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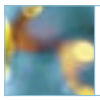

Editorials

Safety concerns with salmeterol

Peter AB Wark, Staff Specialist and Senior Lecturer, Respiratory Medicine, Hunter Medical Research Institute, Newcastle, New South Wales

Key words: adverse effects, asthma, beta agonists, eformoterol.

(Aust Prescr 2006;29:118–9)

The introduction of long-acting beta$_2$ agonists, such as salmeterol and eformoterol, has been an important development in the management of asthma. For patients with persistent symptoms of asthma, despite treatment with inhaled corticosteroids, the addition of a long-acting beta$_2$ agonist results in improved lung function, fewer symptoms, a reduced need for 'rescue' medication and a reduction in acute exacerbations.[1] The recommendation that these patients add a long-acting beta$_2$ agonist to their inhaled corticosteroid therapy has resulted in salmeterol or products containing salmeterol becoming the second most frequently prescribed group of drugs for asthma in Australia. It is therefore of great significance that the US Food and Drug Administration (FDA) has issued advice about long-acting beta agonists that states 'these medicines may increase the chance of severe asthma episodes, and death when those episodes occur'.[2]

Safety concerns regarding beta agonists are not new. Overuse of the potent short-acting beta agonist fenoterol, in New Zealand in the 1980s, was associated with increased asthma mortality.[3] Similar concerns have arisen over reported cases of severe asthma exacerbations associated with the use of long-acting beta$_2$ agonists. In the 1990s a UK trial compared 'add-on' salmeterol to regular salbutamol in 25 000 patients. Those on salmeterol appeared to have a three times greater risk of death. There was one death for every 650 patient years of salmeterol treatment. As there were only 14 asthma-related deaths in the 16-week study, the difference between salmeterol and salbutamol was not statistically significant.[4]

The FDA then requested the makers of salmeterol to clarify these findings and this resulted in the Salmeterol Multicenter Asthma Research Trial (SMART). Patients with persistent symptoms of asthma had salmeterol 42 microgram twice a day or placebo added to their usual treatment and were followed for 28 weeks. In the previous 12 months 26% of these patients had reported emergency room visits and only 47% regularly used inhaled corticosteroids. An interim analysis was performed after 26 335 patients had completed the study. The composite primary outcome of respiratory-related deaths and life-threatening episodes was uncommon and did not show a statistically significant effect. However, there were significant increases in asthma-related deaths in the salmeterol group (Table 1). The risk appeared greater in African Americans, but as this group had more severe disease at baseline this may have been a confounder rather than indicative of a genetic effect.[5] These results led to the FDA announcement and to a change in labelling to include a warning about 'a small, but significant, increased risk of life-threatening asthma episodes or asthma-related deaths'.

It is unclear whether this is an effect unique to salmeterol. There are no published trials similarly assessing the safety of eformoterol. However, in data submitted to the FDA there did appear to be an increase in adverse events. Eformoterol was associated with 5.2 adverse events per 100 patient years compared to 0.6 with placebo and 0 with albuterol (salbutamol).[6] Again this event rate appears low but suggests a real clinical finding that could be a class effect of long-acting beta$_2$ agonists.

Although the events are rare, the association between salmeterol and serious asthma-related episodes and asthma-related deaths appears compelling. How therefore do we explain these results and can we identify those individuals at risk?

Unfortunately the data so far do not give us conclusive answers and data in children are lacking. It is clear that inhaled

In this issue…

Critical appraisal is a useful method for assessing the results of trials. However, Michael Lowe and Bradleigh Hayhow remind us that the information must be considered in a clinical context. Providing health professionals with independent information about drugs is essential for the quality use of medicines. It is therefore unfortunate that an Australian appraisal of a product has been blocked by legal action.

Disseminating drug information is particularly important if there is a question of safety, such as the concerns about salmeterol discussed by Peter Wark.

With warmer weather approaching, Australian snakes will be on the move. Geoffrey Isbister therefore provides a timely review on how to manage snake bites.

Table 1

Relative risks of adverse outcomes with salmeterol [3]

Outcome	Relative risk (95% confidence interval)	Number of events	
		Salmeterol (13 176 patients)	Placebo (13 179 patients)
Respiratory-related deaths and life-threatening experiences	1.40 (0.91, 2.14)	50	36
Respiratory-related deaths	2.16 (1.06, 4.41)	24	11
Asthma-related deaths	4.37 (1.25, 15.34)	13	3
Asthma-related deaths or life-threatening experiences	1.71 (1.01, 2.89)	37	22

corticosteroids are highly successful in improving asthma control and reducing serious asthma-related events. In the SMART study a mixture of poorly controlled asthma and a lack of use of inhaled corticosteroids may have resulted in the adverse outcomes. Inhaled corticosteroids suppress airway inflammation. This disease modification is thought to be central to the way inhaled corticosteroids exert their effect. One hypothesis is that inhaled corticosteroids may also be needed to prevent the serious asthma-related episodes associated with long-acting beta$_2$ agonists. If this is found to be true, patients will need to take inhaled corticosteroids with long-acting beta$_2$ agonists. A combination inhaler may be advantageous, but the safety of combinations of inhaled corticosteroids and long-acting beta$_2$ agonists needs to be defined.

How will the findings about salmeterol affect Australian practice? Currently, long-acting beta$_2$ agonists are recommended as add-on therapy to an appropriate dose of inhaled corticosteroid. The importance of inhaled corticosteroid use and its rationale still needs to be reinforced to patients and health professionals. Non-compliance with inhaled corticosteroids however remains a danger as these drugs, by their preventive nature, do not directly improve asthma symptoms. The Pharmaceutical Benefits Scheme restricts the use of combination inhalers to those who have first been stabilised on inhaled corticosteroids and long-acting beta$_2$ agonists given from separate inhalers. Combination inhalers may be a better insurance against non-compliance with inhaled corticosteroids and the possible adverse outcomes of long-acting beta$_2$ agonists given alone. Long-acting beta$_2$ agonists should not be used to treat acute asthma.

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Further reading

Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med 2006;144:904-12.

Dr Wark has received sponsorship in the form of unrestricted educational grants from GlaxoSmithKline and AstraZeneca to attend conferences. He has spoken at events sponsored by these companies, though not in direct relation to their products. Dr Wark also serves on an advisory board for AstraZeneca.

Schedule of Pharmaceutical Benefits – 'the yellow book'

From December 2006 the Schedule of Pharmaceutical Benefits ('the yellow book') will be available online and updated monthly. Readers will be able to search the online version for information on medicines, brands and prices.

As part of the transition, a printed version of the December 2006 issue will be sent to users who currently receive a printed copy. For more information and to subscribe to email updates of the Schedule, go to www.health.gov.au/pharmbiz

Injunction impedes independent information

John S Dowden, Editor, Australian Prescriber

Key words: *Ginkgo biloba*, tinnitus.

(Aust Prescr 2006;29:120)

A Federal Court injunction has stopped the publication of a review criticising a medicinal product. The injunction concerns claims that the symptoms associated with tinnitus and vertigo can be relieved by a formulation of *Ginkgo biloba*.

These claims were the subject of scrutiny by AusPharm Consumer Health Watch. This is a service which was launched earlier this year to evaluate the evidence behind non-prescription products promoted to pharmacies. The aims were to help pharmacists decide whether or not to stock the products and to help consumers make an informed choice about whether or not to use the products.

The working group behind AusPharm Consumer Health Watch outlined the review process on their website.[1] These processes are similar to those used by *Australian Prescriber* when assessing new drugs, except we do not send draft reviews to the manufacturers.[2]

Although the sponsor of the product provided some supporting information, the working group concluded that there was insufficient evidence to justify promoting the product for the relief of tinnitus. This concurs with a report by the Cochrane Collaboration which concluded 'The limited evidence did not demonstrate that *Ginkgo biloba* was effective for tinnitus…'.[3]

When the company sponsoring the product received a draft copy of the review, it expressed a number of concerns. After these concerns were not addressed to its satisfaction it applied for an injunction to halt publication of the review. Ironically, although the working group's intention had been to publish a critical appraisal for consumers, the company used consumer protection legislation to contend that AusPharm Consumer Health Watch had engaged in misleading and deceptive conduct in contravention of the *Trade Practices Act 1974*, and that the publication constituted an injurious falsehood.

Justice Greenwood determined that there was a serious question to be tried as to whether the publication contravened the Trade Practices Act. He therefore granted an interim injunction[4] which was later made permanent.[5]

The 80 paragraph judgement does not imply that *Ginkgo biloba* is an effective treatment for tinnitus. The scientific evidence was not examined; the judgement was based on the process of preparing the review and the extent to which that process complied with the methodology outlined on the website of AusPharm Consumer Health Watch.[1] For example, a copy of the draft review had been sent to the Therapeutic Goods Administration (TGA) at the same time it was sent to the company. As this distribution was not mentioned on the website[1] the judge said this was a 'failure to act consistently with the expressed methodology'. Health professionals frequently ask drug companies for copies of published papers about pharmaceutical products. However, in this case, the judge said that a request which failed 'to properly describe and identify the purpose for which the papers were sought and the task and scope of the role proposed to be undertaken, was misleading'.[4]

I know of only two other cases where drug bulletins have been taken to court by drug companies. In both cases the judgements went in favour of the independent publications. For example, a Spanish judge rejected a claim that Bulleti Groc had published inaccurate information about rofecoxib.[6] The bulletin's view was later vindicated by the worldwide withdrawal of the drug for safety reasons.

