCR) and the European Society of Urogenital Radiology guidelines recommend that there is no need to stop metformin in these patients. The RANZCR recommendations are based on the extremely low risk of precipitation of contrast-induced nephropathy in this group. The Australian and RCR guidelines were modified along these lines in March and June 2009, respectively, soon after the systematic review was presented at the Radiological Society of North America meeting in December 2008.

Other work by Jeffrey Newhouse supports our findings that the risk of contrast-induced nephropathy has been exaggerated by research focusing on patients who have large volume, intra-arterial administration of iodinated media and by the lack of a genuine control group in many of the studies that have linked iodinated media to high rates of post-procedural contrast-induced nephropathy.

The advice by the radiologist to cease metformin, when this is not necessary, can have many unintended consequences such as the patient forgetting to recommence metformin. In addition, patients may visit their general practitioner for advice about when it is safe to recommence metformin, incurring costs to the health system.

The advice given in the *Australian Prescriber* article is entirely appropriate for patients who:

- are having large contrast volume, intra-arterial procedures (such as coronary angiography or interventional procedures) or
- are known to have abnormal or acutely deteriorating renal function.

However, this important distinction is not made clear in the article and general practitioners may interpret this advice to apply to their own practice context, which is largely CT scanning or other lower dose procedures associated with intravenous contrast media.

Stacy Goergen
Associate Professor, Director of Research
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Southern Health
Clayton, Vic.

Reference

1. Goergen SK, Rumbold G, Compton G, Harris C. Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. Radiology 2010;254:261-9.

Professor Ken Thompson and Dr Dinesh Varma, authors of the article, comment:

When writing this article we were well aware of the RANZCR guidelines and the issues of how to handle a patient with type 2 diabetes taking metformin who requires a contrast CT.

The RANZCR guidelines agree that it is difficult to measure estimated glomerular filtration rate (e-GFR) in all patients in an outpatient setting, although this is our practice.

While it is true that there is little or no high level evidence to recommend stopping metformin in patients with normal, stable renal function receiving a moderate dose of contrast media, the general practitioner who requests the contrast examination has no control over the actual amount of contrast media the patient is given. This may vary for a wide variety of reasons. An extremely low risk is not the same as no risk.

We were also influenced by the drug manufacturer's information and decided to provide advice that is consistent with the packaging information. In our view, the risk that a patient who takes a drug every day will forget to recommence the drug is unlikely.

Iodine allergy

Editor, – We would like to thank Professor Katelaris and Dr Smith for their timely article on the misleading label of iodine allergy (Aust Prescr 2009;32:125–8). This, as the authors indicate, is a marked source of anxiety for patients who need contrast media scanning.

We have also noted similar anxieties in patients who are potential candidates for the use of radioactive iodine (I-131) for the treatment of hyperthyroidism and thyroid cancer.

For patients who have a history of seafood or contrast sensitivity we arrange intravenous access as a precaution. However, in over 3000 administrations of oral high-dose radioactive iodine for thyroid cancer, we have not encountered any significant allergic phenomena.

We therefore feel that patients with seafood or contrast allergy can be reassured that this will not occur with low- or high-dose radioactive iodine.

Roger Allison
Radiation Oncologist and Executive Director
Cancer Care Services, Royal Brisbane and Women's Hospital

Robin Mortimer AO
Senior Endocrinologist, Royal Brisbane and Women's Hospital, and Senior Director, Office of Health and Medical Research

Queensland Health

Aliskiren and angioedema

Editor, – Aliskiren is a novel antihypertensive drug that is an orally-active direct renin inhibitor (Aust Prescr 2009;32:132–5). Its action shares a common biological pathway with angiotensin-converting enzyme (ACE) inhibitors. However, it has been suggested in an article by Professor Duggan that some respiratory and vascular adverse events were less likely than with the older drugs (Aust Prescr 2009;32:135–8). The proposal was fairly reasonable based on the different molecular target of the two drug groups. However, postmarketing experience revealed cases of aliskiren-associated angioedema and drug regulators implemented labelling changes and safety advice.[1–3] Therefore, physicians should be vigilant for the first signs of angioedema in aliskiren users. The biological basis, exact frequency and risk factors of this potentially life-treating event are currently not well understood. Until evidence becomes available, aliskiren and probably other similar drugs should not be used in patients with previous episodes of ACE inhibitor-induced angioedema of any clinical presentation.

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Department of Clinical Pharmacology, Medical Faculty and University Hospital
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3. Aliskiren. New contraindication and warning. WHO Pharmaceuticals Newsletter 2009;2:1.

Associate Professor K Duggan, author of the article, comments:

The true incidence of adverse effects often only becomes apparent after the drug has been marketed and my article was prepared before marketing. *De novo* angioedema as an adverse effect of the angiotensin receptor antagonists only became apparent postmarketing and the same appears to be occurring with aliskiren. Contraindications to the use of aliskiren should now include angioedema occurring as a consequence of the use of other renin-angiotensin drugs. This scenario highlights the importance of practitioners notifying regulatory bodies of adverse effects not previously reported.

Prescription drug subsidies in Australia and New Zealand

Editor, – The recent editorial on 'Prescription drug subsidies in Australia and New Zealand' (Aust Prescr 2010;33:2–4) reveals striking differences between the two countries in expenditure on prescription drugs. This is attributed in part to the New Zealand policy of exclusive contracts for supply of off-patent medications being awarded through competitive tender. The cost savings are obvious enough, but an additional benefit of this system is to make the generic brand instantly recognisable both for prescribers and consumers. The proliferation of generic brands in Australia, by contrast, leads to a great deal of confusion for patients. This often dissuades doctors from prescribing generic brands, at great cost to the health system.

Lachlan Brown
General practitioner/Anaesthetist
Batehaven, NSW

Editor, – The editorial by Steve Morgan and Katherine Boothe (Aust Prescr 2010;33:2–4) makes a number of concerning statements. The authors consider that Australia and New Zealand appear to be 'converging in their use of certain [pharmaceutical procurement] policy tools'.

The authors do not identify the major factor responsible for the success of the Pharmaceutical Management Agency of New Zealand (PHARMAC) in reducing prices paid for pharmaceuticals. PHARMAC is exempt from the entire portion of the New Zealand Commerce Act 1986 that deals with restrictive trade practices. The result is that PHARMAC is in a dominant position as a monopsony and is able to embark on negotiating tactics not allowed under World Trade Organization rules or national legislation in most other first world countries.

The authors have made comparisons of growth in costs between PHARMAC and OECD (Organisation for Economic Co-operation and Development) data. The conclusions drawn are unreliable as the reporting methods used to collect these data are not comparable over time (as stated by the OECD).[1]

Where the authors report 'conspicuously little evidence' of health outcomes related to pharmaceutical access being different between the countries, they indicate no attempt to identify differences in health outcomes. It would be imprudent to assume that the lack of epidemiological evidence to support worse health outcomes in New Zealand linked to pharmaceutical access vindicates the reduced access to medicines.

For these reasons, it is unlikely that Australia could or would choose to align itself more closely with the New Zealand methods of pharmaceuticals procurement.

Kevin Sheehy
Researched Medicines Industry Association of New Zealand
Wellington, New Zealand

Reference

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Editor, – Regarding your editorial on 'Prescription drug subsidies in Australia and New Zealand' (Aust Prescr 2010;33:2–4), there is a point which is not discussed which greatly reduces costs in New Zealand – that of bulk dispensing. New Zealand allows people with common chronic diseases to have three or six months supply of medicines dispensed at one time, as opposed to the monthly dispensing usual in Australia. This means that a New Zealander with say, high blood pressure, will pay two dispensing fees per year, whereas an Australian will likely pay 12 dispensing fees.

I understand the rationale behind monthly dispensing, but really, does a person who will be taking a drug for the rest of their lives need monthly intervention by a pharmacist, and does this happen in any but a small minority of cases? I have monthly prescriptions for blood pressure medication, and invariably I hand the repeat to an assistant, who hands it to a pharmacist, who types out a label saying 'Take one in the morning', passes it back to the assistant, who puts it in a bag and says to me '$33.30 please'.

Jonathan Rout
A concerned consumer
Redwood Park, SA

Multiresistant organisms at the front line

John Turnidge, *Clinical Director, Microbiology and Infectious Diseases, SA Pathology, Adelaide*

Summary

Multiresistant bacterial pathogens such as methicillin-resistant *Staphylococcus aureus*, multiresistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci and multiresistant *Pseudomonas aeruginosa* are being seen with increasing frequency in the community and not just in hospital practice. Treatment options for infections caused by these pathogens are limited, but in most cases a suitable drug can be found. In particular, there are options for the treatment of the community-associated strains of MRSA, such as trimethoprim-sulfamethoxazole, and often macrolides or lincosamides.

Key words: antibiotic resistance, MRSA.

(Aust Prescr 2010;33:68–71)

Introduction

General practitioners are often faced with patients suffering from infections caused by bacteria harbouring some kind of antibiotic resistance. Many of these resistances are so common that we take them for granted – for example, penicillin resistance in *Staphylococcus aureus* occurs in about 90% of community strains, and amoxycillin resistance in about 50% of *Escherichia coli*. Usually there are options for antibiotic treatment (see Table 1), and laboratories attempt to provide susceptibility data. However, for some resistant organisms the options are limited, problematic or both. The generic term for these strains is multiresistant organisms.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Even though methicillin itself is no longer used, the term methicillin-resistant is still used to identify these very important multiresistant organisms. The general practitioner is likely to encounter two types of MRSA. These are the multiresistant MRSA strains that are hospital-associated which are found colonising or occasionally infecting patients who have previously been hospitalised, and the non-multiresistant community-associated MRSA strains which are found in all those common circumstances where one would expect to see susceptible *S. aureus*, namely boils, furuncles, cellulitis and wound infections. Purulent forms of staphylococcal skin infection respond best to drainage, and for small lesions drainage without antibacterial treatment will be usually adequate.[1]

When antibacterial treatment is required for MRSA infection, the choice is driven by whether the infecting strain is hospital- or community-associated. Choices for hospital-associated MRSA are quite limited. Serious infection requires hospitalisation and intravenous vancomycin, while less serious infections require an oral combination of rifampicin and fusidic acid. This oral combination is essential to avoid the selection of further resistance during treatment. Unfortunately, the Pharmaceutical Benefits Scheme (PBS) only subsidises rifampicin for indications other than staphylococcal infection, while fusidic acid – which the PBS states must be used in combination – is available for just such an indication. Hence, adequate treatment for hospital-associated MRSA often requires a return visit to hospital to ensure timely access to appropriate drugs.

There are usually more treatment options for community-associated MRSA than for hospital-associated infections. Most strains are susceptible to macrolides (erythromycin, roxithromycin, clarithromycin and azithromycin) and lincosamides (clindamycin and lincomycin), as well as trimethoprim/sulfamethoxazole and tetracyclines. Susceptibility to erythromycin predicts susceptibility to clindamycin, which is considered the drug of choice (when one is required) for mild to moderate community-associated MRSA. The other drug for which there is most experience in less severe infection is trimethoprim/sulfamethoxazole. This is recommended for young children as clindamycin suspension is not available, or when resistance to erythromycin (which more often than not predicts resistance to clindamycin) is suspected or proven. Tetracyclines such as doxycycline can be used for minor community-associated MRSA, although their use should probably be reserved for patients allergic to a trimethoprim/sulfamethoxazole component, and only in those more than eight years of age. Patients with serious infections caused by community-associated MRSA should be hospitalised and treated with vancomycin initially.