Drug bulletins are usually written for health professionals, but they act in the public interest. However, in the Australian case publication was not seen to be in the public interest. The judge felt the public interest would be served by the regulatory authorities examining the evidence supporting the efficacy of *Ginkgo biloba*. Unfortunately, the Department of Health and Ageing has said that any investigation by the TGA will be commercial-in-confidence and the results will not be disclosed to the public.

The manufacturers of prescription medicines are gradually becoming more willing to allow the release of information about their products, for example the public summaries of the decisions of the Pharmaceutical Benefits Advisory Committee. The complementary medicines industry should follow this lead to increased transparency. If the company had not taken legal action, it would not have drawn international attention to questions about the effectiveness of its product.[7]

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Letters

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

Discharge medication

Editor, – In the editorial about discharge medication (Aust Prescr 2006;29:58–9), the authors state 'trials of interventions to improve the transfer of drug information from the hospital to the community have been disappointing'. We recently conducted a randomised controlled trial of a multi-faceted intervention called Med eSupport, which included information and communication technology solutions. This trial involved 487 patients across five sites, and included the following elements:

- a secure bi-directional electronic communication pathway between community and hospital pharmacies for the transfer of medication profiles to facilitate medication reconciliation
- supply of a comprehensive medication information sheet at discharge to the patient or carer, general practitioner and community pharmacist, which is uploaded to a secure website for viewing and printing
- a model system in which patients were automatically referred for a post-discharge medicines review within 5–7 days of discharge.

Initially, we found that 66% of all hospital drug charts contained at least one error. Significantly more patients in the intervention group had medication discrepancies resolved within 48 hours of their admission compared with control patients. Almost all of the medicines reviews started by the hospital were completed in a timely manner and were highly appreciated by patients and general practitioners. Only 0.6% of the intervention patients were re-admitted to hospital within five days of discharge compared to 3% of the control patients. An economic evaluation indicated potential savings of $60 million per year with a national roll-out to 50 sites.

We believe the results illustrate the value of developing a strategy for the national roll-out of a medication information sharing process and post-discharge medication reviews for high-risk patients.

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Editor, – We read with interest the editorial 'Discharge medication' (Aust Prescr 2006;29:58–9). Communication between hospitals and community-based providers with regards to patient medication is less than adequate.[1] This is of particular concern with warfarin therapy.[2,3]

We have conducted an audit of 51 consecutive electronic discharge letters of patients who started warfarin while in hospital. This focused on the clinically important issues of indication and dosing. Warfarin therapy and its indication were documented in 50 of the 51 discharge letters, but eight discharge letters (16%) had no dose information. INR test results were present in 29 letters (57%) but only four give a recommended duration of treatment.

While it is not feasible to list every single detail of a patient's medication regimen in a discharge letter, it is reasonable to mention that the patient is taking warfarin, the indication, the dose being taken, any INR results, the recommended target INR range and the next review date of warfarin therapy. We have therefore modified our electronic discharge summaries to include a mandatory field requesting this information. This should help general practitioners continue the clinical care with minimal harm and inconvenience to the patient.

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Editor, – Further to the editorial 'Discharge medication' (Aust Prescr 2006;29:58–9), readers may be interested to learn of South Australian initiatives on this topic.

As part of the careconnect.sa programme (formerly known as Open architecture clinical information system

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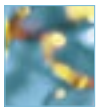

Beyond critical appraisal

Michael P Lowe, Clinical Dean, Northern Territory Clinical School, Royal Darwin Hospital, Darwin, Northern Territory, and Bradleigh D Hayhow, Resident Medical Officer, Kimberley Population Health Unit, Broome, Western Australia

Summary

All doctors require skills to critically appraise medical research. Critical appraisal is important but limited by its focus on the internal logic of research publications. A broader knowledge of the context in which studies are generated is sometimes necessary to understand their conclusions and their implications for clinical practice.

Key words: clinical trials, evidence-based medicine.

(Aust Prescr 2006;29:122–4)

Introduction

A key foundation of evidence-based medicine (EBM) is that clinicians with appropriate training can critically appraise research papers. Techniques of critical appraisal are taught to students and have been explained in several publications.[1,2]

Critical appraisal has at least one major limitation – it suggests that by examining the content of publications alone one can assess the truth of their conclusions. The difficulty with this lies in a fundamental distinction between 'validity' and 'soundness'. Validity relates to the methodology used in a study, whereas soundness relates to the truth of the original data and its interpretation. Critical appraisal examines the validity of scientific studies to determine whether the evidence that is cited supports the conclusions, but it is unable to vouch for the soundness of those conclusions.

We tend to rely on researchers' assertions that their data are true. However, medical research occurs in an environment in which there are many conflicts of interest and powerful influences on researchers. We therefore need to know about the context in which evidence is generated before a true picture of the research findings can be made.

Academic fraud

Deliberate academic fraud represents one situation in which published data may be misleading. In one study almost 5% of medical authors reported fabrication or misrepresentation of results within the previous 10 years, and 17% of authors personally knew about a case of fraud in the previous 10 years.[3]

For example, in 1990 Werner Bezwoda appeared to begin trials of high-dose chemotherapy with bone marrow transplantation in high-risk breast cancer patients. His published results showed markedly improved outcomes with this technique and therefore exerted a substantial influence on clinical practice worldwide. In 2000, a site visit to his laboratory revealed that the original results could only have been obtained by fraud.[4]

Academic fraud cannot necessarily be detected by critical appraisal. It is occasionally revealed by whistleblowers or by the discrepant results of subsequent studies but may take many years to come to light. Researchers do not often wish to repeat previous studies and ethics committees may say it is unethical to do so. Yet our vulnerability to academic fraud can only be reduced by independent corroboration of findings.

Inappropriate sub-group analysis

When evaluating clinical results one must be careful about the results of inappropriate sub-group analysis. Comparisons of multiple sub-groups can easily result in exaggeration of differences that are found. To avoid such problems, researchers are urged to clearly state their major hypotheses before their study begins.[5] This requires researchers to be honest about their intentions as well as their data.

An example of inappropriate sub-group analysis occurred in the reporting of the CLASS trial.[6] This trial was reported as a three-arm trial comparing the effects of celecoxib with two older non-steroidal anti-inflammatory drugs (NSAIDs) over a time period of six months. It showed a decrease in gastrointestinal complications for people treated with celecoxib. These results led to a marked rise in celecoxib prescribing around the world.

One year after the CLASS publication, it was revealed that the original intention of the trial had been very different, with a planned follow-up of 12–15 months, not six months.[7] The trial had shown no difference in gastrointestinal adverse effects over the longer period, but when results had been restricted to six months a difference had emerged. To the original readers of the CLASS trial, none of this was evident and critical appraisal of the original article could only conclude that celecoxib was beneficial.

Leading medical journals now require all major trials to be registered at their onset and all Australian trials must be registered with the Australian Clinical Trials Registry (www.actr.org.au). However, doctors will continue to be bombarded with information from poorer quality trials in which problems of inappropriate analysis will be undetectable.

Not including all relevant outcomes

When analysing clinical study data all relevant outcomes should be considered, however it may not be clear which outcomes are important. Often clinical trials do not have the statistical power to detect important adverse events.

Rofecoxib was withdrawn after showing an increase in cardiovascular deaths with sustained use. Trials of rofecoxib (such as the VIGOR trial[8]) had noted but not emphasised this outcome, and attempted to explain it away. As a result, approval of the drug in world markets was based purely on equivalence of pain-relieving effects and decreased gastrointestinal adverse effects. Yet the possibility of adverse cardiac outcomes was apparent to experts soon after the drug's release.[9]

When trials are stopped early it may also be difficult to assess all relevant outcomes. Rules for stopping trials tend to rely on only one outcome (such as improvements in mortality) and may lead to other outcomes being ignored.

Placebos and semi-placebos

Trials need to ask the right question. Testing a drug against an inappropriate comparator or an inappropriate dose of a comparator can mislead practitioners. While there continues to be a place for placebo-controlled trials, there is no justification for use of 'semi-placebos' such as an inappropriately small dose of a competitor's drug.

A 1994 article entitled 'The continuing unethical use of placebo controls' suggested that wherever an established treatment existed, it should be used in trials in place of a placebo.[10] Avoidance of placebos began to be seen as an important ethical principle and led to increasing numbers of so-called 'equivalence trials' in which new drugs were shown to be equivalent to older drugs rather than superior to placebos. Such trials may not always be clinically useful, and they assume that the established treatment has previously been shown to be significantly superior to a placebo.[11] Critical appraisal of any drug trial that is not placebo-controlled must therefore rely on expert knowledge of the evidence for the comparator drug.

Conflation and other complexities

An excellent summary of the problems encountered in critical appraisal warns about the issues that arise from 'conflating' trials.[12] It uses the example of the PROGRESS trial – which purported to show the benefits of ACE inhibitors after stroke.[13]

In fact, the PROGRESS trial actually shows a benefit from indapamide as a second-line agent, or from combinations of antihypertensives, rather than from an ACE inhibitor alone. Although the problem was noted by the editorial that accompanied the trial[14], the result was so obscured within the paper that we believe only expert epidemiologists could come to the correct conclusion.

Evidence-based medicine downplays the role of experts, suggesting that we can all undertake critical appraisal. Yet an expert view of trials such as VIGOR would have differed from that of a general medical reader, not because of differing skills in critical appraisal, but because of a different knowledge of background issues. High levels of expertise in critical appraisal are also required for the interpretation of some trials in which key features may be deliberately hidden.