Table 1

Treating multi-drug resistant infections in the community

Multiresistant organism	Resistance pattern	Infection	Drug of choice for mild to moderate infection
Hospital-associated MRSA	Pattern 1 Penicillin **R** Methicillin **R** Erythromycin **R** Tetracycline **R** Trimethoprim/sulfamethoxazole **R** Ciprofloxacin **R** or **S** Pattern 2 Penicillin **R** Methicillin **R** Erythromycin **R** mostly Tetracycline **S** Trimethoprim/sulfamethoxazole **S** Ciprofloxacin **R**	Any	Rifampicin plus fusidic acid
Community-associated MRSA	Penicillin **R** Methicillin **R** Erythromycin **S** mostly Tetracycline **S** Trimethoprim/sulfamethoxazole **S** Ciprofloxacin **S**	Any	Clindamycin
Multiresistant *Streptococcus pneumoniae*	Penicillin **R** Amoxycillin **S** or **R** Erythromycin **R** Tetracycline **R** Trimethoprim/sulfamethoxazole **R**	Otitis media, sinusitis, acute exacerbations of chronic bronchitis, pneumonia	Amoxycillin Moxifloxacin for adult patients (≥18 years) with penicillin allergy
Vancomycin-resistant enterococci	Penicillin and/or amoxycillin **S** or **R** Vancomycin **R**	Urinary tract	Nitrofurantoin or norfloxacin
Multiresistant *Escherichia coli*	Amoxycillin **R** Amoxycillin/clavulanate **S** / **I** / **R** Cefazolin/cephalexin **R** Trimethoprim/sulfamethoxazole **R** Cefotaxime or ceftriaxone **S** or **R**	Urinary tract	Amoxycillin-clavulanate if susceptible. Otherwise norfloxacin if susceptible.
		Other sites	Amoxycillin-clavulanate if susceptible. Otherwise ciprofloxacin if susceptible.
Other multiresistant enteric bacteria	*Klebsiella* species Amoxycillin **R** Amoxycillin/clavulanate **S** or **R** Cefazolin/cephalexin **R** Trimethoprim/sulfamethoxazole **S** or **R** Cefotaxime or ceftriaxone **S** or **R** *Enterobacter* species Amoxycillin **R** Amoxycillin/clavulanate **R** Cefazolin/cephalexin **R** Trimethoprim/sulfamethoxazole **S** or **R** Cefotaxime or ceftriaxone **S** or **R**	Urinary tract	Amoxycillin-clavulanate if susceptible. Otherwise norfloxacin if susceptible.
		Other sites	Amoxycillin-clavulanate if susceptible. Otherwise ciprofloxacin if susceptible.
Multiresistant *Pseudomonas aeruginosa*	Ticarcillin **S** or **R** Ceftazidime **S** or **R** Meropenem **S** or **R** Gentamicin **S** or **R** Tobramycin **S** or **R** Norfloxacin **S** or **R** Ciprofloxacin **S** or **R**	Urinary tract	Norfloxacin or ciprofloxacin if susceptible

MRSA methicillin-resistant *Staphylococcus aureus*
R resistant
S susceptible
I intermediate

Colonisation

In general, treatment should not be administered to patients who are merely colonised with MRSA, even in long-term care facilities, where the risk of transmission is higher. Topical (nasal) mupirocin in particular has a very limited role because its effect is short-lived and confined to the nostrils. Eradication of the colonised state is difficult and treatment should only be considered if the patient has proven recurrent furunculosis due to nasal carriage of MRSA. Topical treatment should only be used as part of a more intensive regimen involving systemic antimicrobials not readily available in community practice.

Multiresistant *Streptococcus pneumoniae*

Before the introduction of a conjugate pneumococcal vaccine into the childhood immunisation schedule, the proportion of multiresistant *S. pneumoniae* strains in the community was increasing. They are less prevalent now, in part due to the overall decrease in pneumococcal infections as a result of the conjugate vaccine, but they will still be encountered.[2]

As many multiresistant *S. pneumoniae* strains are isolated from young children, the combination of multiresistance and a more restricted range of oral suspensions makes optimising treatment difficult. Resistance to macrolides, lincosamides, tetracyclines and trimethoprim/sulfamethoxazole is common in *S. pneumoniae*, especially in strains with reduced susceptibility to penicillins. Over 10% of Australian isolates have this resistance pattern. Paradoxically, strains with reduced susceptibility to penicillins generally remain susceptible to oral amoxycillin in higher doses (up to 1 g every eight hours). This makes amoxycillin the drug of choice for mild to moderate infections, even for the great majority of multiresistant strains, and it is currently recommended in Australian guidelines.[3]

Penicillin-allergic patients

Problems arise in the penicillin-allergic patient. Oral cephalosporins are ineffective against strains of *S. pneumoniae* with even slightly reduced susceptibility to penicillin. In adults, moxifloxacin is the most suitable choice, although this is not readily available on the PBS. For children with an allergy to beta-lactam antibiotics (12 years or younger) there is currently no entirely satisfactory oral treatment. Fortunately, penicillin allergy in young children is uncommon. Options range from trying a macrolide or trimethoprim/sulfamethoxazole if they are only mildly unwell, to hospitalisation for parenteral therapy in a sicker child.

Vancomycin-resistant enterococci

Vancomycin-resistant enterococci are usually hospital-associated multiresistant organisms. While they are unlikely to spread widely in the community, an increasing number of patients are becoming colonised in hospital and a small percentage will subsequently develop an infection with the colonising strain after being discharged. Most of these infections will be in the urinary tract.

Vancomycin-resistant enterococci strains are difficult to manage for a number of reasons, including their high transmissibility in the hospital setting, and more importantly because of the very limited range of antimicrobials available to treat them. Enterococci are naturally resistant to many antibacterial drugs including macrolides, lincosamides, cephalosporins and trimethoprim/sulfamethoxazole. There are two prominent vancomycin-resistant enterococci phenotypes: resistant to vancomycin and teicoplanin (so-called VanA), and resistant to vancomycin but susceptible *in vitro* to teicoplanin (so-called VanB). Unlike in other countries, the predominant phenotype in Australia is VanB.

The choice of treatment for vancomycin-resistant enterococci infection depends on the severity of the infection and which species is causing it. *Enterococcus faecalis* strains are mostly susceptible to penicillin and amoxycillin, and these drugs can be used (in higher dosages) provided the patient is not allergic to penicillin. On the other hand, most *Enterococcus faecium* strains are resistant to penicillin and amoxycillin, and drugs that are only available in hospital may be the only option. These important reserve drugs, such as linezolid and daptomycin, are effective parenteral drugs. Fortunately, nitrofurantoin and norfloxacin remain options for urinary tract infections caused by either VanA or VanB.

Colonisation

There are no effective treatments for the colonised state. Furthermore, if the isolate is from the urine of a patient with an indwelling catheter without any systemic symptoms, this represents colonisation rather than true infection and treatment is not warranted.

Multiresistant *Escherichia coli*

Over 5% of clinical *E. coli* isolates in Australia are resistant to more than three antibacterial drugs recommended for use – resistance to amoxycillin, cefazolin/cephalexin and trimethoprim/sulfamethoxazole is the commonest profile.[4] Reduced susceptibility or resistance to amoxycillin-clavulanate is also found in more than 8% of all *E. coli* and in up to 13% of amoxycillin-resistant strains, so strains with multiresistance are encountered in general practice. Fortunately, most strains at present still remain susceptible to the fluoroquinolones (norfloxacin and ciprofloxacin) and to nitrofurantoin. The recent increase in community strains harbouring extended-spectrum beta-lactamases is concerning – these enzymes make *E. coli* resistant to third-generation cephalosporins

(cefotaxime and ceftriaxone). These strains are often resistant to gentamicin and/or fluoroquinolones so when treating multiresistant *E. coli* infection, the susceptibility test results are required to ensure that an appropriate effective drug is chosen.

Other multiresistant enteric bacteria

Klebsiella species are found in similar clinical settings to *E. coli* in community practice. They are naturally resistant to amoxycillin, and have a higher propensity to acquire resistances than *E. coli*. Almost 10% of strains are multiresistant (more than three acquired resistances).[4] Treatment options are similar to *E. coli*, again taking careful heed of the susceptibility test results.

Less commonly encountered multiresistant enteric bacteria are *Enterobacter* species, which are naturally resistant to amoxycillin, amoxycillin-clavulanate and cefazolin/cephalexin. Furthermore, these species can become resistant to third-generation cephalosporins during treatment. Treatment choices are restricted to trimethoprim/sulfamethoxazole or fluoroquinolones if susceptible on testing, or carbapenems for serious infection.

Multiresistant *Pseudomonas aeruginosa*

P. aeruginosa is naturally resistant to many antibacterial drugs. Without acquired resistance, this species is only susceptible to a limited range of beta-lactams (ticarcillin, piperacillin, ceftazidime, cefepime and meropenem), aminoglycosides (gentamicin, tobramycin and amikacin) and fluoroquinolones (norfloxacin and ciprofloxacin). Furthermore, *P. aeruginosa* has a high propensity to mutate to or acquire resistance to any of these drugs. Hence, in certain clinical settings such as intensive care and in patients with cystic fibrosis, multiresistant strains of *P. aeruginosa* are common.

Multiresistant strains may be encountered in the community, most commonly in complicated urinary tract infection. Treatment of mild to moderate urinary infection caused by these strains will be defined by the results of susceptibility tests. If the isolate is susceptible to ciprofloxacin, this drug can be given orally to outpatients. Otherwise, all other drugs must be administered parenterally, and hospital management is usually required. Strains isolated from otitis externa will usually respond adequately to topical treatment.

Conclusion

Although there are limited treatment options for infections caused by multiresistant organisms, there are still drugs available in the community in many cases and hospitalisation for more complex parenteral therapy can be avoided. In general, treatment of colonisation with multiresistant organisms is not required.

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In the last two years, Professor Turnidge has sat on anti-infective advisory boards for Janssen-Cilag and Pfizer.

Dental notes

*Prepared by **Michael McCullough**, Chair, Therapeutics Committee, Australian Dental Association*

The increasing prevalence of multiresistant bacteria in community-associated infections is most likely caused by over-prescription of antibiotics. The majority of dental infections can be successfully treated with an accurate diagnosis and timely dental treatment without antibacterial medication. When antibacterial drugs are needed, the principle of using a drug with the narrowest spectrum has long been held and is clearly outlined in recent guidelines.[1] Studies have shown that 85% of oral bacteria are susceptible to penicillin V. This is only marginally higher – 91% – with amoxycillin.[2] Over 10% of Australian *Streptococcus pneumoniae* isolates have reduced susceptibility to penicillins, yet these isolates paradoxically remain susceptible to higher doses of oral amoxycillin. Potentially life-threatening *S. pneumoniae* infections in children can be effectively treated with high-dose amoxycillin and this is one of the clinical reasons why amoxycillin is not recommended as the first drug of choice for oral infections.[1] Dentists should be aware of changing drug-resistance patterns and use antibiotics judiciously.

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Managing cardiovascular disease in Aboriginal and Torres Strait Islander people

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Summary

Cardiovascular diseases are responsible for much of the reduced life expectancy of Aboriginal and Torres Strait Islander people. Modification of cardiovascular risk factors is important, especially as calculators may underestimate the absolute risk of a cardiovascular event. Smoking cessation is a key component of primary and secondary prevention. As cardiovascular disease can begin early in life, screening for risk factors from the age of 18 years is recommended. Drug therapy is similar to that for other patients, but may need to be started sooner, particularly as comorbidities are common. Risk factors do not account for all of the increased mortality, so psychosocial and other factors need to be considered.

Key words: hypertension, preventive medicine.

(Aust Prescr 2010;33:72–5)

Introduction

Aboriginal and Torres Strait Islander Australian people born in 2005–2007 are expected to die approximately 11 years earlier than other Australians.[1] Many factors are responsible for this gap in life expectancy and comprehensive approaches are required to address this inequality. Primary healthcare providers can play an important role, particularly in prevention.

Cardiovascular disease is the leading cause of reduced life expectancy. Between 2002 and 2005 cardiovascular disease accounted for 27% of all Aboriginal and Torres Strait Islander deaths.[2] There are excess death rates in every age category and across all jurisdictions where reliable data are available. The incidence of cardiovascular events in urban communities is likely to be similar to that in rural and remote communities.[3]

The specific diseases contributing to these excess deaths are coronary heart disease, cerebrovascular disease, heart failure and hypertension. Rheumatic heart disease contributes a small proportion of the overall mortality, but the rate of rheumatic heart disease in Aboriginal and Torres Strait Islander people is among the highest in the world.

While the management of cardiovascular disease has similarities for all patients, some approaches are specific to Aboriginal and Torres Strait Islander people. Relevant resources and management recommendations are summarised in Table 1 and Box 1.