Until 2003, the Medical Journal of Australia published a series called 'EBM in action' in which the authors attempted to answer clinical questions by using techniques of critical appraisal. At the end of the series the authors appeared somewhat bemused by the reactions they had received:

> There was a side effect that we did not anticipate. Content experts often disagreed with the evidence that we found – a collision between the findings of evidence expertise and content expertise. This often spilled over into the columns of the Journal's 'Letters to the Editor', generating about two letters for each 'EBM in action' article.[15]

This should not have been surprising. The content of the medical literature can really only be interpreted within the context of clinical medicine. Specialists in the field are 'content experts' who are ideally placed to assess the value of trials within this context. For this reason we believe that it is important to continue to emphasise the role of the content expert in augmenting the process of critical appraisal. However, we must be aware that experts may have conflicts of interest or be subject to influences that affect their views.

We believe that clinicians, in addition to paying attention to the method and results sections of a paper, should take note of editorials and any non-biased expert commentary that is available.

Conclusion

Critical appraisal uses techniques for analysing the validity of published evidence, however it is far less attuned to the soundness of that evidence. A solution to this problem is to pay greater attention to the context in which data are generated, but it seems unlikely that this will fall within the scope of most busy practising clinicians.

We believe that some simple rules can help prevent general medical readers from being misled by unreliable evidence. These include:

- not changing practice on the basis of single trials or trials from a single research centre
- sourcing information from trials that have been registered at their inception
- seeking expert opinion and commentary from content specialists as well as 'critical appraisal' specialists
- remaining aware of the possibility of biased original data.

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Conflict of interest: none declared

Book review

Therapeutic Guidelines: Rheumatology, Version 1.

Melbourne: Therapeutic Guidelines Limited; 2006. 314 pages. Price: $39, students $25.30, plus postage

Paul Kubler, Rheumatologist/Clinical Pharmacologist, Royal Brisbane and Women's Hospital, Brisbane

The first edition of Therapeutic Guidelines: Rheumatology is a welcome addition to this series. The pocket-sized published version is well formatted and covers a broad spectrum of rheumatic complaints. In general, it provides clear, accurate and practical information.

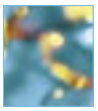
The first chapter on 'Getting to know your drugs' is contemporary and succinct. It includes detailed information on analgesics, corticosteroids and disease-modifying antirheumatic drugs (especially the biologically active treatments), and many of the commonly used complementary medicines frequently taken or asked about by patients with musculoskeletal complaints.

As expected, there are chapters outlining the evaluation and management of common rheumatic disorders such as rheumatoid arthritis, gout and autoimmune connective tissue diseases. Regarding the book's format, I particularly liked the way that topics are presented by pattern of arthritis (for example, recent onset arthritis) and regional pain. For a general practitioner, patients usually present with an undifferentiated symptom pattern rather than a clearly established diagnosis so the book may help the doctor navigate through the period of initial care until a clear diagnosis becomes apparent.

There are also very good sections on the assessment and management of spinal pain, and the care of musculoskeletal conditions in children, adolescents and pregnant women.

My only criticism of this publication is that some sections are textbook-like in their detail which somewhat diminishes the value of this book as a quick and easy therapeutic guideline for busy practitioners. A brief description with diagrams on the intra-lesional injection techniques for common conditions such as rotator cuff tendinitis would improve its appeal to general practitioners.

In summary, the first edition of Therapeutic Guidelines: Rheumatology comes with my strong recommendation as a useful resource for many practitioners in the assessment and management of a broad range of musculoskeletal conditions.



Snake bite: a current approach to management

Geoffrey K Isbister, Senior Research Fellow, Tropical Toxinology Unit, Menzies School of Health Research, Charles Darwin University, Northern Territory, Clinical Toxicologist and Emergency Physician, Newcastle Mater Misericordiae Hospital, Newcastle, New South Wales, and Clinical Toxicologist, New South Wales and Queensland Poisons Information Centres

Summary

Snake envenoming is uncommon but potentially life-threatening. It is characterised by systemic effects including coagulopathy, neurotoxicity, myotoxicity and renal impairment. Pressure immobilisation bandaging is safe and appears to be effective first aid if applied correctly soon after the bite. Each Australian snake causes a characteristic clinical syndrome which can be used with information about the geographical distribution of snakes to determine which snake is involved when a patient is envenomed. Snake venom detection kits are available to help identify the causative snake. Antivenoms are available for the five major groups of snakes and are the mainstay of therapy in patients with systemic envenoming. Antivenom should be administered by slow intravenous infusion in a critical care area. Serious adverse reactions to antivenoms are uncommon.

Keywords: antivenom, coagulopathy, envenoming, venom.

(Aust Prescr 2006;29:125–9)

Introduction

Australia has a unique snake fauna including snakes with highly potent venoms. The major Australian snakes are the brown snakes, tiger snake group, mulga/black snakes, taipans and death adders. Estimates suggest that there are between 500 and 3000 snake bites annually. In about 200 to 500 cases antivenom is required.[1,2] Snake envenoming is an uncommon but potentially life-threatening medical condition.[3] Between one and four deaths occur each year with most resulting from brown snake bites. Bites occur in the warmer months and are more common in regional and rural areas. Exotic snakes are kept legally in zoos and illegally by collectors so bites by non-Australian snakes sometimes occur.

Clinical effects

In many snake bites only local effects occur because insufficient venom is injected or the snake is non-venomous. With more significant envenoming there may be local or systemic effects. These range from non-specific effects (nausea, vomiting, headache, abdominal pain, diarrhoea, dizziness and collapse) to major organ effects (coagulopathy, neurotoxicity, rhabdomyolysis or renal damage).[4]

Local effects

Brown snake bites have minimal local effects, whereas local pain, swelling and occasionally tissue injury can follow black and tiger snake bites. Bites from some snakes such as whip snakes (*Demansia* species) can cause immediate significant local swelling and pain.

Coagulopathy

The majority of dangerous Australian snakes cause a procoagulant coagulopathy. The venom contains a prothrombin activator that leads to consumption of major coagulation factors including fibrinogen, resulting in a defibrination coagulopathy which should be referred to as venom-induced consumptive coagulopathy. This is characterised by very high d-dimers, undetectable fibrinogen, and unrecordable prothrombin time and activated partial thromboplastin time. Recovering from this takes many hours after venom neutralisation has been achieved with antivenom.

Some black snakes (mulga and Collett's snake) cause an anticoagulant coagulopathy, probably due to an inhibitor, that is rapidly reversed with antivenom. It is not associated with consumption of clotting factors, so fibrinogen and d-dimer levels are normal.

Neurotoxicity

Paralysis is a classic effect of snake bite and is due to presynaptic or postsynaptic neurotoxins in the venom. Presynaptic neurotoxins disrupt neurotransmitter release from the terminal axon. This takes days to resolve and does not respond to antivenom. Postsynaptic neurotoxins competitively block acetylcholine receptors but the effect can be reversed by antivenom.

Neurotoxic envenoming causes a progressive descending flaccid paralysis. Ptosis is usually the first sign, then facial and bulbar involvement progressing to paralysis of the respiratory muscles and peripheral weakness in severe cases.

Myotoxicity

Some Australian snakes, such as the mulga snakes and tiger snakes, have venom containing myotoxins that cause rhabdomyolysis with muscle pain, tenderness and weakness, a rapidly rising creatine kinase and myoglobinuria.

Renal damage

Renal impairment or acute renal failure can occur secondary to severe rhabdomyolysis, in association with microangiopathic haemolytic anaemia (reported with brown snakes) or can occur rarely in isolation.

Major types of Australian snakes: clinical syndromes

The five major groups of medically important Australian snakes which cause characteristic clinical syndromes are included in Table 1. Identifying the snake is important for diagnosis and determining the appropriate antivenom to be administered, but is not always possible. Venom detection kits are available to assist with identification.

Brown snakes

Brown snakes occur widely throughout mainland Australia. They are fast moving and easily alarmed snakes that strike readily. However, they have a high rate of dry bites with envenoming occurring in less than half of bites. Bites cause minimal local effects and non-specific systemic effects are uncommon. Severe envenoming is characterised by an early collapse, within an hour of the bite, usually with spontaneous recovery within 5 to 10 minutes. Collapse appears to occur at the time of onset of the coagulopathy, but the mechanism is unclear. The major clinical feature is a venom-induced consumption coagulopathy.[4] Renal damage and microangiopathic haemolytic anaemia have been reported and neurotoxicity is rare.

Tiger snake groups

Tiger snakes occur in southern and eastern Australia. The major clinical effects are a venom-induced consumption coagulopathy, presynaptic neurotoxicity and rhabdomyolysis. An early collapse can occur and initially the only detectable effect may be a coagulopathy.

Rough-scaled snakes are closely related to tiger snakes and cause similar effects. Copperheads are less well characterised, but appear to cause neurotoxicity and coagulopathy. The Hoplocephalus genus (Table 1) cause coagulopathy and are clinically similar to brown snakes except that tiger snake antivenom is used for treatment.

Mulga and black snake groups

Mulga snakes occur across Australia except the south and east. They cause severe rhabdomyolysis and anticoagulant coagulopathy associated with non-specific symptoms. Collett's snake causes a similar clinical picture, but only bites in snake handlers have been reported due to its isolated distribution.

The red-bellied black snake is common in southern and eastern Australia, but only causes non-specific systemic effects, mild rhabdomyolysis and local effects which are usually managed without antivenom.