Table 1

Resources specific for Aboriginal and Torres Strait Islander people

Resource	Source *
Calculator for absolute risk assessment with provision for estimation of risk for Aboriginal and Torres Strait Islander people from age 35 years	www.heartfoundation.org.au
National guide to a preventive health assessment in Aboriginal and Torres Strait Islander peoples, NACCHO and RACGP, NACCHO 2005	www.racgp.org.au
Guidelines for the diagnosis and management of acute rheumatic fever and rheumatic heart disease	www.heartfoundation.org.au
Preferential access to Pharmaceutical Benefits Scheme items for Aboriginal and Torres Strait Islander people, e.g. nicotine replacement therapy	www.pbs.gov.au
Cultural safety training	www.culturalsafetytraining.com.au

NACCHO National Aboriginal Community Controlled Health Organisation
RACGP Royal Australian College of General Practitioners
* See full URLs online with this article at www.australianprescriber.com

Primary prevention

Modifying risk factors with Aboriginal and Torres Strait Islander patients is a key preventive health strategy. They are more likely than other Australians to smoke and to have hypertension, obesity, hyperlipidaemia, diabetes and renal disease.[4]

Absolute risk assessment is important in the prevention of cardiovascular disease.[5] Modifications have been made to absolute risk assessment tools to facilitate the estimation of risk from age 35 years in Aboriginal and Torres Strait Islander people not already known to be at high risk for cardiovascular disease. It is likely, however, that these tools will still underestimate the risk in this population.[5] Clinical judgement is therefore required when using absolute risk calculators for Aboriginal and Torres Strait Islander people.

Individual risk assessment every 1–2 years is recommended for Aboriginal and Torres Strait Islander people from 18 years of age. This screening is supported by access to the Aboriginal and Torres Strait Islander Adult Health Check Medicare items.

Screening includes lifestyle assessment and measurement of blood pressure, weight, body mass index, waist circumference and fasting lipid status. Given the high prevalence of diabetes and renal disease and the impact of these diseases on cardiovascular disease risk, routine screening should include dipstick testing for proteinuria and fasting blood glucose, starting from 15–18 years of age.[6] Screening should also include assessment of pulse and follow-up of irregularities to diagnose and treat atrial fibrillation. Screening provides an ideal opportunity to promote a healthy diet, physical activity, smoking cessation, moderation of alcohol consumption and weight control.[6]

These risk factors do not, however, explain all of the increased burden of cardiovascular disease among Aboriginal and Torres Strait Islander people. Psychosocial,[7] socio-economic and *in utero* factors[8] are likely to contribute substantially to the risk in these communities. The synergistic effect of multiple risk factors also impacts on the differential burden of cardiovascular disease.[4]

Given the multiple morbidities common in their communities, Aboriginal and Torres Strait Islander people are more likely than other Australians to fall within a group defined as at high risk of cardiovascular disease.[5] Those at high risk will benefit from intensive management including drug therapy.

Secondary prevention

Secondary prevention strategies aim to prevent further deterioration in those who have been diagnosed with cardiovascular disease.[4] The reduction of risk of a major coronary event or death has been quantified (Box 2).[4] These benefits are likely to apply to Aboriginal and Torres Strait Islander people.

Smoking cessation

Aboriginal and Torres Strait Islander people are approximately twice as likely to smoke as other Australians. Addressing this risk factor is likely to have a substantial impact on reducing morbidity and premature death rates. In general practice, a brief intervention counselling approach is recommended.[9] Nicotine replacement therapy is available on the Pharmaceutical Benefits Scheme (PBS) for Aboriginal and Torres Strait Islander patients. The use of other drugs to assist in smoking cessation requires careful consideration of the benefits and risks for the individual patient. There is also evidence in Aboriginal and Torres Strait Islander communities of the efficacy of community-based approaches.[9]

Box 1

Recommended approaches to cardiovascular disease in Aboriginal and Torres Strait Islander people

Screening and prevention

Individual risk assessment every 1–2 years from age 18 years including:[9]

- measurement of blood pressure, weight, body mass index, waist circumference, pulse for atrial fibrillation, fasting lipid and blood glucose, and urine testing for proteinuria
- calculation of absolute cardiovascular risk from age 35 years[5]
- promotion of healthy diet, weight control, physical activity, smoking cessation and moderation of alcohol consumption

Treatment

Early use of antihypertensives[4] – consider ACE inhibitors or angiotensin receptor antagonists as first-line drugs
Start treatment with cholesterol-lowering drugs when LDL cholesterol remains >2.5 mmol/L after lifestyle modification[12]
Cholesterol-lowering drugs may be prescribed on the Pharmaceutical Benefits Scheme:

- at any lipid level for patients with diabetes
- if total cholesterol >6.5 mmol/L or total cholesterol >5.5 mmol/L and HDL cholesterol <1 mmol/L

ACE angiotensin-converting enzyme
HDL high density lipoprotein
LDL low density lipoprotein

Box 2

Relative reduction in risk of major coronary event or death following secondary prevention activities [4]

67% risk reduction for people under 65 years who have never smoked

40% risk reduction for people 65 years and over who have never smoked

22% risk reduction with ACE inhibitors

20% risk reduction with beta blockers

20% risk reduction if cholesterol controlled

20% risk reduction in people who are physically active

19% risk reduction with aspirin

14% risk reduction if blood pressure controlled

Nutrition and physical activity

Adoption of traditional dietary and food gathering practices has been shown to reduce risk factors for metabolic syndrome.[10] For most Aboriginal and Torres Strait Islander people this is not possible. There is also often difficulty in accessing affordable, healthy food.[6] Community-based programs may assist in improving both access to and acceptability of healthy foods. Reduction in alcohol consumption may reduce the risk of cardiovascular disease through its impact on diet, blood pressure and weight.[5] It may also increase adherence to other risk reduction measures.

Regular physical activity prevents the development of risk factors for cardiovascular disease. When combined with other secondary prevention strategies in cardiac rehabilitation programs it has been shown to reduce cardiovascular mortality.[4]

Pharmacological management

Recommendations for pharmacological management for those at risk or with a past history of cardiovascular disease are similar to those for non-indigenous Australians.[11] Aspirin in a dose of 75–150 mg/day reduces the risk of serious vascular events in those who have been diagnosed with cardiovascular disease. For those who are intolerant or allergic to aspirin, clopidogrel is an appropriate alternative.[11]

In recognition of the risk for Aboriginal and Torres Strait Islander people, cholesterol-lowering drugs are available through the PBS at lower thresholds than for other patients. 'Statin' therapy is recommended for Aboriginal and Torres Strait Islander patients if their low density lipoprotein cholesterol remains above 2.5 mmol/L after lifestyle modification.[12]

Early treatment with antihypertensive medication is recommended for Aboriginal and Torres Strait Islander patients with hypertension.[13] While the first choice of drug depends on comorbidities and contraindications, in Aboriginal and Torres Strait Islander patients, given the high prevalence of diabetes, an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor antagonist is recommended.[4]

Polypill formulations including combinations of the recommended pharmaceutical drugs are currently being trialled to evaluate their usefulness as an aid to adherence to the long-term use of multiple drugs. The results of these studies are likely to inform best practice guidelines in the future.

Acute management of symptomatic disease

Health professionals working in Aboriginal and Torres Strait Islander communities need to maintain a high index of suspicion regarding cardiovascular disease. It occurs in people of all ages and in women as well as men. Patients may also overlook or minimise symptoms.

Even where relevant health facilities are available, Aboriginal and Torres Strait Islander patients are less likely to receive cardiovascular procedures including angiography, percutaneous coronary interventions and bypass surgery.[4] The primary healthcare provider has a key role in recognising the need for procedural intervention and advocating for access to appropriate intervention and to subsequent cardiac rehabilitation.

Primary healthcare approaches

A key to effective primary health care is identification of Aboriginal and Torres Strait Islander patients and awareness of their increased prevalence of cardiovascular disease and related risk factors at a much earlier age. Computerised alerts and practice-based screening can assist in preventive and follow-up activities.

Cultural issues, the history of Aboriginal and Torres Strait Islander people and the overwhelming burden of disease may make lifestyle change and access to appropriate health care a challenge for some Aboriginal and Torres Strait Islander patients. It is important to avoid judgement and blame and to seek to understand the barriers and facilitators for each patient. Cultural safety training may assist healthcare providers in understanding these issues (Table 1). A health professional who understands the barriers for a patient in accessing health care is able to work more effectively with the patient and other health professionals to improve access, rather than assuming that a referral will result in the required health care.

The 'normality' of premature death and multiple morbidity in Aboriginal and Torres Strait Islander communities can result in an acceptance of ill health that at times becomes a barrier to change. If healthcare providers focus on each disease, this can sometimes contribute to the patient's sense that it is 'all too much'. It is critical to work with the patient using an optimistic and holistic approach to identifying changes they are able to make. This is best grounded in a trusting long-term

relationship with a respectful practitioner who is willing to learn from and advocate for their patient.

Community-based approaches

Access to care is a key consideration in the management of cardiovascular disease. Aboriginal and Torres Strait Islander people are disadvantaged by reduced access to medicines, delayed access to acute care facilities and lower rates of intervention once they are admitted to these facilities.[4]

There is a need to address community awareness as well as systemic barriers contributing to premature death from cardiovascular disease. Primary healthcare providers have a key role in improving awareness and access to local services for Aboriginal and Torres Strait Islander people. Community-based programs with a focus on education and empowerment as a means of improving access to integrated health services have been shown to improve health outcomes.[14]

Health services controlled by Aboriginal communities also provide expertise and often a range of relevant programs including access to Aboriginal health workers and other allied and specialist healthcare providers. These services may also offer programs addressing psychosocial and other risk factors contributing to the increased burden of cardiovascular disease.

Indigenous-specific resources such as information brochures and waiting room posters which address cardiovascular disease and related risk factors may be available from state and territory health departments.

Conclusion

Effective management of cardiovascular disease in Aboriginal and Torres Strait Islander communities has the potential to make a huge difference in health outcomes beyond those of the individual patient. The management tools are the same as, or adaptations of, those used in the general community and are readily accessible to the practitioner with Aboriginal and Torres Strait Islander patients.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 95)

1. Lifestyle interventions for cardiovascular disease are ineffective in Aboriginal and Torres Strait Islander people.
2. Screening for cardiovascular risk factors in Aboriginal and Torres Strait Islander people should begin from the age of 18 years.

The safety of plasma-derived products in Australia

***Andrew Guirguis**, Transfusion Medicine Registrar, and **Erica Wood**, Transfusion Medicine Specialist, Australian Red Cross Blood Service, and Alfred Hospital, Melbourne*

Summary

Plasma-derived products are used in Australia in a wide variety of clinical settings. The majority of these products are manufactured locally from voluntary blood donations. The preparation of plasma products is subject to rigorous safety measures, including screening blood donors, testing plasma for infectious material, and subjecting plasma to dedicated pathogen inactivation steps. The safe use of plasma derivatives requires correct storage and handling.

Key words: coagulation, intravenous immunoglobulin, pathogen inactivation.

(Aust Prescr 2010;33:76–9)

Introduction

Plasma derivatives, prepared by fractionating donated human plasma, are used in a wide range of medical conditions. Australia's national policy for these essential products is to strive for self-sufficiency. A recent review of the policy found that, while Australia has never completely produced all of its own plasma derivatives, 'Australia should be as self-sufficient as possible, and that self-sufficiency should remain an important goal'.[1]

Plasma products used in Australia

Plasma-derived products can be divided into three broad categories: immunoglobulins, coagulation factors and albumin (Table 1). These are primarily used to replace missing or dysfunctional elements of the immune or coagulation systems. In the case of RhD immunoglobulin or intravenous immunoglobulin, their primary role is to modulate the immune system's responses. The uses of intravenous immunoglobulin continue to increase,[2] particularly as immunological bases for more conditions are revealed. Future demand for intravenous immunoglobulin may be altered by the advent of new, more targeted therapies for conditions with an autoimmune basis. The demand for coagulation factors is influenced by the availability of specific recombinant products which are not plasma-derived.

Plasma supply

The Australian Red Cross Blood Service, under medical oversight and operating within the principles of Good Manufacturing Practice and a licence from the Therapeutic Goods Administration (TGA), collects plasma from volunteer, non-remunerated donors.

The safety of these blood-derived products remains of utmost importance. Although Australia's blood supply is safer than it has ever been from an infectious diseases point of view, vigilance is still required against known pathogens (such as prions associated with variant Creutzfeldt-Jakob disease), currently unknown pathogens and other associated risks. The Blood Service actively monitors for new and emerging infectious threats to blood safety.

Screening blood donors

Stringent criteria must be met before the donation of blood is permitted in Australia, and recruitment and retention of low-risk, volunteer donors is a key element in maintaining the safety of the plasma supply. Donors with temporary or indefinite ineligibility are deferred as appropriate, to minimise the risks of pathogens being present in the plasma sent for fractionation. Each donor undergoes a detailed, confidential interview and health screen.

Collecting, testing and processing plasma

Once donor eligibility has been established, collection of whole blood or plasma (by plasmapheresis) occurs in accordance with strict safety and quality requirements. Whole blood is separated into its components (red cells, platelets and plasma) within specified time and temperature conditions to maintain plasma integrity. Bar coding of all samples and kits permits traceability at each step of the process.

All donor samples undergo pathogen screening using routine serological and nucleic acid testing (see box). Targeted serological testing may also be performed, such as malaria testing for a donor with a relevant travel history.

Nucleic acid-based amplification tests are used to directly detect viral genomes, while most serological tests rely upon detection of an immune response to infection, such as an antibody. The exquisite sensitivity of nucleic acid testing can reduce the window period for detection (from time of infection to time of detection) from 66 days to approximately 5 days for hepatitis C, and from 22 days to 9 days for HIV. Only donations with acceptable test results are released for further processing.

Table 1

Fractionated plasma products commonly used in Australia

Product	Indication or use	Comments*
Immunoglobulins		
Normal immunoglobulin		
- intravenous	Immune replacement in congenital and acquired immune deficiencies Immunomodulation in a range of haematological (e.g. immune thrombocytopenic purpura), neurological (e.g. Guillain-Barré syndrome), dermatological and other conditions (e.g. Kawasaki syndrome), usually only when other treatments have failed or are contraindicated	No alternative therapy for many patients with immune deficiency. There has been increased demand in recent years for immunomodulation, with a wide range of conditions reported to benefit from treatment with IV immunoglobulin. See 'Criteria for the clinical use of intravenous immunoglobulin in Australia',[2] www.transfusion.com.au, www.cslbioplasma.com.au and www.octapharma.com
- intramuscular	For passive immunisation of contacts of cases – hepatitis A, measles, poliomyelitis and rubella	Less commonly used for these indications since vaccination programs have been expanded. See www.transfusion.com.au and www.cslbioplasma.com.au
Hyperimmune immunoglobulin		
- RhD	Prevention of antenatal and postnatal RhD sensitisation in RhD negative women. Also used to prevent RhD alloimmunisation in the unlikely event of an RhD incompatible transfusion.	More information on prophylaxis in pregnancy including types of sensitising events, doses used at different stages of pregnancy and postpartum is available at www.transfusion.com.au For large doses or if IM preparation cannot be used (e.g. very large fetomaternal haemorrhage, or RhD incompatible red cell transfusion, or RhD incompatible platelet transfusion in a patient with thrombocytopenia), an IV preparation is available.
- cytomegalovirus	Prevention or treatment of cytomegalovirus infection in immunocompromised patients	See www.transfusion.com.au and www.cslbioplasma.com.au
- zoster	Prevention of chickenpox or shingles in immunocompromised patients exposed to varicella zoster virus	
- tetanus	Prevention of tetanus in tetanus-prone wounds (IM formulation) or treatment of clinical tetanus (IV formulation)	
- hepatitis B	Post-exposure prophylaxis for hepatitis B where vaccination has not been given or is incomplete, including infants born to hepatitis B-positive mothers	
- others (e.g. rabies immunoglobulin)		Used rarely in Australia and only with specialist advice
Coagulation factors		
Prothrombin complex concentrate	Warfarin reversal and prophylaxis and treatment of bleeding in patients with single or multiple congenital or acquired deficiencies of factor II or X or multiple acquired prothrombin complex factor deficiencies requiring partial or complete reversal	Contains factor IX, II and X and low levels of factor VII. Use in accordance with guidelines.[8]
Factor VIII, von Willebrand factor	Prophylaxis and management of bleeding in patients with von Willebrand disorder	Contains both coagulation factor VIII and von Willebrand factor. Most patients with haemophilia A are now treated with recombinant factor VIII.
Other plasma-derived factor concentrates (e.g. factor XI, XIII, antithrombin)	These are used in very limited circumstances under the supervision of a specialist	For more information on the use of plasma-derived products for bleeding disorders, see the Australian Haemophilia Centre Directors' Organisation www.ahcdo.org.au
Albumin		
Albumin 4%	For hypovolaemia associated with hypoalbuminaemia, and in therapeutic plasma exchange	Albumin and saline for volume replacement in the critically ill were found to be equally safe and effective.[9]
Albumin 20%	Used in shock and hypoproteinaemic states such as burns and paracentesis of ascites	The 20% formulation is hyperoncotic and fluid overload can develop rapidly

* See full URLs online with this article at www.australianprescriber.com

IM intramuscular

IV intravenous

Box

Routine pathogen screening tests for blood donor samples in Australia

Nucleic acid tests

HIV-1
Hepatitis B (this test will be implemented in 2010)
Hepatitis C

Serological tests

HIV-1/2
Hepatitis B
Hepatitis C
Syphilis
Human T cell lymphoma virus I/II

Current risks of transfusion-transmitted infections from fresh blood components – red cells, platelets and plasma – collected in Australia are extremely low. These estimates are available from the Australian Red Cross Blood Service[3] and are updated annually.

Once pathogen screening is complete, most plasma is dispatched for manufacturing. A small percentage is retained for clinical use as fresh frozen plasma and cryoprecipitate. Transport and storage occurs at below –20° C to retain plasma coagulation factor levels and other functional activity.

Manufacturing plasma products

The majority of plasma-derived products used in Australia are manufactured from Australian-sourced plasma. Some products are imported, including some coagulation factors and immunoglobulins, either to supplement domestic supplies (for example, intravenous immunoglobulin) or to provide products which are not presently manufactured in Australia, such as fibrinogen concentrates. A review of Australia's plasma fractionation arrangements found that maintenance of product safety, quality and availability would be best achieved by fractionation of Australian plasma continuing locally.[1] Other advantages of local production were also noted, in terms of overall costs, turnaround times, management of risks to safety and availability of plasma supplies and, importantly, maintaining the confidence and support of Australian blood donors.

Plasma-derived products are typically prepared from pooled plasma, with a pool often consisting of thousands of donations. All plasma samples are uniquely identified to ensure ongoing traceability. Pooling minimises the infective risk, should the plasma pool be contaminated by a potentially infected donation. Infectious material present in one donation may be rendered below the infectious threshold by dilution in a pool of thousands of donations or may be neutralised by protective antibody present from other donations in the pool. However, pooled plasma products are usually distributed to many patients, so infectious material not eliminated during manufacturing could potentially cause harm to many recipients. Further serological and nucleic acid testing is also performed on starting pool samples and only pools with acceptable testing results proceed to further manufacturing.

Plasma fractionation

The fractionation process includes physical separation using precipitation and chromatography. Chromatography separates molecules from a liquid solution based on chemical and physical properties, enabling partition and purification of immunoglobulins, clotting factors and albumin from plasma.

The fractionation process also contributes to non-specific reduction of viruses and other pathogens, including prions (although variant Creutzfeldt-Jakob disease has not been identified in Australia). Each component manufactured from Australian plasma undergoes two dedicated pathogen reduction steps. These have been validated to remove or inactivate potential pathogens[4] and include:

- dry heat treatment (80° C for 72 hours) or pasteurisation (vapour heat at 60° C for 10 hours)
- use of solvents and detergents
- exposure to low pH conditions
- nanofiltration.

These are performed according to approved manufacturing processes for each product. No confirmed transmissions of viruses have occurred from products used in Australia since effective dedicated pathogen inactivation and removal steps were introduced. However, non-enveloped viruses such as parvovirus B19 and hepatitis A remain a concern for some products, as current viral inactivation or removal techniques are variably effective against these.

Quality control

The fractionation process proceeds under strict regulatory oversight in a highly controlled manufacturing environment. Cleaning and sanitation protocols prevent cross-contamination of batches. Quality control and release testing monitors interim and final products against approved plasma specifications agreed upon by the manufacturer and the TGA.

All therapeutic products used in Australia, whether manufactured locally or imported, are registered on the Australian Register of Therapeutic Goods and must meet the stringent regulatory requirements of the TGA. However, some variations between local and imported products can occur, and these may have clinical consequences. For example, the differences in intravenous immunoglobulin products, such as antibody profile, may reflect the:

- geographic locations, infectious exposures and immunity of the donor population
- plasma collection (whole blood donation, or by apheresis)
- testing performed
- manufacturing methods.

Using fractionated plasma products

Blood products should only be prescribed with awareness of their associated harms and benefits. All plasma products used in Australia have approved product information and consumer medicine information available from the manufacturer or distributor or the TGA (www.ebs.tga.gov.au). Other resources are available for clinicians and patients,[5,6] and medical specialists and transfusion nurses at the Australian Red Cross Blood Service can provide expert advice (www.transfusion.com.au/Contact-Us.aspx). Ultimately, informed prescribing equates to maximal safety, efficacy and appropriate use of plasma-derived products.

Storage and handling

Storage and transport requirements are defined for all plasma-derived products. They require storage in secure, monitored environments to ensure their safety and efficacy. Some require refrigeration, while others may be stored at controlled room temperature routinely or for short periods.

Although safety-related recalls are rare, the ability to trace each product to its final destination (transfusion to a patient) is a requirement documented in health department circulars and other regulations in a number of states.[7]

Adverse reactions

Adherence to the manufacturer's guidance and institutional infusion policies, and careful monitoring of the patient during infusion, can minimise the likelihood of adverse events, or allow for early intervention should they occur.

Serious adverse reactions to plasma products are rare, but minor reactions are not uncommon. When serious reactions do occur, they should be reported promptly to the local transfusion service (hospital blood bank or issuing laboratory), and the manufacturer. Medical advice regarding reporting and management of adverse reactions is available through the manufacturer or distributor and the Australian Red Cross Blood Service.

Recombinant products

Currently, recombinant products are used primarily for coagulation factor therapy in patients with bleeding disorders and include factor VIIa, factor VIII (haemophilia A) and factor IX (haemophilia B). They should be used in consultation with a specialist experienced in the care of these patients, such as through a haemophilia treatment centre. Complications of therapy can still occur, such as development of inhibitory antibodies in patients with haemophilia.

Recombinant activated factor VII (VIIa) is approved in Australia only for very limited indications, such as for patients with haemophilia who have inhibitory antibodies. However, there has been recent growth in 'off label' use in patients with critical bleeding in a range of settings. Evidence to support this use remains limited.

Conclusion

The process from blood donation to administration of a fractionated blood product is lengthy and complex, with multiple checkpoints to deliver safe and effective products. As treating clinicians, it is our responsibility to ensure that they are administered correctly and for the appropriate indications.

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Medicines Safety Update

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AUST R and AUST L numbers – why are they important?

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Recent media articles have highlighted the importance of identifying the AUST L number on the label of complementary medicines suspected of causing adverse reactions.

The Therapeutic Goods Administration (TGA) can use the AUST L number to determine the exact identity of the complementary medicine suspected of causing the adverse reaction.

All medicines entered onto the Australian Register of Therapeutic Goods (ARTG) include a unique AUST L or AUST R number on the label. This labelling is required for the lawful supply of a therapeutic good in Australia.[1]

The L refers to listed medicines (primarily complementary medicines) and the R to registered medicines (primarily prescription and over-the-counter medicines) and should be readily identifiable on the label (Fig. 1).

If a health practitioner suspects that a medicine is responsible for an adverse event, requesting further information from the patient, including where it was purchased, is important in assisting to correctly identify the product. Where a serious adverse event is thought to have occurred, reporting the event to the TGA is strongly encouraged. Including the AUST L or AUST R number (or the absence of an Australian Register number) of the suspected medicine in the report will allow the TGA to ensure appropriate investigation and subsequent action.

Where the medicine label does not include an AUST L or AUST R number the TGA has not evaluated the quality, safety or efficacy of the product and therefore the safety of the product is unknown. Products without an Australian Register number may have been supplied illegally if bought in Australia, purchased over the internet by the consumer or have been imported from overseas for personal use.

The increasing use of the internet by Australian consumers to access medicines has resulted in the increased use of medicinal products that have not been evaluated by the TGA. As a result the importance of identifying an AUST L or AUST R number on the product label has increased. The identification of the AUST L or AUST R number and its concomitant entry on the ARTG can reassure consumers and practitioners of the product's safety.

The TGA encourages all healthcare practitioners and consumers to report adverse events related to any medicine or medical device via the electronic reporting system available through the TGA website (www.tga.gov.au) or via the blue card system. Further information about medicine labels can be obtained on the TGA website.[2]

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Fig. 1

Label of complementary medicine

Sibutramine

Summary

Interim results of the SCOUT trial of sibutramine have revealed higher rates of heart attack and stroke in subjects who were overweight or obese and at high baseline risk of a cardiovascular event. The TGA is reviewing the safety of the product and while that review is ongoing has reinforced existing advice to healthcare professionals to carefully review the sibutramine Product Information (PI), before prescribing the product.