Taipans

Taipans occur in northern Australia and are very dangerous with a high envenoming rate. The mortality rate is high in untreated cases. Clinical effects include a venom-induced consumption coagulopathy, presynaptic neurotoxicity and mild rhabdomyolysis. Thrombotic microangiopathy, haemolytic anaemia and renal failure have been rarely reported.

Death adders

Death adders are widespread but secretive ambush predators that have a characteristic 'viper-like' appearance. The major clinical effect is a postsynaptic neurotoxicity associated with non-specific systemic features.[4]

Diagnosis

In the majority of cases there is a history of a snake bite or suspected snake bite. History, examination and investigations focus on whether the patient is envenomed or not and by which snake so that the correct antivenom can be given. Occasionally the diagnosis is not obvious if a snake is not seen or the patient presents with coagulopathy or neurotoxicity and no history of a bite.

A careful history is required to determine the circumstances of the bite and what first aid has been applied. Early symptoms suggest severe envenoming. The examination should include the bite site, and palpation of the lymph nodes draining the site for tenderness. In addition to standard observations, the examination includes looking for signs of paralysis (ptosis, bulbar palsy, respiratory effort and peripheral weakness), any evidence of coagulopathy (bleeding) or evidence of rhabdomyolysis (muscle tenderness and weakness).

Investigations should include a full blood count, coagulation studies including d-dimer, and biochemical tests including creatine kinase. A urine analysis is helpful for detecting blood or myoglobin.

A whole blood clotting time may be useful if coagulation studies are not available. Blood is collected in a clean glass tube and the time to clot is measured. The normal clotting time is less than 10 minutes. If the clotting time is greater than 20 minutes, this is highly suggestive of a procoagulant coagulopathy. If the clotting time is between 10 and 20 minutes, the result is indeterminate, but may be consistent with an anticoagulant coagulopathy.[5] This test may be useful in remote situations to determine if a patient has significant coagulopathy.

Table 1

Clinical effects of envenoming by Australian snakes and initial dose of antivenom required

Snake genus	Early collapse	Local effects	Non-specific systemic features	Coagulopathy	Neurotoxicity	Myotoxicity	Renal impairment	Antivenom dose
1. Brown snake	++	+/–	+/–	+++	+/–	–	+ [e]	2–5 vials [f]
2. Tiger snake [a]	+	++	++	+++	++	++	+/–	4 vials
Hoplocephalus species [b]	–	+/–	+/–	+++	–	–	–	4 vials
3. Black snake:								
Mulga snake/Collett's snake	–	+++	+++	++	–	+++	+	1 vial
Red-bellied black snake [c]	–	+++	++	+/–	–	+	–	1 vial of tiger or black
4. Taipan	+	+	++	+++	+++	+	+	3 vials
5. Death adder	–	+/–	+	–	+++	–	–	1 vial
Whip snake [d]	–	++	+/–	–	–	–	–	nil

[a] Includes rough-scaled snake and copperhead snake

[b] Includes broad headed, pale headed and Stephen's banded snakes and is treated as tiger snake

[c] Includes blue-bellied and spotted black snake

[d] Not one of the 5 major types of snakes but a common snake causing mild envenoming

[e] Renal failure usually occurs in the setting of microangiopathic haemolytic anaemia

[f] Recent research suggests that the previously recommended larger doses of brown snake antivenom are unnecessary, and further research is required. The Poisons Information Centre (phone 13 11 26) should be contacted for current recommendations.

+++ major feature of envenoming that almost always occurs

++ common feature

+ reported but uncommon, absence does not exclude this snake

+/– rarely reported

– not reported

Significant systemic envenoming has been defined as any of the following:

- neurotoxic paralysis
- coagulopathy (confirmed by laboratory)
- myotoxicity
- renal impairment/failure.

Determination of the snake involved and more importantly the selection of the appropriate monovalent antivenom is based on:

- knowledge of the local snake fauna
- clinical syndrome
- snake venom detection kit.

Snake venom detection kit

The snake venom detection kit is a useful diagnostic test to confirm which of the five major snake groups is responsible for the envenoming. This will determine which antivenom is needed. The test is therefore only useful in healthcare facilities that have antivenom supplies. It should be done in a laboratory. The test has no value in non-envenomed patients because of false positives and it cannot be used to confirm or exclude snake envenoming. In many cases the determination of the snake involved can be made on geographical and clinical grounds, and results from the venom detection kit should always be interpreted in the context of these. It is prudent to collect and store bite site swabs for venom detection in all suspected snake bite cases and only do the test in cases where envenoming is confirmed and antivenom is required.

Management of snake bite

Many snake bites do not result in envenoming. The rate of envenoming varies depending on the species of snake. Whether envenoming has occurred cannot be immediately determined when the patient presents. This means all suspected snake bites must be triaged as a medical emergency and observed for a sufficient period of time in a hospital with adequate supplies of antivenom and laboratory facilities. Immediate expert advice can be obtained from the Poisons Information Centre network (phone 13 11 26).

First aid

The bite site should not be washed so that the area can be swabbed for venom detection. Pressure immobilisation is the recommended first aid treatment for all snake bites.[6] It has been effective in animal studies and case studies, but has not been tested in clinical trials.

A broad (15 cm) bandage is applied at the same pressure as for a sprained ankle over the entire limb. The patient must then remain completely immobilised, not just the bitten limb. For bites on areas other than limbs the patient should be immobilised to slow the spread of venom.

Pressure immobilisation should only be removed once the patient is in a hospital stocked with antivenom. If the patient is envenomed, pressure immobilisation can be removed once antivenom therapy has commenced. If the patient has no clinical or laboratory signs of envenoming, the bandage can be removed if antivenom and resuscitation equipment are available.

General management

Initial management includes basic resuscitation and assessment of the patient. Once airway, breathing and circulation have been assessed and stabilised, the diagnosis can be made and specific management undertaken.

All cases of suspected snake bite should be observed for sufficient time to exclude delayed envenoming. Close observation is needed to look for early signs of neurotoxicity such as ptosis.[3] There has been significant controversy over the appropriate duration of observation and this is highly dependent on regional snake fauna and healthcare facilities. The current recommendation is that patients should be observed for a period of at least 12 hours and if this period extends into the night the patient should remain overnight. The duration of observation may be longer in regions where delayed envenoming occurs, for example the delayed neurotoxicity following death adder bites in northern Australia.[4]

The patient is unlikely to be envenomed if they have normal laboratory tests on admission, 1–2 hours after pressure immobilisation removal and before discharge.

Wound site infection is rare and only requires treatment if there is clear clinical evidence of an infection. Local swelling often resolves without treatment so antibiotics are not recommended. Tetanus prophylaxis is recommended for all bites.

Antivenom

Antivenom is the mainstay of treatment in patients with systemic envenoming (see Table 2). It is not recommended in patients who only manifest non-specific features as these may be misleading. Antivenom should always be administered intravenously after 1:10 dilution with normal saline or Hartmann's solution. The degree of dilution may need to be modified for large volume antivenoms and in young children. Premedication with adrenaline, antihistamines or corticosteroids is not recommended, but the patient must be monitored in a critical care area with adrenaline and resuscitation equipment readily available.

After the first dose, further doses and the intervals between them are dependent on the type of snake, the reversibility of the clinical effects and the time it takes the body to recover once the venom has been neutralised. The response to antivenom differs for the various clinical and laboratory effects. The postsynaptic neurotoxicity seen with death adder bites is reversed by

Table 2

Potential benefits of antivenom

Clinical effect	Benefits
Procoagulant coagulopathy	Neutralises toxin effect allowing clotting factors to be resynthesised and clotting to recover over 6–12 hours
Anticoagulant coagulopathy	Neutralises a toxin inhibitor of coagulation with immediate improvement in coagulation studies
Presynaptic neurotoxicity	Neutralises toxin in the intravascular compartment and will prevent further development of neurotoxicity but not reverse already present neurotoxic effects
Postsynaptic neurotoxicity	Neutralises toxin in the intravascular compartment and reverses neurotoxicity
Rhabdomyolysis	Neutralises myotoxins and will prevent further muscle injury but not reverse myotoxic effects
Local effects	Unlikely to reverse any local effects that have already developed
Renal damage	Unlikely to have any discernible effect because this is usually secondary to other toxin-mediated effects
Generalised systemic effects: nausea, vomiting, headache, abdominal pain, diarrhoea and diaphoresis	Rapidly reverse non-specific effects. This is a useful indication of antivenom efficacy

antivenom, but presynaptic neurotoxicity seen with taipan and tiger snakes is irreversible once it has developed and antivenom will only prevent further progression. Procoagulant toxins are neutralised by antivenom, but recovery of normal coagulation takes 6–12 hours on average. Anticoagulant coagulopathy is rapidly reversed by antivenom. Development or progression of rhabdomyolysis can be prevented by antivenom but it cannot be reversed.

There continues to be debate about initial doses, further doses and the dosing interval[7] and discussion with an expert is often safest. The Australian Snakebite Project is a multicentre prospective study of snake bite where serial samples are being collected for quantification of venom and antivenom concentrations. This study should help to address the questions of initial dose and appropriate laboratory and clinical end points for antivenom treatment. (Patients can be enrolled by contacting the Poisons Information Centre or the author).

Adverse effects

Early and delayed allergic reactions can occur with any antivenom, but are uncommon with Australian antivenoms. Early allergic reactions occur in less than 5% of cases and are thought to be due to complement activation. True hypersensitivity reactions are rare except in snake handlers who have had previous exposure to antivenom.