Introduction

Sibutramine is an orally administered serotonin (5-hydroxytryptamine, 5HT) and noradrenaline reuptake inhibitor, indicated for weight loss, and maintenance of weight loss, as part of a weight management program in obese adults. It should only be prescribed to patients who have not adequately responded to an appropriate weight-reducing regimen alone. Sibutramine is not recommended for use in patients with a history of cardiovascular disease including inadequately controlled hypertension.

The SCOUT trial

Late last year the interim results of a clinical trial known as the Sibutramine Cardiovascular OUTcomes (SCOUT) trial, conducted by Abbott Laboratories, became available.[1] This study was a double-blind, randomized, placebo-controlled, parallel-group study into the effects of sibutramine (10 mg once-daily) on mortality in overweight and obese subjects at high risk of a cardiovascular event. All subjects were older than 55 years and had a history of manifest cardiovascular disease, or type 2 diabetes mellitus.

The study showed higher rates of cardiovascular events such as heart attack and stroke in patients using sibutramine, than in those receiving a placebo. While the rates were statistically significant in overweight and obese patients at high risk of a cardiovascular event, the difference was not statistically significant in overweight and obese patients with type 2 diabetes mellitus.

TGA monitoring

A review of the TGA's adverse drug reactions database (as at end March 2010) shows that 61 reports of suspected adverse reactions have been received by the TGA. The majority of these have occurred in women (47) who are also the predominant users of sibutramine. The most commonly reported adverse events were dizziness, palpitations, tachycardia and hypertension (which are listed in the PI); in addition chest pain and dyspnoea were also reported. There have been four reports each of angina, ventricular fibrillation and cardiac arrest in association with the use of sibutramine. Of concern is the number of reports where sibutramine has been used 'off label', i.e. prescribed for example to patients with a BMI less than that specified in approved indications for use (BMI greater or equal to 30 kg/m^2 in obese patients, and greater or equal to 27 kg/m^2 where diabetes mellitus type 2 or dyslipidaemia are present).

TGA action

In light of the interim results of the SCOUT study, the TGA has reinforced existing advice in the sibutramine PI regarding its use in patients with cardiovascular risk factors (current or past history of myocardial infarction or angina etc). It has also added a description of the SCOUT study and a precaution that the use of sibutramine should be ceased if it has not been effective in achieving weight loss within the expected timeframe (3 months for non-diabetics and 6 months for diabetics).

A statement regarding the use of sibutramine was published on the TGA's website safety alerts page in January 2010.[2]

Recommendations

Healthcare practitioners are advised to review any information regarding sibutramine, including 'Dear healthcare professional' letters sent by Abbott Australasia, the Australian sponsor of sibutramine, advising doctors of the changes to the PI and to ensure they consult the most current PI when prescribing. A copy of the current PI may be obtained from the TGA eBS Product and Consumer Medicine Information site.[3] In addition prescribers should note the use of sibutramine should be limited to one year in any patient and should not be recommenced if the patient had failed to lose weight with prior use of the drug.

The TGA's review of the safety of the product remains ongoing, and health practitioners are encouraged to report any adverse events occurring in association with the use of sibutramine to the TGA.

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Drug-induced pancreatitis and exenatide (Byetta)

Dr Margaret Ward, Office of Medicines Safety Monitoring

Introduction

Drug-induced pancreatitis is estimated to account for between two and five percent of acute presentations of the condition. Medicines cause pancreatitis either by inducing a hypersensitivity reaction or by the generation of a toxic metabolite.[1] A 2005 review of drug-induced pancreatitis in the *Journal of Clinical Gastroenterology* lists many different medicines that may be implicated and suggests that drug-induced pancreatitis should always be considered when other aetiologies have been excluded.[2]

The review identified certain 'at risk' groups, including those who were:

- the elderly
- on multiple medications
- HIV positive
- diagnosed with cancer; or
- receiving immunomodulatory agents.

Adverse drug reaction reports of drug-induced pancreatitis

The TGA's adverse drug reactions database included 581 reports of pancreatitis as of February 2009. Eighteen of these reports documented a fatal outcome. Many different medicines have been implicated, but the most frequent reports include azathioprine (41 reports), valproate (35 reports) and simvastatin (26 reports).[3] Commonly implicated medicine classes include antiviral agents, hypolipidaemic agents and atypical antipsychotic medications.

Exenatide (Byetta)

While many different medicines have been associated with pancreatitis, prescribers should be aware that international postmarketing reports of adverse events associated with exenatide (Byetta) have included cases of pancreatitis.

Exenatide is a peptide amide with several antihyperglycaemic actions of glucagon-like peptide (GLP-1) and is registered for use as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes who are taking metformin, a sulfonylurea, or a combination of these drugs, but are not achieving adequate glycaemic control.

To October 2007 the US Food and Drug Administration (FDA) had received 30 spontaneous adverse drug reaction reports of acute pancreatitis associated with the use of exenatide. A further six cases of haemorrhagic or necrotising pancreatitis, two of which were fatal, were reported by the FDA in August 2008.[4]

Reviews of the original case series of 30 patients (median age 60 years) showed the median time to onset of symptoms after initiation of therapy was 34 days. Abdominal pain was a presenting feature in 75% of cases.[5-7] At presentation amylase and lipase levels were usually substantially elevated, with amylase levels ranging from 40 to 1845 U/L (median 384 U/L; normal range 30–170 U/L) and lipase levels from 62 to 16970 U/L (median 545 U/L; normal range 7–60 U/L). There was at least one confounding factor (e.g. obesity, hypertriglyceridaemia or alcohol consumption) in 27 (90%) of the patients. In 22 cases the pancreatitis resolved on withdrawal of the drug and in three cases the pancreatitis recurred on resumption of the medicine. Hospitalisation was required in 21 cases and serious complications included acute renal failure and paralytic ileus.

Despite these spontaneous adverse drug reaction data, an analysis of data from a claims-based active drug surveillance system in the USA found no evidence of an increased risk of acute pancreatitis among patients treated with exenatide (around 28 000 patients) compared with those treated with metformin or a sulfonylurea.[8]

Australian adverse reaction reports

To date the TGA has received a total of 22 reports of suspected adverse drug reactions for exenatide. Eight (36%) of these reports relate to pancreatitis and/or elevation of pancreatic enzymes. In 4 of 5 cases reported as pancreatitis, exenatide was the sole suspected medicine. An additional four reports describe episodes of upper abdominal pain and/or ileus, raising the possibility of underlying pancreatitis, so that as many as 12 of the 22 reports may relate to an episode of pancreatitis.

While acute pancreatitis is listed as a rare adverse drug reaction in the Australian PI for exenatide, the TGA recommends that patients are informed of the characteristic symptoms of acute pancreatitis, and if this diagnosis is suspected exenatide and other potentially suspect medicines should be discontinued.

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WHAT TO REPORT? (You do not need to be certain, just suspicious!)

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. The TGA particularly requests reports of:

- ALL suspected reactions to **new medicines**
- ALL suspected medicines interactions
- Suspected reactions causing
  - death
  - admission to hospital or prolongation of hospitalisation
  - increased investigations or treatment
  - birth defects

For blue cards

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ('blue card') which is available from the website: www.tga.gov.au/adr/bluecard.pdf or from the Office of Medicines Safety Monitoring, phone 1800 044 114.

Reports can also be submitted:

online on the TGA website www.tga.gov.au click on 'Report a problem' on the left
by fax 02 6232 8392
by email ADR.Reports@tga.gov.au

For further information from the Office of Medicines Safety Monitoring:
Phone 1800 044 114 Fax 02 6232 8392 Email ADR.Reports@tga.gov.au

Tests for cell-mediated immunity

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Summary

Patients with cell-mediated immunodeficiency experience recurrent infections with a broad range of pathogens, and an accompanying humoral immunodeficiency is not uncommon. A persistently low lymphocyte differential on a full blood count may provide a clue and should prompt further testing with quantification of lymphocyte subsets. Measurement of total immunoglobulins is a first-line screening investigation in suspected humoral immunodeficiency. Further investigations, which provide an *in vitro* or *in vivo* functional assessment, are highly specialised assays which are difficult to perform and interpret. Consultation with a specialist immunologist and the diagnostic laboratory is recommended.

Key words: hypogammaglobulinaemia, immunodeficiency.

(Aust Prescr 2010;33:84–7)

Introduction

Defence against potentially harmful pathogens is achieved by physical barriers such as skin and mucous membranes, and the coordinated efforts of the innate and adaptive immune systems. Innate immune responses are carried out by macrophages, neutrophils and natural killer cells, together with cytokines, complement and acute phase reactants such as C-reactive protein. Adaptive immunity relies upon B and T lymphocytes which express antigen-specific surface receptors. It can be divided into humoral (antibody-mediated and dependent upon B lymphocytes) and cellular (coordinated by T lymphocytes) immunity. While this distinction is oversimplified and somewhat inaccurate in that both types of responses are dependent upon helper T lymphocytes, it provides a useful model for classifying and evaluating suspected immunodeficiency.

Immunodeficiency

This occurs when failure of any part of the immune system leads to an increased predisposition to infection and associated sequelae such as autoimmunity and malignancy. Primary immunodeficiency results from genetic mutations of components intrinsic to the immune system. Clinical diagnosis should be accompanied by molecular identification of a genetic mutation wherever possible to confirm the diagnosis, identify genotype-phenotype correlation, assist with genetic counselling and identify suitable candidates for gene-specific therapy. Secondary immunodeficiency results from defective immune function as a consequence of another condition such as HIV infection. Drugs such as corticosteroids, azathioprine, methotrexate or cyclosporin can also cause secondary immunodeficiency. Subtle impairment of immune function can also accompany certain chronic medical conditions including diabetes and chronic renal failure.

Immunodeficiency can be classified functionally into humoral or cell-mediated arms, as dysfunction of either pathway is characterised by specific clinical presentations (Table 1). Possible investigations for suspected immunodeficiency are presented in Table 2. These tests should be performed when the patient is clinically well, and not during an acute infective illness.

Humoral immunodeficiency

Antibody deficiency, or hypogammaglobulinaemia, can occur as a result of intrinsic defects of humoral immunity (primary), or secondary to another pathological condition. It is the most common manifestation of primary immunodeficiency and encompasses a broad range of clinical diagnoses. Clinical presentation can range from asymptomatic, to recurrent, atypical or life-threatening infections. Encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseriae* species and *Haemophilus influenzae*, pose a particular threat as well as other bacterial species including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Campylobacter fetus* and *Mycoplasma* species. Recurrent or unusually severe sinopulmonary infection, other infections (gastrointestinal, skin, joint or central nervous system), or evidence of end-organ damage such as bronchiectasis, should alert the doctor to the possibility of an underlying humoral immunodeficiency.

Measuring humoral immunity

The simplest initial investigation for this condition is to quantify immunoglobulin (Ig) concentrations (IgG, IgA and IgM). Normal levels, however, do not exclude a humoral defect and if clinical suspicion is high, then more advanced investigations can be undertaken. This includes measuring antibodies to specific

Table 1

Characteristic clinical presentations of immunodeficiency

Type of immunodeficiency	Clinical presentation
Humoral immunodeficiency	
Hypogammaglobulinaemia	Recurrent sinopulmonary infection: - *Streptococcus pneumoniae* - *Haemophilus influenzae* - *Neisseria* species Other bacterial infections such as gastrointestinal, central nervous system, joint Evidence of end-organ damage such as bronchiectasis, conductive hearing loss
Cellular immunodeficiency	
T cell dysfunction	Infections with: - intracellular bacteria (mycobacteria, salmonella) - viruses (Epstein Barr, cytomegalovirus, varicella zoster, herpes simplex) - fungi (candida, aspergillus, cryptococcus, histoplasma, pneumocystis) - protozoa (toxoplasma, microsporidium, cryptosporidium)
Interleukin-12 interferon gamma axis deficiency	Atypical mycobacterial and salmonella infections
Impaired response to *Candida* species	Persistent mucocutaneous candidiasis Autoimmune endocrinopathy
Combined immunodeficiency	
Combined T and B cell dysfunction	Combined features of T cell deficiency and hypogammaglobulinaemia
Severe combined immunodeficiency syndromes	Failure to thrive in children Opportunistic infection Overwhelming sepsis
Wiskott-Aldrich syndrome	Thrombocytopenia Eczema Infection with encapsulated bacteria
Ataxia telangiectasia	Sinopulmonary disease Cerebellar ataxia Oculocutaneous telangiectasia
DiGeorge syndrome	Hypocalcaemia Recurrent infection Cardiac disease Abnormal facial features
Hyper IgM syndromes	Recurrent pyogenic infection Opportunistic infection
Natural killer cell dysfunction	Recurrent herpes virus infection Recurrent papillomavirus infection (warts)
Phagocyte defects	Recurrent pyogenic infections Recurrent abscesses

Ig immunoglobulin

antigens following vaccination to assess if the patient produces a functional antibody response. This is usually performed in conjunction with assessment by a clinical immunologist. Immunoglobulin G subclasses can also be quantified – however the clinical utility of this investigation is somewhat controversial.