Serum sickness is a delayed reaction that develops 5–10 days after antivenom administration and is characterised by fever, rash, arthralgia, myalgia and non-specific systemic features. This should be treated with a one-week course of corticosteroids. When greater than 25 mL of antivenom is administered it is advisable to give a prophylactic course of oral corticosteroids.

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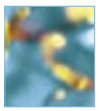
For images of snakes: see Clinical Toxinology Resources website. http://www.toxinology.com/ [cited 2006 Sep 12]

Conflict of interest: none declared



Monoclonal antibody therapy for non-malignant disease

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Summary

Advances in technology have enabled monoclonal antibodies to be produced which bind to specific antigens associated with disease processes. By targeting these antigens the antibodies can destroy or alter the function of cells which express the target. They may also bind and thereby inhibit pro-inflammatory cytokines such as tumour necrosis factor. In addition to cancer treatment, monoclonal antibodies may be useful in diseases with an immune component such as rheumatoid arthritis and psoriasis. Monoclonal antibodies can have serious adverse reactions such as severe allergy and infection.

Key words: allergy, arthritis, inflammation, tumour necrosis factor.

(Aust Prescr 2006;29:130–3)

Introduction

The use of monoclonal antibodies in clinical medicine stems from their ability to modulate the natural course of disease by targeting critical pathogenic molecules. As cancer cells have particular surface antigens, they are suitable targets for therapy.[1] Monoclonal antibodies are now finding roles in many non-malignant diseases such as inflammatory joint, skin and bowel diseases, organ transplantation, allergy and asthma. They are also used as antithrombotic drugs. The role of monoclonal antibodies is, however, limited by expense, the requirement for parenteral administration and concerns about new adverse effects.

Nomenclature

Monoclonal antibodies are created by a single clone of antibody-producing cells so they share the same unique antigen target. Although initially produced using hybridoma technology, recombinant techniques are now used.

The names of monoclonal antibodies use a suffix to characterise the structure and method of production (Table 1). The most recent products are wholly human molecules generated by recombinant techniques and carry the suffix '-umab'.

Mechanisms of action

The effectiveness of monoclonal antibodies is dependent on:

- the function and characteristics of the target antigen
- the cell surface density or tissue distribution of the antigen
- factors associated with the monoclonal antibody itself (specificity, avidity and isotype).

Monoclonal antibodies work by a number of mechanisms such as blocking the function of the target molecule, inducing the death of cells that express the target, or by modulating signalling pathways.[2]

These actions have been exploited in a range of proven and experimental indications (Table 2). Immune-mediated inflammatory diseases are particularly suitable candidates for this form of therapy. This is because key immune control molecules are secreted or expressed transiently on the surface of cells during the pathogenic process. Blocking these molecules with monoclonal antibodies may have specific effects on the disease.

Inhibition of tumour necrosis factor

Tumour necrosis factor (TNF) is a major pro-inflammatory cytokine with a wide range of roles in immunity. Anti-TNF monoclonal antibodies (infliximab and adalimumab) have been an advance in the treatment of rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease and psoriasis/psoriatic arthritis. Although etanercept is also widely used to inhibit TNF in rheumatoid arthritis, it is not a monoclonal antibody. It is a soluble TNF-receptor-IgG Fc fusion molecule.

In rheumatoid arthritis, the benefits of infliximab and adalimumab have included reduced pain, improvements in all disease measures, inhibition of structural damage, and reduction in surgery and hospitalisation.[3] Synergistic effects with methotrexate have been observed. However, partial responses are more common than complete responses and treatment is not curative.

In Crohn's disease, infliximab is useful for inducing and maintaining clinical remission, closing fistulae (enterocutaneous, perianal, rectovaginal) and for reducing steroid dependence. Infliximab is also effective at inducing a clinical response in patients with moderate to severe ulcerative colitis.

Inhibition of lymphocyte traffic

Multiple sclerosis is likely to be an immune-mediated demyelination in the central nervous system. The migration of activated T cells into the brain and spinal cord is thought

Table 1

Nomenclature of monoclonal antibodies

Type of monoclonal antibody	Structure	Suffix	Example
Murine 	Wholly mouse derived antibody	-omab	edrecol**omab**
Chimeric 	Murine antigen binding site; human Fc portion	-ximab	infli**ximab**
Humanised 	Murine complementarity determining regions only	-zumab	dacli**zumab**
Human 	Wholly human derived antibody	-umab	adalim**umab**

Table 2

Monoclonal antibodies available for clinical use

Monoclonal antibody	Target antigen	Current use	Potential use
Cell surface molecules			
Rituximab	CD20 (B cells)	Oncology	Cryoglobulinaemia, bullous pemphigoid, Wegener's granulomatosis, other B cell-mediated autoimmune diseases
Basiliximab, daclizumab	CD25	Prevention of organ rejection	
Muromonab	CD3	Treatment of acute organ rejection	Type 1 diabetes mellitus
Abciximab	Platelet IIb/IIIa	Acute coronary syndromes	
Efalizumab	CD11a component of LFA-1		Psoriasis
Affecting cell traffic			
Natalizumab	α4 integrin		Crohn's disease, multiple sclerosis
Cytokine directed			
Infliximab, adalimumab	TNF	Rheumatoid arthritis, Crohn's disease, ankylosing spondylitis	Psoriasis
Directed against antibodies			
Omalizumab	IgE		Asthma, eczema, peanut allergy

IgE immunoglobulin E
LFA-1 lymphocyte function-associated antigen-1
TNF tumour necrosis factor

to be part of the pathogenesis. These activated lymphocytes have antigens called integrins on their surface. Natalizumab, a humanised monoclonal antibody directed against alpha$_4$ integrin, has been studied in multiple sclerosis and Crohn's disease. Compared to placebo, natalizumab led to increased remission rates in multiple sclerosis. In Crohn's disease there were higher rates of sustained response when natalizumab was added to standard treatment.[4] Subsequent studies have questioned the safety of natalizumab. Studies were halted because of case reports of progressive multiple leucoencephalopathy, a devastating degenerative opportunistic viral disease of the central nervous system.

Preventing organ rejection

Allogeneic transplantation can only succeed if immune rejection of the graft by the host can be controlled. Host T cells, and the cytokines/cytokine receptors that activate them, are key targets for control. T cell depletion using muromonab has been a successful strategy in patients suffering acute organ rejection, although it is broadly immunosuppressive. The monoclonal antibodies basiliximab and daclizumab (targeting T cell activation) are as effective as traditional immunosuppressive drugs in preventing organ rejection.[5,6,7]

Drugs successfully used in preventing transplant rejection are often subsequently studied in other immune-mediated conditions. Daclizumab, for example, is effective in some patients with psoriasis. The scope of these drugs in other conditions has yet to be fully explored.

B cell depletion

Rituximab is a monoclonal antibody that targets a molecule (CD20) on the surface of B lymphocytes. The main use of rituximab is in oncology especially in B cell lymphomas.

B cell depletion using rituximab has also been successfully used in a number of other antibody-mediated conditions including cryoglobulinaemia, Wegener's granulomatosis and bullous pemphigoid. After single cycles of rituximab, circulating mature CD20+ B cells are promptly lost from the circulation, but serum concentrations of pathogenic antibody may not be acutely reduced. Clinical improvement without measurable improvement in antibody concentrations challenges a simplistic model of B cell pathology mediated solely by antibody production. Other roles of relevance might include antigen presentation and cytokine production, and this has been supported by recent studies in animal models of autoimmune disease.

Use in skin disorders

The pathogenesis of psoriasis involves a number of immune mechanisms including the activation of T lymphocytes and the release of inflammatory cytokines such as TNF.[8] Inhibitors of TNF can induce an improvement in many patients with moderate to severe plaque psoriasis. For example, a placebo-controlled trial of infliximab infusions showed that after 50 weeks 61% of patients had a 75% improvement in their psoriasis.[9] This response may be sustained following treatment cessation.

Efalizumab is a monoclonal antibody that targets part of the lymphocyte function-associated antigen-1 (LFA-1) on T cells. This antigen has roles in both T cell activation and migration so binding to it can improve moderate to severe psoriasis.

Use in preventing thrombosis

When a monoclonal antibody binds to the glycoprotein IIb/IIIa receptor on the platelet surface it disrupts the final common pathway of platelet activation and aggregation. Abciximab, a chimeric monoclonal antibody that blocks this receptor, successfully reduces myocardial infarctions in patients with acute coronary syndromes who are having angioplasty. The infusion can be complicated by bleeding, but the risk can be reduced by altering the concomitant heparin therapy.

Use in allergic diseases

Immunoglobulin E (IgE) is a pivotal antibody in the allergic response. When allergen-specific IgE on the surface of mast cells is cross-linked by allergen exposure it results in degranulation and the release of mediators such as histamine in sensitised individuals.

Allergic eosinophilic inflammation is driven by cytokines such as interleukin-5 (IL-5) so these molecules are suitable targets for monoclonal antibodies. Unfortunately, anti-IgE and anti-IL-5 therapies have failed to deliver on their therapeutic promise. Anti-IgE antibodies such as omalizumab have been used with some success in the treatment of allergic disorders such as asthma, eczema and in raising tolerance to certain food allergens. However, omalizumab is yet to find a routine place in management.

Limitations of monoclonal antibody therapy

Monoclonal antibody therapies are not used more widely because of:

- expense
- requirement for parenteral administration
- adverse effects
- host anti-drug responses limiting ongoing therapy
- limitations in current concepts of molecular pathogenesis of disease.

The first monoclonal antibodies were mouse derived and anti-mouse antibodies were common although they only occasionally caused adverse effects. Nevertheless, this limited repeat exposures to the drugs. As monoclonal antibodies now resemble human antibodies this problem has been reduced, but not entirely eliminated. On re-exposure to the initial monoclonal antibody an allergic and/or anaphylactic reaction may occur.

Adverse effects

Monoclonal antibodies have to be administered parenterally. The costs of cannulation and injection site reactions may be considerable.

New and unexpected serious adverse effects are emerging. Anti-TNF therapies are limited by serious infections including, but not restricted to, reactivation of latent tuberculosis. In addition, there are concerns that TNF inhibition might precipitate episodes of central nervous system demyelination, worsen heart failure, increase the risk of lymphoma, or trigger lupus-like syndromes. Natalizumab has been associated with progressive multiple leucoencephalopathy. Therapy aimed at depleting either B cells (rituximab) or T cells may lead to infections with opportunistic pathogens. There is therefore a need for patients to be informed of these problems when they are considering treatment.

Conclusion

Monoclonal antibodies collectively represent a significant advance in clinical medicine. Due to their expense and mode of administration they tend to be reserved for when conventional drugs have failed to elicit a response. Although these drugs are highly targeted, adverse effects do occur and clinicians should be aware of the risk of hypersensitivity reactions and infection. The future may see combinations of monoclonal antibodies being used to better target complex disease processes.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 143)

1. Patients should have a chest X-ray before starting treatment with a tumour necrosis factor inhibitor.
2. By binding to the surface of platelets, abciximab reduces the risk of bleeding during angioplasty.

Letters (continued from page 121)

(OACIS)), paper-based hospital discharge summaries are being replaced by a standardised web-based application. Summaries can be automatically faxed via computer to the relevant general practitioner or specialist, or emailed to desktop patient management systems.

Approximately 60% of all hospital discharge summaries in the eight major Adelaide hospitals are now completed this way. Over 125 000 completed summaries are stored within the system and are accessible to treating clinicians at Adelaide public hospitals. New summaries are being generated at a rate of approximately 220 per day.

Legibility problems are now avoided. Changes in discharge medication as well as reasons for these changes must be declared. The duration of treatments must also be stated. The summary may be accompanied by an interim medication list which can be reviewed by the hospital pharmacist before discharge. If a patient is re-admitted the previous discharge medications can be imported into the new summary, reducing errors.

South Australia has improved practice in this area, nevertheless thoroughness and timeliness in clinical practice remain paramount.

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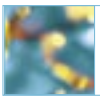

Diagnostic tests

Echocardiography

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Summary

Technological advances have led to a broader range of indications for echocardiography. For some conditions such as endocarditis, echocardiography has a key role, while in others such as hypertension it provides useful supporting information. Although most conditions can be assessed with transthoracic ultrasound, a transoesophageal approach under anaesthetic may be more useful for conditions such as aortic dissection. Stress echocardiography, using exercise or pharmacological stress, can help in the investigation of coronary artery disease and the assessment of patients following myocardial infarction.

Key words: cardiovascular disease, ultrasound.

(Aust Prescr 2006;29:134–8)

Introduction

We have come to enjoy the convenience and accuracy of echocardiography to diagnose and monitor a wide variety of cardiac conditions with safety and at a relatively low cost. The indications are now broad. In some cases echocardiography is the investigation of first choice, while in others it provides important supplementary data. By selecting the most appropriate form of echocardiographic imaging we can obtain the greatest benefit for our patients with minimum adverse effects.

It is important to remember that the quality of information may be influenced by the technician's skill, the standard of equipment used and the interpretation of the reporting doctor. As with any imaging modality, the report should be considered in the context of the clinical setting.

Indications

The patient's condition and the clinical question determine whether a transthoracic or a transoesophageal approach under anaesthetic is used.

Heart failure

All patients with suspected heart failure should have echocardiography for the assessment of left ventricular function and its aetiology. Ejection fraction may be estimated qualitatively or quantitatively. Regardless of the method there are limitations of the ejection fraction as a reflection of myocardial performance as it is load-dependent, and this should be considered when interpreting the results. Rhythm disturbances such as atrial fibrillation can make the image difficult to interpret.

Oedema and dyspnoea are common indications for echocardiography. Cardiac aetiologies such as myocardial dysfunction, valvular disease and pericardial abnormalities can usually be readily diagnosed. Significantly, echocardiography can play an important role in excluding left ventricular dysfunction in those previously diagnosed with heart failure. It also has a role in following patients' responses to the treatment of heart failure.

Diastolic dysfunction is another important cause of heart failure. It can be diagnosed non-invasively by measurements performed in a standard transthoracic echocardiogram. There are some recognised limitations including a broad overlap between normal and abnormal filling parameters, and a dependence on load, heart rate and rhythm.

Murmurs

Murmurs caused by valvular disease and other aetiologies can be readily differentiated from benign flow murmurs (Table 1). Incompetence and stenosis of each of the four cardiac valves can be diagnosed by the transthoracic approach. This provides qualitative and quantitative data which can help in determining prognosis, disease progression and guidance for treatment.

Septal defects

Septal defects may be diagnosed by echocardiography. Not uncommonly, the septal defect is an incidental finding and, particularly in the case of an asymptomatic patent foramen ovale, no further action may be required. As always, the patient's clinical condition is important when interpreting such incidental findings.

Transoesophageal echocardiography has a vital role in the selection of patients for the percutaneous occlusion of septal defects, the sizing and deployment of the devices and in follow-up.

Ischaemic heart disease

Abnormalities in the motion of the cardiac wall are characteristic of myocardial ischaemia and correlate with coronary

Table 1

Quantitative echocardiographic parameters of valvular lesions

Mitral regurgitation			
	Regurgitant fraction (%)		Effective regurgitant orifice (mm^2)
Mild	<30		<20
Moderate	30–39		20–29
Moderately severe	40–49		30–39
Severe	≥50		≥40
Aortic stenosis *			
	Mean gradient (mmHg)	Peak velocity (m/sec)	Area (cm^2)
Mild	<25	<3.5	>1.0
Moderate	25–50	3.5–4.5	0.76–1.0
Severe	>50	>4.5	<0.76
Mitral stenosis			
	Mean gradient (mmHg)		Area (cm^2)
Mild	<5		>1.5
Moderate	5–10		1.0–1.5
Severe	>10		<1.0

* good ventricular function is needed to get an accurate assessment

distribution. Following a known ischaemic event, transthoracic echocardiography can detect complications such as pump failure, acute mitral regurgitation, septal defects or free wall rupture, intracardiac thrombus (Fig. 1), right ventricular involvement and pericardial effusion. Later, echocardiography can provide important prognostic information regarding remodelling.

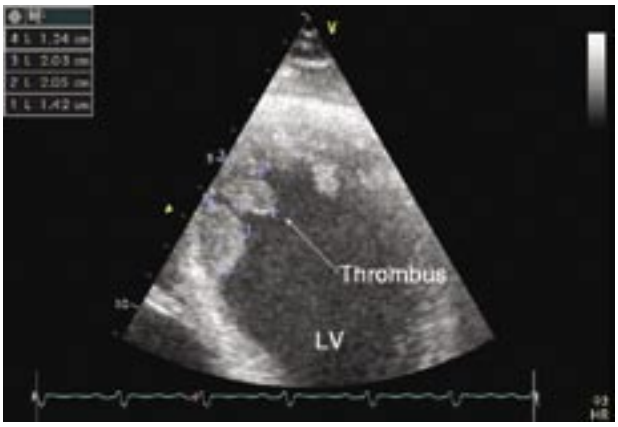
Stress echocardiography

Stress echocardiography is an important tool in the evaluation of known or suspected coronary artery disease.[1] It can also be used in valvular heart disease, hypertrophic cardiomyopathy and pulmonary hypertension. Physical stress is preferred (either treadmill or bicycle) for the assessment of chest pain, dyspnoea, valvular disease or post-myocardial infarction risk. Pharmacological stress testing with dobutamine is the method of choice for studies of myocardial viability, and preoperative risk assessment before non-cardiac surgery (usually because the patient is not well enough or able to exercise before the surgery) or if the patient cannot exercise.

The sensitivity of exercise echocardiography ranges from 71%[6] to 97%[2]. The accuracy of dobutamine echocardiography is similar. Due to its availability, convenience, versatility and ability to evaluate other forms of cardiac disease simultaneously, it is preferred to radionuclide scintigraphy in some centres. It is also cheaper and avoids a dose of radiation. Compared to stress ECG alone, echocardiography is more specific for detecting stress-induced ischaemia or left ventricular dysfunction.

Fig. 1

Transthoracic image of left ventricular apical thrombus



LV left ventricular cavity

Systemic hypertension

The cardiac effects of hypertension can be evaluated by echocardiography. Left ventricular hypertrophy can be more accurately diagnosed than by ECG and echocardiography is less expensive and more accessible than magnetic resonance imaging. The presence of increased mass or even increased wall thickness impacts adversely on morbidity and mortality.

Arrhythmias and palpitations

Arrhythmias may be the manifestation of a variety of cardiac abnormalities including congenital defects, acquired valvular lesions, pericardial disease and ischaemia. Conversely, arrhythmias may be the cause of cardiac pathology such as atrial thrombus or dilated cardiomyopathy. In patients with atrial fibrillation echocardiography can unmask otherwise unsuspected cardiac disease in 10% of cases and can help predict which patients are more likely to remain in sinus rhythm post-cardioversion. Before cardioversion, transoesophageal echocardiography has a vital role in excluding intra-atrial thrombus in patients who have had atrial fibrillation for more than 48 hours without anticoagulation.