Cell-mediated immunodeficiency

Defective T cell-mediated immunity predisposes patients to a broader range of infections than humoral immunodeficiency, including intracellular pathogens, persistent superficial candidiasis or recurrent viral, fungal or protozoal infections

(Table 1). Defects can again be classified as either primary, or secondary to extrinsic factors. HIV infection resulting in progressive depletion of CD4 T cells is a particular consideration. As helper T cells are required for B cell-mediated antibody production, T cell immunodeficiency can result in functional B cell defects, thus patients with cell-mediated immunodeficiency often have an accompanying hypogammaglobulinaemia. This is termed combined immunodeficiency.

Measuring cellular immunity

Measurement of cell-mediated immunity can be undertaken by both *in vitro* and *in vivo* methods. It is, however, more problematic than humoral assessment as assays are plagued by difficulties in standardisation, biological variability, imprecision and technical complexity. Most tests are highly specialised and referral to a clinical immunologist is recommended.

Flow cytometry

The first step in the evaluation of cell-mediated immunity is to quantify circulating immune cells and their subsets by flow cytometric analysis. Patients' blood cells are incubated with fluorochrome-labelled monoclonal antibodies directed against cell surface molecules and analysed by a flow cytometer, which measures light scatter and fluorescence emission from individual cells. Different cell populations (B cells, and CD4/CD8 T cells and natural killer cells) can be distinguished based on their scatter profile and surface molecule expression. Absolute cell numbers are calculated as a percentage of the total white cell count and results are compared to age-matched reference ranges. It is important to note, however, that analogous to immunoglobulin measurement, quantification of lymphocyte numbers does not give an indication of their functional capacity. Lymphocyte subset analysis aids in the diagnosis and classification of paediatric severe combined immunodeficiency syndromes, and is also recommended in the evaluation of hypogammaglobulinaemia in common variable immunodeficiency. Quantifying CD4 T lymphocytes provides prognostic information and gives an indication of susceptibility to opportunistic infections in patients with HIV infection.

Delayed-type hypersensitivity skin testing

Delayed-type hypersensitivity skin testing provides a functional *in vivo* assessment of cellular immunity. The skin response following intradermal inoculation of antigen is dependent on antigen-specific memory T cells and results in local inflammation after 48–72 hours due to the recruitment of mononuclear cells (lymphocytes, monocytes) and neutrophils. By convention, a diameter of 5 mm induration is accepted as a positive result. The most widespread use of this type of test is the Mantoux test, which assesses previous exposure to *Mycobacterium tuberculosis* or Bacillus Calmette-Guérin (BCG) vaccination by evaluating the skin response to intradermal tuberculin. Other ubiquitous antigens that can be tested include tetanus, candida and certain bacterial antigens. Skin responses are dependent upon previous exposure to the antigen and thus this test is of little use in infants less than six months of age.

Table 2

Investigations for suspected immunodeficiency

Suspected immunodeficiency	Screening tests	Advanced investigations
Humoral immunodeficiency	IgG, IgA, IgM Full blood count and differential* Lymphocyte subsets*	IgG subclasses Specific antibody titres and response to vaccination
Cellular immunodeficiency	Full blood count and differential* Lymphocyte subsets* HIV testing if indicated IgG, IgA, IgM	Delayed-type hypersensitivity skin tests Lymphocyte proliferation assays Natural killer cell cytotoxicity

Ig immunoglobulin

* defer testing until resolution of acute infective illness

Skin testing identifies functional memory T cells to a particular antigen, or the presence of cutaneous anergy. The latter is defined as an impaired cutaneous hypersensitivity response to a panel of common antigens and is consistent with cellular immune dysfunction. Causes of cutaneous anergy are listed in Table 3.

Lymphocyte proliferation assays

Lymphocyte proliferation assays are indicated if there is a suspicion of a defective cellular immune response either globally or to a specific antigen such as candida. The patient's peripheral blood mononuclear cells are incubated *in vitro* for 3–5 days with either a mitogen (substance which induces cellular division) or a recall antigen (to which the patient has been previously exposed). Radioactive thymidine is added to the culture and subsequently incorporated into the DNA of dividing cells. Radioactivity of the cell culture is measured after 24 hours and is directly proportional to the degree of induced cellular proliferation. Peripheral blood mononuclear cells from a healthy control are evaluated in parallel for comparison.

These assays are technically complex and are only performed by specialist laboratories. As the investigation can be time-consuming, it is advisable to first discuss the appropriateness of testing and choice of assay with the laboratory. Results are affected by immunosuppressive drugs, severe nutritional deficiencies and intercurrent illness[1] and these factors must be considered when interpreting results. As with skin testing, the patient must have been previously exposed to the antigen, thus antigen proliferation assays are not feasible in babies less

Table 3

Causes of cutaneous anergy*

Cause	Examples
Drugs	Corticosteroids (usually high dose) Immunosuppressants Chemotherapy
Immunodeficiency	Ataxia telangiectasia Severe combined immunodeficiency syndrome DiGeorge syndrome Wiskott-Aldrich syndrome
Infection	HIV Influenza Measles Mumps Active tuberculosis
Other conditions	Malignancy Chronic lymphocytic leukaemia Sarcoidosis Chronic renal failure Chronic liver disease
Testing errors	Poor technique Inadequate antigen dose

* impaired skin response to antigen

than six months of age. Response to mitogens, however, can be performed at any age from birth onwards.[2]

Other assays measuring lymphocyte activation

Other functional *in vitro* measures of lymphocyte activation include determining changes in surface marker expression (CD25, CD69, CD71) following activation[3] or measurement of intracellular cytokines of T lymphocytes.

T cell proliferation following stimulation can be measured by succinimidyl ester of carboxyfluorescein diacetate (CFSE) dilution techniques,[4] or T cell cytokine production quantified by ELISPOT assays. These assays, however, are not in routine use and are confined to research or specialised reference immunology laboratories.

The recently introduced interferon gamma (IFNγ) release assays measure T lymphocyte production of IFNγ in response to antigen exposure thereby providing an assessment of cell-mediated immunity. As with delayed-type hypersensitivity skin testing, clinical application is currently confined to the domain of tuberculosis latency and exposure.

Natural killer cell cytotoxicity assays

Assessing natural killer cells is indicated in patients suffering recurrent infection with herpes virus, or papillomavirus (associated with cutaneous warts). Natural killer cell cytotoxicity is assessed by a ^{51}Cr-release assay in which patients' natural killer cells are incubated with ^{51}Cr-labelled target cells. Lysis of the target cells by natural killer cells leads to the release of radioactivity which can be measured. Natural killer cell dysfunction may occur in patients with CD16 genetic mutations, chronic mucocutaneous candidiasis, severe combined immunodeficiency and other cellular immunodeficiency syndromes.[5] These conditions need to be considered and excluded if natural killer cell dysfunction is confirmed. As with T and B lymphocytes, functional natural killer cell deficits can occur even when natural killer cell counts are normal. Natural killer cell assays are technically complex and are rarely performed in diagnostic immunology laboratories.

Conclusion

The evaluation of suspected immunodeficiency is guided by clinical presentation. Screening tests of humoral and cellular immune function are initially performed, followed by referral to a specialist for more advanced investigations if clinically indicated (Table 2). Secondary causes of immunodeficiency, including HIV infection, need to be considered and excluded. When interpreting results, confounding factors such as immunosuppressive drug therapy and patient comorbidities, as well as analytical variables such as assay precision and reproducibility, need to be considered.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 95)

1. Persistent superficial candidiasis may be a sign of T cell dysfunction.
2. Normal immunoglobulin concentrations exclude a humoral immunodeficiency.

Medicinal mishap

Tamsulosin-induced intraoperative floppy iris syndrome during cataract surgery

*Prepared by **Adrian Fung**, Senior Registrar, Sydney Eye Hospital; and **Peter McCluskey**, Director of Save Sight Institute, and Professor of Clinical Ophthalmology, Sydney Eye Hospital, Sydney*

Case

A 67-year-old man was referred for cataract surgery. He had noticed deteriorating vision in the left eye, greater than the right, over the last eight months with difficulty driving due to glare. He had a history of essential hypertension controlled by perindopril and had been taking tamsulosin for three years for benign prostatic hypertrophy with some symptomatic relief.

On examination, best-corrected visual acuity was 6/12 in the right and 6/24 in the left eye. Both pupils dilated minimally with topical tropicamide 1%, but light responses were normal. Apart from nuclear sclerotic cataracts, the rest of the anterior and posterior segment examination including intraocular pressures was normal.

Cataract surgery to the left eye was performed under local anaesthesia. Despite routine preoperative dilation with topical tropicamide 1%, cyclopentolate 1% and phenylephrine 2.5%, the patient's pupil remained miosed at 3 mm in diameter. This did not improve with instillation of topical phenylephrine 10%. Further intervention only increased the pupillary diameter to 3.5 mm.

The iris was noted to be atonic and had a propensity to prolapse out of the main clear corneal incision. A diagnosis of intraoperative floppy iris syndrome was suspected. Routine cataract surgery could not proceed with such a small pupil size. Four iris retracting hooks were needed to stretch the pupil to over 6 mm to enable the cataract to be removed (Fig. 1). Postoperatively, the patient's best-corrected visual acuity in his left eye improved to 6/12 on day one and 6/6 at four weeks.

Comment

Intraoperative floppy iris syndrome is a condition characterised by:

- poor preoperative pupil dilation
- a floppy iris with a propensity to billow and prolapse from surgical wounds
- progressive intraoperative miosis.

A floppy iris makes cataract surgery more difficult, with a higher incidence of complications including posterior capsular rupture, vitreous loss and iris trauma.[1]

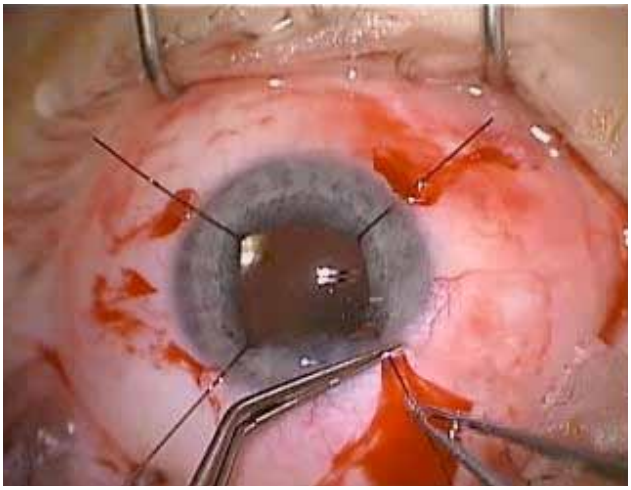
Intraoperative floppy iris syndrome has most commonly been associated with tamsulosin, a selective alpha$_1$ adrenergic antagonist used for relief of lower urinary tract symptoms associated with benign prostatic hypertrophy. The syndrome is nine times more prevalent in males.[2] Between 40%[3] and 90%[1] of patients on tamsulosin develop intraoperative floppy iris syndrome. Tamsulosin has also been associated with a 2.3 times increased postoperative cataract complication rate.[3] Other less selective alpha$_1$ adrenergic antagonists including terazosin and prazosin have also been implicated. Although it can occur without use of alpha$_1$ adrenergic antagonists, no statistically significant association has been found between intraoperative floppy iris syndrome and other medications or disease.[2]

Alpha$_1$ adrenergic antagonists relax smooth muscle, including that of the dilator muscle of the iris.[3] However, the mechanism by which tamsulosin induces intraoperative floppy iris syndrome is likely to be more complex given the multiple signalling pathways in the iris.[2] Histological studies have also failed to show changes in the dilator muscle.[1] Disappointingly, preoperative cessation of alpha$_1$ adrenergic antagonists does not prevent intraoperative floppy iris syndrome, even when stopped years before surgery, whereas they can induce intraoperative floppy iris syndrome within weeks of first use.[1,3]

The most important factor governing cataract surgery outcomes in patients on an alpha$_1$ adrenergic antagonist is recognition of its ability to induce intraoperative floppy iris syndrome. The astute surgeon can then plan a suitable management approach. Some studies have shown

Fig. 1

Iris retracting hooks used to stretch the pupil during cataract surgery



intraoperative cataract complication rates (posterior capsular rupture with vitreous loss) with undiagnosed intraoperative floppy iris syndrome as high as 12%,[2] falling to 0.6% when the surgeon is aware the patient has used tamsulosin.[1]

Conclusion

As cataracts and the use of alpha$_1$ adrenergic antagonists increase with age, it is not surprising that the incidence of intraoperative floppy iris syndrome has been reported to occur in up to 3.7% of cataract surgeries.[2] It is important that patients due for cataract surgery are told to remind their ophthalmologist if they have ever taken tamsulosin. The ophthalmologist should also seek this history. Preoperative cessation of the drug is not currently recommended. With recognition of the potential problem and careful pre- and intraoperative planning, the ophthalmologist can minimise surgical complications associated with intraoperative floppy iris syndrome.

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Conflict of interest: none declared

Drug information resources

As of 1 July 2010 the Therapeutic Advice and Information Service (TAIS) national drug information service for health professionals will no longer be operational. The National Prescribing Service acknowledges the dedication and expertise of the staff who contributed to the high quality of TAIS over its ten years of operation.

Closer to the cessation date, health professionals will be able to access an index of other sources of drug information on the NPS website at www.nps.org.au/health_professionals. Please note that while some of these linked resources are open access, others may require a subscription fee.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and 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.

Azacitidine

Vidaza (Celgene)

vials containing 100 mg as lyophilised powder for reconstitution

Approved indication: myelodysplasia, leukaemia

Australian Medicines Handbook section 14

The myelodysplastic syndromes are disorders in which the pluripotent stem cells function abnormally. As any cell lines can be affected the patient may have anaemia, neutropenia or thrombocytopenia. The syndromes include chronic myelomonocytic leukaemia and the myelodysplasia may progress to acute myeloid leukaemia.

In myelodysplasia, tumour suppressor genes may be inactivated by hypermethylation. Preventing hypermethylation may reduce the proliferation of abnormal cells.

Azacitidine is an analogue of cytidine, one of the nucleosides which make up nucleic acids. When azacitidine is incorporated into DNA it inhibits DNA methyltransferase, reducing hypermethylation, and has a direct cytotoxic effect on abnormally proliferating cells.

In the first treatment cycle azacitidine is given by daily subcutaneous injection for seven days. This cycle is repeated every four weeks for as long as the patient continues to benefit.

Most of the dose is excreted in the urine as azacitidine and its metabolites. Azacitidine is contraindicated in patients with malignant hepatic tumours and those with renal failure.

After phase II trials of intravenous and subcutaneous doses produced favourable results, a phase III trial was carried out in 191 patients with myelodysplasia. These patients were randomly assigned to azacitidine or supportive care. They were assessed after four treatment cycles, and those who had responded to azacitidine could continue. Responses were assessed by changes in the blood and bone marrow and the need for transfusion. In the azacitidine group, 16% of the patients had a partial response and 7% had a complete response. The median duration of all the improvements was 15 months. No-one in the supportive care group had a complete or a partial

response. With supportive care, the median time to death or the development of acute leukaemia was 12 months, compared with 21 months in the patients treated with azacitidine.[1]

Data from this trial and the phase II trials were reanalysed when an application was made to market the drug in the USA. The assessment criteria had changed and the reanalysis showed that few patients had partial remissions, but 10–17% had complete remissions and 23–36% had some haematological improvement. Under the new criteria some patients were found to have had acute myeloid leukaemia at the start of the studies. Those treated with azacitidine had a median survival of 19.3 months compared with 12.9 months for supportive care.[2]

Another study compared azacitidine with conventional care which could include chemotherapy. This study randomised 358 patients with myelodysplastic syndromes including chronic myelomonocytic leukaemia. Acute myeloid leukaemia developed after a median of 17.8 months with azacitidine and 11.5 months with conventional care. The patients had a median survival of 24.5 months with azacitidine and 15 months with conventional care. However, only 25 patients in the conventional care group received intensive chemotherapy and their survival rate was not statistically different from that of the azacitidine group. Patients given azacitidine had higher haemoglobin concentrations so there was a reduced need for red blood cell transfusions. The approved indications for azacitidine are based on this trial. These are specified forms of myelodysplastic syndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia, when allogenic stem cell transplant is not indicated.[3]

Although azacitidine may reduce transfusion requirements it is a cytotoxic drug so patients still need to be monitored for anaemia, neutropenia and thrombocytopenia, particularly at the start of treatment. Infections are common and some patients will develop febrile neutropenia. In addition to full blood counts the patient's liver and renal function should be regularly checked because of the risk of toxicity. As gastrointestinal problems are frequent, antiemetic drugs should be given before each treatment. Other frequent adverse reactions include injection site reactions, dyspnoea, anorexia, arthralgia, dizziness and bruising. Despite the wide range of potentially severe adverse effects, there is evidence that azacitidine leads to a better quality of life by improving the patient's physical functioning, fatigue and dyspnoea.[1]

Most of the patients with myelodysplastic syndromes are elderly. They are not usually suitable for stem cell transplantation, so management has involved supportive care. Azacitidine seems to offer improved survival to specific groups of these patients.

T T manufacturer provided additional useful information

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Caffeine citrate

Cafnea (Phebra)

2 mL vials containing 40 mg/2 mL for injection and 7 mL vials containing 25 mg/5 mL oral solution

Approved indication: apnoea of prematurity

Australian Medicines Handbook section 19

Premature babies are at risk of apnoea. This can occur in the absence of other problems, such as infection. Primary apnoea appears between two and seven days after birth and is most common in premature babies with a low birth weight. If the apnoea of prematurity is recurrent and prolonged, ventilation may be needed. Methylxanthines such as theophylline have been used as respiratory stimulants. Caffeine is also a methylxanthine and it has been used overseas to treat the apnoea of prematurity.

The mechanism of action is uncertain, but caffeine is thought to increase the response to hypercapnia and increase the respiratory rate. A loading dose is given intravenously over 30 minutes. The subsequent daily maintenance doses can be given intravenously or by mouth. Some of the dose is converted to theophylline, but this occurs slowly in premature babies. The half-life of caffeine in these babies is 80–120 hours. Most of the dose is excreted unchanged in the urine.

A study compared caffeine citrate with placebo in 82 babies, born between 25 and 32 weeks of gestation, who were having at least six episodes of apnoea in 24 hours. Over 7–10 days 69% of the caffeine group, but only 43% of the placebo group, achieved at least a 50% reduction in episodes of apnoea.[1]

A larger placebo-controlled study included babies with birth weights of 500–1250 g. The 2006 babies had an average gestational age of 27 weeks. Many were being treated for apnoea, but some babies were given treatment to prevent apnoea or to assist the removal of an endotracheal tube. The

first doses were given at a median age of 28 weeks and were stopped before 35 weeks. Supplemental oxygen was needed by 36% of the babies given caffeine citrate and 47% of those given a placebo. Compared to the placebo group, babies given caffeine citrate were significantly less likely to require surgical closure of a patent ductus arteriosus.[2]

Babies given caffeine may initially gain less weight than other premature babies. Most adverse effects are probably related to the stimulant action of caffeine. They include tachycardia, tachypnoea and jitteriness. Maternal consumption of caffeine should be considered when prescribing caffeine citrate.

Premature babies are very vulnerable patients. In long-term follow-up, 40% of the babies given caffeine died or survived with a neurodevelopmental disability. This was a statistically better outcome than the 46% rate seen in the placebo group. To prevent one adverse outcome 16 babies need to be treated for 37 days. Much of the benefit of caffeine is from earlier discontinuation of positive airways pressure.[3]

The results of the larger study are difficult to interpret because of the different indications for giving caffeine. In Australia the use of caffeine citrate will be restricted to the short-term treatment of the apnoea of prematurity in babies between 28 and 33 weeks of gestational age.

T T T manufacturer provided clinical evaluation

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Human C1 esterase inhibitor

Berinert (CSL)

vials containing 500 units as freeze-dried powder for reconstitution

Approved indication: hereditary angioedema

Australian Medicines Handbook Appendix A

C1 esterase inhibitor is a protein derived from human plasma. It is indicated for the treatment of acute attacks of hereditary angioedema. This condition is characterised by episodes of swelling in the skin or mucosa and can occur anywhere in the body (face, larynx, gut, limbs). It can be painful, particularly with gastrointestinal attacks, and if the larynx is affected asphyxiation and death can occur.

Type I and type II hereditary angioedema are caused by mutations in the gene encoding the C1 esterase inhibitor. Although not well defined, the absence or dysfunction of this protein is thought to lead to increased vascular permeability due to unregulated bradykinin activation. Replacing C1 esterase inhibitor intravenously during an acute attack reduces ongoing inflammatory processes. Treatments for histamine-induced angioedema, such as corticosteroids, antihistamines or adrenaline, have no effect in patients with hereditary angioedema.

The efficacy of C1 esterase inhibitor has been investigated in a randomised controlled trial in 125 adults and children with confirmed acute moderate to severe hereditary angioedema. Overall, 79% of patients presented with a gastrointestinal attack and 20.2% with a facial attack. Patients were randomised to receive C1 esterase inhibitor 10 U/kg or 20 U/kg (39 and 43 patients) or placebo (42 patients). Within four hours of treatment, 70% of patients had responded in the C1 esterase inhibitor 20 U/kg group compared to 43% in the placebo group. The median time to onset of symptom relief was significantly shorter for C1 esterase inhibitor 20 U/kg (0.5 hours) than for placebo (1.5 hours). The median response time for the lower-dose C1 esterase inhibitor (10 U/kg) was only slightly shorter than for placebo (1.2 vs 1.5 hours). Median time to complete resolution of symptoms was much shorter for C1 esterase inhibitor 20 U/kg than for placebo (4.9 vs 7.8 hours) but not for C1 esterase inhibitor 10 U/kg (20 hours).[1] The 20 U/kg dose is currently recommended for hereditary angiodema.

In the trial, the most frequent adverse events were nausea, diarrhoea, abdominal pain and muscle spasms. Most of the adverse events were more common with placebo than with C1 esterase inhibitor 20 U/kg (43.9% vs 19.6%) and may have been related to the patients' angioedema attacks.[1] Taste disturbance was reported with C1 esterase inhibitor 20 U/kg (2/46 patients) but not with placebo (0/41 patients). An increase in severity of pain associated with hereditary angioedema was the most severe adverse effect reported by patients who received the active treatment. Antibodies to C1 esterase inhibitor and their effect on efficacy or adverse reactions were not measured in the trial.

In an observational study of three women, the commencement of frequent treatments with C1 esterase inhibitor was associated with an increase in angioedema attacks (4-fold, 5-fold and 12-fold). A control group of 24 age-matched men and women did not show the same increase in attacks over a nine-year period. It was not clear what caused this increase, but investigators speculated that frequent treatments may have lowered the threshold for activation of an attack.[2]

This C1 esterase inhibitor is made from human plasma sourced from overseas. Like all plasma products, it has

the potential to transmit infections caused by viruses and prions (e.g. variant Creutzfeldt-Jakob disease). During the randomised controlled trial, none of the patients seroconverted to produce antibodies to HIV, hepatitis or human parvovirus 19 virus.[1] The infectious disease risk of C1 esterase inhibitor has been reduced by screening blood donors and their plasma for evidence of viral infections such as HIV and hepatitis C. Also during fractionation, plasma undergoes processes to inactivate or remove certain viruses. Nevertheless, patients should be warned that there is still an infectious disease risk with this product. Vaccination against viruses that could potentially be present in plasma, such as hepatitis B, should be considered.

Severe hypersensitivity reactions can occur with C1 esterase inhibitor and adrenaline should be available when injections are given. For patients who are known to have a tendency to allergies, antihistamines and corticosteroids should be given prophylactically. Prescribers should be aware that thrombosis has been reported with C1 esterase inhibitor when used at doses higher than 20 U/kg and for unapproved indications.

C1 esterase inhibitor seems to be an effective treatment for hereditary angioedema and has been used overseas for more than 30 years. However, there have been reports in a minority of patients that it may increase the frequency of angioedema attacks.

☒ manufacturer declined to supply data

References *A

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Miglustat

Zavesca (Actelion)

100 mg capsules

Approved indication: type I Gaucher disease and Niemann-Pick disease type C

Australian Medicines Handbook Appendix A

Miglustat is indicated for people with mild to moderate type I Gaucher disease, and for progressive neurological manifestations in adults and children with Niemann-Pick type C disease. These are both rare inherited disorders which result in the build-up of glycosphingolipids in the body.