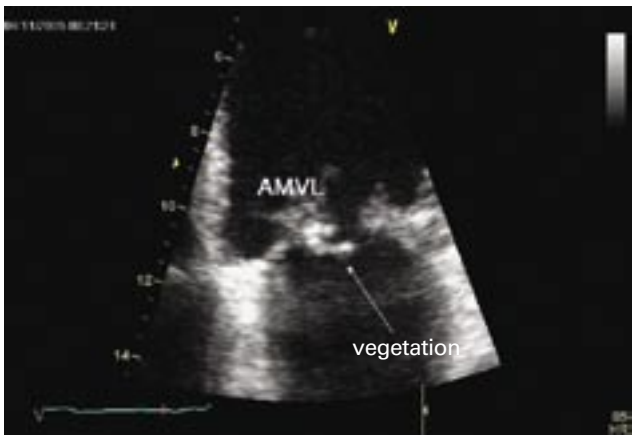
Although not an absolute indication, an echocardiogram showing a structurally normal heart in a patient troubled by isolated ectopic beats can be very reassuring for both physician and patient. Similarly, echocardiography is useful in the evaluation of patients with an abnormal ECG.

Endocarditis

Echocardiography is vital in the workup of a patient with suspected endocarditis particularly for the diagnosis of

Fig. 2

Transthoracic image of vegetation on the anterior leaflet of the mitral valve



AMVL anterior mitral valve leaflet

vegetations (Fig. 2). Transoesophageal echocardiography is more sensitive than transthoracic imaging for detecting small vegetations, abscess cavities and leaflet perforation, and is superior for the imaging of prosthetic valves.[3] Indications for transoesophageal echocardiography include a diagnostically inadequate transthoracic echocardiogram, a negative transthoracic echocardiogram despite ongoing high clinical suspicion of endocarditis, prosthetic valve involvement and staphylococcal (or suspected) bacteraemia.

Prosthetic valves

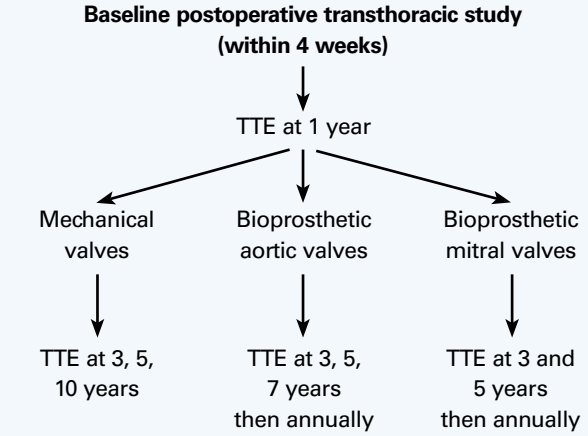
Prosthetic valves are susceptible to infection, degeneration, stenosis and thrombosis. They are routinely checked with transthoracic echocardiography (see box). Transoesophageal echocardiography is indicated when the assessment of prosthetic valve function is hampered by acoustic shadowing, or the detection of vegetations is made difficult by other artifacts. It is essential when evaluating complicated endocarditis in patients with prosthetic valves.

Embolic disease

Echocardiography plays a very important role in finding the source of an embolus following a stroke or peripheral embolic event. Younger patients or those who have suffered occlusion of a large peripheral vessel are more likely to have suffered a purely cardiac embolic event. Older patients are more likely to have intrinsic cerebrovascular disease or atrial fibrillation.

Transthoracic echocardiography is easier, carries negligible risk and is less expensive, but has a lower yield than transoesophageal echocardiography. Sources of emboli that are usually better defined by transoesophageal echocardiography include left atrial appendage thrombus, small vegetations, septal defects or aneurysm and aortic arch atheroma.

Follow-up of patients with prosthetic valves



TTE transthoracic echocardiography

From: Guidelines of the Prince Charles Hospital Echocardiography Laboratory, Brisbane

Cardiac masses and tumour

Patients in whom the diagnosis of an intracardiac mass should be considered are those with cryptogenic stroke or other embolic events, those with atrial fibrillation, dilated cardiomyopathy, anteroapical infarction, bacteraemia or fever of unknown origin. Echocardiography can accurately diagnose primary and secondary cardiac tumours, thrombi and vegetations.

Pericardial disease

Echocardiography is the investigation of choice for the diagnosis and evaluation of a pericardial effusion (Fig. 3). The effusion's presence, size, haemodynamic significance and response to therapy are well demonstrated. Echocardiographic signs in keeping with tamponade include right atrial invagination at the onset of systole (sensitive), right ventricular collapse in diastole (specific) and marked respiratory variation in transvalvular inflow velocities. Transthoracic echocardiography assists in the planning and the execution of pericardiocentesis.

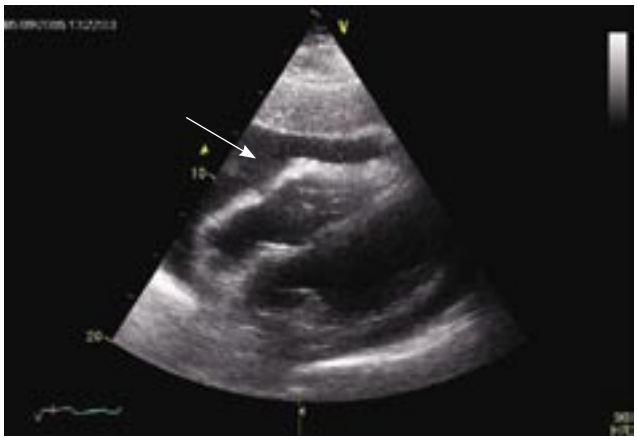
Constrictive pericarditis may be diagnosed on echocardiography, however the assessment of the pericardium can be difficult and investigation such as magnetic resonance imaging may be more helpful.

Diseases of the great vessels

Transthoracic echocardiography shows the main pulmonary arteries as far as the proximal main branches, the hepatic veins as they drain into the inferior vena cava, and the inferior vena cava as it emerges from the liver and enters the right atrium. Three of the four pulmonary veins can usually be seen transthoracically where they connect with the left atrium, but for a complete examination of pulmonary venous drainage, transoesophageal echocardiography is usually required. The

Fig. 3

Transthoracic image of pericardial effusion



arrow pericardial fluid

superior vena cava can occasionally be seen as it enters the right atrium, but this vessel is best seen by transoesophageal echocardiography.

Transoesophageal echocardiography, magnetic resonance imaging and CT scanning have similar sensitivity and specificity for the detection of aortic dissection. With the exception of a sometimes encountered blind spot at the upper ascending aorta, the remaining thoracic aorta can be accurately visualised by transoesophageal echocardiography.

Pulmonary disease

Although pulmonary disease often contributes to poor image quality, echocardiography can be useful in the non-invasive evaluation of pulmonary pressures, right heart size and function and in the exclusion of a cardiac cause for dyspnoea. Echocardiography is not the investigation of choice for pulmonary emboli. However, it can provide indirect evidence such as elevated right heart pressures or right ventricular dilatation and dysfunction. Large proximal pulmonary emboli (for example, saddle embolus) can be diagnosed by transoesophageal imaging.

Syncope

Transthoracic echocardiography can be considered if there is syncope in the presence of an abnormal ECG or cardiovascular disease. Some common cardiac aetiologies that can be excluded are obstructive lesions such as hypertrophic cardiomyopathy or significant aortic stenosis, and conditions providing a substrate for malignant arrhythmias such as left ventricular dysfunction or right ventricular dysplasia.

Screening

Echocardiography can screen for abnormalities in the relatives of patients with familial cardiomyopathies (dilated and hypertrophic) and Marfan's syndrome.

Technological advances

Intravascular imaging has given greater insights into coronary atherosclerotic disease. While the applications of intracardiac echocardiography are still emerging, this technology has proved useful in percutaneous closure of cardiac defects, the evaluation of double prosthetic valves and the exclusion of pacing lead endocarditis.

Three-dimensional imaging can provide accurate anatomic information. There has been preliminary work on three-dimensional imaging during pharmacological stress.[4]

Doppler tissue imaging examines the velocity of the systolic and diastolic motion of the myocardium at various sites. It provides insight into diastolic function and has become a routine part of the standard transthoracic imaging. Recently, Doppler tissue imaging has been used in stress-testing to improve sensitivity compared with visual analysis alone.[5] Strain rate imaging is a promising application of Doppler tissue imaging in the assessment of ischaemia and viability via detection of subtle alterations in myocardial contractility.[6]

Lightweight and less expensive hand-held devices are now available. Their image quality is sufficient to make basic diagnostic assessments.

Conclusion

Echocardiography is widely available in Australia. Its use is likely to increase as technological developments increase its accuracy and portability. While echocardiography has many potential indications, it is best used when it will provide information that will add to the clinical findings and help to guide treatment. This principle is particularly important when considering the need for the more invasive transoesophageal echocardiography.

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Further reading

ACC/AHA/ASE 2003 Guideline update for the clinical application of echocardiography. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. http://guideline.gov/summary/summary.aspx?doc_id=4020 [cited 2006 Sep 12]

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 143)

3. Arrhythmias limit the usefulness of echocardiography in the diagnosis of diastolic heart failure.
4. Echocardiography is useful for detecting small pulmonary emboli.