Miglustat is a synthetic analogue of D-glucose and is a competitive inhibitor of glucosylceramide synthase, an enzyme involved in the synthesis of most glycosphingolipids. Treatment with miglustat aims to reduce the production of glycosphingolipids.

Type I Gaucher disease is caused by a deficiency in beta-glucocerebrosidase – an enzyme which breaks down the glycosphingolipid glucocerebroside. This lipid builds up in macrophages found primarily in the liver, spleen and bone marrow. Clinical features of this disease include hepatomegaly, splenomegaly, anaemia, thrombocytopenia and bone lesions.

Regular intravenous infusion of recombinant glucocerebroside (see Aust Prescr 1999;22:95–8) is the mainstay of treatment and benefits most patients with type I Gaucher disease. Miglustat is an oral option for people who cannot have enzyme therapy.

The safety and efficacy of miglustat has been assessed in several open-label studies.[1–4] In the main trial of 28 patients, treatment with oral miglustat 100 mg three times a day reduced mean liver size by 12% (CI‡ 7.8–16.4) and mean spleen size by 19% (CI 14.3–23.7) after 12 months. (Seven patients had had a previous splenectomy.) Nine of the 22 patients who completed treatment had anaemia (<115 g/L) at baseline. After 12 months, haemoglobin had increased by more than 5 g/L in five of these people. Of the 21 patients who could be assessed for platelet count, four had an increase of at least 15 x 10^9/L platelets. Glycolipid biosynthesis – assessed by measuring surface expression of G_{m1} on leucocytes – was found to have decreased by an average of 38.5% over 12 months in a sample of five patients. Plasma chitotriosidase activity – a measure of stored lipids – had also decreased by the end of the trial.[1] The benefits of miglustat were maintained for up to three years in an extension of the trial.[2] Similar effects on the liver and spleen were observed in the other open-label trials.[2–4]

The most frequent adverse event during the trial was diarrhoea (79% of patients). Six patients dropped out – two of these were because of gastrointestinal problems. Two patients were withdrawn because of paraesthesiae which were confirmed to be peripheral neuropathy.[1] Other common adverse events reported in the open-label trials included weight loss, tremor, flatulence and abdominal pain.[2–4]

Dose reduction or discontinuation may be required for tremor. Peripheral neuropathy may be related to vitamin B_{12} deficiency, which is common in type I Gaucher disease, so regular monitoring of vitamin B_{12} as well as neurological evaluation is recommended.

Niemann-Pick type C disease is an incurable progressive disease that leads to premature death. Impaired transport of lipids within cells causes some fatty acids including glycosphingolipids to accumulate in tissues and organs,

‡ confidence interval

particularly the brain. This can lead to supranuclear gaze palsy, ataxia, problems with speech and swallowing, dystonia, seizures, dementia, psychiatric problems and gelastic cataplexy[§].

Until now, treatment for this disease has mainly been supportive. As miglustat can cross the blood–brain barrier, its efficacy has been assessed in Niemann-Pick type C disease. In a randomised controlled 12-month trial, oral miglustat 200 mg given three times a day was compared to standard care (drug treatment and physical, speech and occupational therapy) in a 2:1 ratio in 28 patients aged 12 years or older. In addition, 12 children aged under 12 years enrolled in the trial were all given miglustat (dose was adjusted according to body surface area). Most of the participants had severe clinical manifestations at baseline and were allowed to continue their medications which included analgesics, antibiotics, antidiarrhoea drugs, sedatives and hypnotics, antiepileptics and drugs to treat dystonia.[5]

The main measure of efficacy in the trial was the speed of horizontal eye movements between fixed points. After a year of treatment, improvements were observed in patients given miglustat, but this was not significantly different to results seen in patients given standard care alone. Improvements in the ability to swallow and in intellectual performance (mini-mental status examination) were also seen in older patients (>12 years old) given miglustat compared to those who received standard care.[5] Open-label extensions of this study (up to three years) reported that patients' neurological symptoms did not progress while taking miglustat.[6,7]

A retrospective observational study analysed physician questionnaires about ambulation, manipulation, language and swallowing in patients who had been taking miglustat for an average of 1.5 years. Overall, 74.5% (49/65) of patients had reduced disease progression or stabilisation of neurological symptoms.[8]

Adverse events in Niemann-Pick disease were similar to those seen in type I Gaucher disease, with diarrhoea being the most common (85% of patients). Weight loss (63%), tremor (46%) and flatulence (44%) were also frequently reported. Severe adverse events included severe confusional state and salivary hypersecretion, severe dehydration and respiratory syncytical virus infection. These were thought to be unrelated to miglustat. Three people were withdrawn from the trial because of an adverse event – one because of insomnia and confusional state, one due to diarrhoea related to Crohn's disease and one from lethargy, impaired memory and depression (in a child).[5]

As weight loss was commonly reported with miglustat, growth rate should be monitored in children and adolescents taking miglustat. Reductions in platelet counts have occurred with miglustat in Niemann-Pick disease so blood counts should be monitored. Dizziness was a common adverse effect and patients should not drive if they experience this. The benefit of miglustat in Niemann-Pick disease should be reviewed at six-month intervals.

To reduce gastrointestinal effects such as diarrhoea, miglustat should not be taken with food. After a 100 mg dose, maximum plasma concentrations are reached after approximately two hours. Its half-life is about 6–7 hours so steady-state concentrations are predicted to be reached after 1.5–2 days. Miglustat is excreted mainly by the kidneys so dose adjustment may be necessary with milder renal impairment. It is not recommended in severe renal impairment.

Miglustat showed modest efficacy in mild to moderate type I Gaucher disease and Niemann-Pick disease, although numbers of patients in the trials were small. It has been approved as an orphan drug in Australia and is only available through the Life Saving Drugs Program.

T manufacturer provided only the product information

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§ sudden weakness or collapse associated with strong emotion, particularly laughter

Vildagliptin

Galvus (Novartis)

50 mg tablets

Approved indication: type 2 diabetes

Australian Medicines Handbook section 10.1.3

Patients with type 2 diabetes often need more than one drug to control their blood glucose. When first-line treatment fails, the incretin mimetics and enhancers are a class of drugs which can be added to treatment (see Aust Prescr 2008;31:102–8). Within this class are the inhibitors of dipeptidyl peptidase 4 (DPP4) such as sitagliptin. These drugs block incretin metabolism and this leads to reductions in blood glucose concentrations.

Vildagliptin is a DPP4 inhibitor which is taken twice daily with metformin or a thiazolidinedione and once daily with a sulfonylurea. A 50 mg dose will inhibit most DPP4 activity for at least 12 hours. Most of the dose is converted to inactive metabolites. This metabolism does not involve the cytochrome P450 system so the potential for metabolic drug interactions is reduced. The elimination half-life is three hours with most of the metabolites being excreted in the urine. Vildagliptin is not recommended for patients with hepatic or moderate or severe renal impairment.

A systematic review which included 14 trials of vildagliptin involving 6121 patients concluded that treatment reduces glycated haemoglobin (HbA1c) by 0.6%.[1] Several studies have investigated if this makes a significant difference when vildagliptin is added to other drugs.

Vildagliptin 50 mg daily was added to the treatment of 56 people whose diabetes was not completely controlled by metformin. After 12 weeks their mean HbA1c had reduced by 0.6% from a baseline of 7.7%. There was no change in control in 51 other patients who were given a placebo to take with their metformin. Some of the patients continued in an extension of the trial with 32 of the vildagliptin group and 26 of the placebo group completing one year of treatment. There was no significant change in the vildagliptin group, but HbA1c increased in the placebo group so that there was a difference of 1.1% between the groups after a year. An HbA1c below 7% was achieved by 41.7% of those who added vildagliptin, but only 10.7% of those who added a placebo.[2]

Another trial studied vildagliptin 100 mg, as well as 50 mg, as an addition to treatment with metformin. After 24 weeks the HbA1c concentration had fallen by 0.9% in the 185 people randomised to add 50 mg twice daily, by 0.5% in the 177 randomised to add 50 mg once daily, and increased by 0.2% in the 182 randomised to add a placebo. The proportion of patients achieving an HbA1c under 7% depended on their baseline concentrations. If the baseline HbA1c was greater than 8.5%, it was only reduced below 7% in 16.3% of patients given vildagliptin 100 mg, 7.5% of those given 50 mg and 2.1% of those given placebo.[3]

When type 2 diabetes is not controlled by metformin alone a sulfonylurea can be added. This approach has been compared with adding vildagliptin in a study of 2789 patients. There were 1396 who were randomised to add vildagliptin 50 mg twice daily and 1393 who were randomised to add glimepiride. After 52 weeks the mean reduction in HbA1c was 0.44% with vildagliptin and 0.53% with glimepiride. From a mean baseline of 7.3%, a target HbA1c of under 7% was reached by 54% of the vildagliptin group and 56% of the glimepiride group.[4]

Vildagliptin has also been added to the treatment of patients with diabetes which was inadequately controlled by a sulfonylurea. Their mean HbA1c was 8.5%. While 170 patients were randomised to add vildagliptin 50 mg once daily and 169 to add vildagliptin 50 mg twice daily, another 176 patients were given a placebo. All the patients also took glimepiride. After 24 weeks the mean HbA1c declined 0.58% with vildagliptin 50 mg and 0.63% with vildagliptin 100 mg while it increased by 0.07% in the placebo group. Only 12% of the patients in the placebo group achieved an HbA1c below 7% compared to 21% of the vildagliptin 50 mg group and 25% of the 100 mg group. As there was no significant advantage with the higher dose, the recommended daily dose of vildagliptin, in combination with a sulfonylurea, is 50 mg.[5]

Although monotherapy with a thiazolidinedione is not the usual first-line therapy, a trial, in 463 people with type 2 diabetes, has studied the effect of adding vildagliptin to treatment with pioglitazone. After 24 weeks, adding vildagliptin 50 mg once daily reduced the mean HbA1c by 0.8%, twice daily reduced it by 1%, while placebo reduced it by 0.3%. The HbA1c fell below 7% in 29% of those given 50 mg, 36% of those given 100 mg and 15% of those given a placebo.[6]

In trials of monotherapy the incidence of adverse events has been similar for vildagliptin and placebo. However, the frequency of infections (1.4% vs 0.3%) and neurological symptoms (0.9% vs 0.6%) was greater with vildagliptin than with placebo. Tremor, dizziness and headache are common when vildagliptin is given with metformin or a sulfonylurea. Peripheral oedema is more frequent with vildagliptin, than with placebo, when added to treatment with a thiazolidinedione.[6] Adding vildagliptin to other oral hypoglycaemic drugs can increase the risk of hypoglycaemia. The frequency with glimepiride is 1.2% and 1% with metformin. Hypoglycaemia is more likely to occur if glimepiride, rather than vildagliptin, is combined with metformin.[4] There have been rare cases of angioedema and hepatitis during treatment with vildagliptin. Liver function should be checked before and during treatment. The patient's renal function should also be checked before treatment with vildagliptin.

In animal studies vildagliptin has caused problems with skin ulceration and cardiac conduction, while the significance in humans is unknown. Animal studies also show increased mammary tumours at high doses.

Sulfonylureas can cause patients to gain weight and there was a significant difference between the weight of patients who added glimepiride compared to those who added vildagliptin to treatment with metformin. However, over a year the weight of the patients taking vildagliptin only fell an average of 0.23 kg.[4] This was similar to the 0.2 kg reduction seen in both groups in the 52-week placebo-controlled trial of metformin and vildagliptin.[2]

A role for the DPP4 inhibitors as add-on treatments is yet to be established, particularly in patients who are already using more than one drug. Their long-term safety is also unknown. The systematic review concluded that DPP4 inhibitors currently have no advantage over other drugs which lower blood glucose.[1]

☒ manufacturer declined to supply data

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The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2009;32:80–1.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

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

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/pmeds/auspar.htm)

Corrections

Nebivolol (Aust Prescr 2010;33:52–9)

In the SENIORS trial, the reduction of 4.2% in the composite end point of all-cause mortality or hospitalisation, is the absolute risk reduction, not the relative risk reduction.

Ustekinumab T-score (Aust Prescr 2010;33:52–9)

☒ manufacturer declined to supply data

Janssen-Cilag did respond to the request for data, but their response was not received in the *Australian Prescriber* office. The company declined to provide the clinical evaluation.

Answers to self-test questions

1. False
2. True
3. True
4. False

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