New drugs

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

Butoconazole nitrate 2%

Gynazole-1 (Arrow Pharmaceuticals)

single dose applicator containing 5 g of cream

Approved indication: local treatment of candidal vulvovaginitis

Australian Medicines Handbook section 17.11.1

Candida albicans is a common cause of vulvovaginitis.[1,2] These infections are usually treated with imidazole antifungal drugs. Butoconazole nitrate is the fifth imidazole agent to be registered in Australia, after clotrimazole, ketoconazole, miconazole and econazole. These drugs come in a number of different formulations (including cream, pessaries and oral tablets) and dosing regimens. Although butoconazole nitrate 2% cream is a new product in Australia, it was first introduced in the USA as a prescription drug in 1986 and is currently marketed there as an over-the-counter product.

Depending on the formulation, up to 6% of an intravaginal dose is absorbed, with peak plasma levels being reached 12–24 hours after administration. The drug is excreted mainly as metabolites in the urine and faeces.

The Australian butoconazole cream has been formulated to adhere to the vaginal wall for longer than the standard butoconazole cream.[3] The prolonged retention time means that this formulation can be given as a single-dose application rather than a three-day course.

In a randomised open-label trial of 181 American women with vulvovaginal candidiasis, a single application of butoconazole cream was compared to a single 150 mg oral tablet of fluconazole. Twelve hours after treatment, 44.4% of women given topical butoconazole experienced first relief of symptoms compared with 29% of women given oral fluconazole. The time to complete relief of symptoms was similar in both treatment groups. Yeast cultures to confirm the presence or absence of candida were not performed in this study so the true microbiological cure rates could not be assessed. The most common butoconazole-related adverse events were vulvovaginal pruritis (3 events) and vulvovaginal burning (3 events). In the fluconazole group, headache (6 events), diarrhoea, nausea, skin sensitivity and upset stomach were the most common drug-related adverse events.[4]

In another trial, a single-dose butoconazole cream was compared to a seven-day miconazole cream. Similar levels of drug efficacy in both treatment groups were observed with regard to clinical symptoms and microbiological cultures.[5]

Two unpublished studies compared butoconazole nitrate 2% cream with a clotrimazole pessary (500 mg) in women with confirmed vulvovaginal *Candida albicans* infection. Microbiological and symptomatic signs of candidiasis were resolved 30 days after treatment in 79 of 118 (67%) women treated with butoconazole compared with 71 of 116 (61%) given clotrimazole.

In trials comparing butoconazole and clotrimazole vaginal treatments, irritation of the vulva, vagina or urethra were the most common drug-related adverse event. These were reported by approximately 1% of patients receiving either treatment.

The use of latex or rubber products such as condoms or contraceptive diaphragms is not recommended within 72 hours of butoconazole application. Additional topical antifungal cream may be required for the treatment of external vulval or perianal areas.

In Australia, 10% clotrimazole is the only single-dose cream

already available for the treatment of candidal vulvovaginitis. It is not known whether the single-dose butoconazole formulation will be more effective.

[T] [T] manufacturer provided some data

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Darifenacin hydrobromide

Enablex (Novartis)

7.5 mg and 15 mg prolonged-release tablets

Approved indication: overactive bladder

Australian Medicines Handbook section 13.1.1

The contraction of detrusor smooth muscle involves stimulation of muscarinic receptors by acetylcholine. Anticholinergic drugs have therefore been used to relax the bladder in patients with urge incontinence. These drugs have unwanted systemic effects so there is a need for a drug with an action that is more specific to the bladder. The M_3 muscarinic receptor has been a target for drug development as it is thought to be the subtype responsible for bladder contraction.

Darifenacin is an anticholinergic drug which has a greater affinity for the M_3 receptor than for other subtypes. Its action diminishes the frequency of detrusor contractions and increases bladder capacity.

Once-daily dosing is possible with the prolonged-release formulation. Peak plasma concentrations are reached seven hours after an oral dose, with a steady state reached in six days. Bioavailability depends on the patient's metabolism. Darifenacin is extensively metabolised in the liver and its pharmacokinetics are affected by moderate hepatic impairment. As the metabolism involves cytochrome P450 2D6 and 3A4, there are several potential drug interactions. The risk of adverse events may be increased by CYP2D6 inhibitors such as cimetidine, fluoxetine and paroxetine. Daily doses of darifenacin should not exceed 7.5 mg if the patient is taking an inhibitor of CYP3A4 such as itraconazole. The anticholinergic adverse effects of tricyclic antidepressants and drugs for Parkinson's disease may be increased by darifenacin.

In one trial 561 patients were randomised to take darifenacin 3.75 mg, 7.5 mg, 15 mg or a placebo for 12 weeks. The respective median reductions in weekly incontinence episodes were 8.6, 9.0, 10.4 and 7.6. The reduction in weekly incontinence episodes was 68% with 7.5 mg and 73% with 15 mg. This was significantly greater than the 56% reduction with placebo.[1] Other placebo-controlled studies had similar results so the recommended starting dose is 7.5 mg daily, increasing if necessary after two weeks to 15 mg daily. In a dose titration trial, 59% of patients needed to increase to 15 mg daily.

Compared with placebo, patients taking darifenacin complain more frequently of dry mouth and constipation. These adverse effects appear to increase with the dose. Other adverse effects include altered vision, dyspepsia and abdominal pain. Caution is needed if darifenacin is considered for patients with decreased gastrointestinal motility or at risk of urinary retention.

Darifenacin has been studied in people with overactive bladder. These people have urinary urgency, but not all of them have urge incontinence. The benefits of darifenacin may be less certain in these patients. Although it achieved statistical advantages over placebo, the absolute changes may be small. For example, a patient given darifenacin 15 mg will have one less micturition per day than a patient given a placebo. They may also have one less episode of urgency per day. Darifenacin does not decrease the number of times a patient is awoken by their overactive bladder significantly more than placebo.[1]

Comparative studies are limited, but tolterodine has been included in a placebo-controlled trial of darifenacin. Unfortunately, a comparative analysis of the 15 mg dose of darifenacin was not done for all the outcomes. Darifenacin only achieved a statistical advantage, over tolterodine, for some outcomes if it was given at a daily dose of 30 mg. It appears that darifenacin's selective action does not give it a large clinical advantage.

[X] manufacturer did not respond to request for data

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Entecavir

Baraclude (Bristol-Myers Squibb)

0.5 mg and 1 mg tablets

Approved indication: chronic hepatitis B

Australian Medicines Handbook section 5.3.1

Hepatitis B can become chronic particularly if the infection occurs in childhood. While some carriers of the virus have

no liver damage, others develop chronic inflammation and cirrhosis. Antiviral drugs, such as lamivudine, adefovir or interferon alfa, can be considered for patients with active inflammation of the liver.

Entecavir is an antiviral drug with activity against hepatitis B viral polymerase. As entecavir is an analogue of the nucleoside guanosine, it competes with the enzyme's usual substrate. This reduces the synthesis of viral DNA. Entecavir is therefore indicated when there is evidence of viral replication. At present it is only approved for adults who have active liver inflammation.

Patients take entecavir once daily. A higher dose is needed if there is resistance to lamivudine because these viral strains are also less susceptible to entecavir. As food reduces absorption, entecavir is taken on an empty stomach. Most of the dose is excreted unchanged in the urine so it should be reduced in people with renal impairment.

Entecavir was compared with placebo in a dose-ranging study of 42 patients with chronic hepatitis B. They took the drug for 28 days and were followed up for a further 24 weeks. All doses of entecavir significantly reduced the concentration of viral DNA.[1]

Another phase II study randomised 185 patients to take entecavir or lamivudine for 24 weeks. Entecavir had a greater effect on viral load with 26% of the patients taking 0.5 mg having undetectable concentrations of viral DNA compared with 18% of the patients taking 100 mg lamivudine. Concentrations of alanine transaminase (ALT) returned to normal in 69% of those taking entecavir and 59% of those taking lamivudine.[2]

The phase III studies of entecavir looked at the effect of treatment on liver histology as well as on laboratory tests. Approximately 1600 patients participated with the majority having two liver biopsies. In patients who were positive for hepatitis B e antigen, inflammation improved in 72% with entecavir and in 62% with lamivudine.[3] The corresponding figures were 70% and 61% in patients without the e antigen.[4] These differences show a statistical advantage for entecavir. Both treatments resulted in an improvement of liver fibrosis in 35–39% of patients. ALT concentrations were more likely to become normal with entecavir. In a study of 286 patients with lamivudine-refractory infections, switching to entecavir was associated with improved liver histology. After a year of treatment improvements were seen in 55% of the patients given entecavir compared with 28% of those who continued lamivudine.[5]

During the clinical trials the most common adverse events were headache and fatigue. After treatment stopped in the dose-ranging study the viral load soon increased.[1] There is a risk that the hepatitis will flare up when the patient stops taking treatment. Safety and efficacy have not been confirmed for more than 48 weeks of treatment and the optimum duration of treatment is unknown. Hepatocellular carcinoma and other cancers have appeared during studies of animals, but the risk in humans is unknown. Like other nucleoside analogues there may be a risk of lactic acidosis.

Resistance to entecavir has been reported. Although there is some cross-resistance with lamivudine, there does not appear to be cross-resistance with adefovir. Currently, there appear to be no published clinical trials comparing lamivudine and adefovir.

Entecavir has efficacy against hepatitis B, but assessing its safety and effectiveness on long-term outcomes will require more study. There is greater certainty that immunisation will prevent more people becoming chronically infected.

T T manufacturer provided some data

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Human papillomavirus vaccine

Gardasil (Merck Sharp & Dohme)

vials containing 0.5 mL liquid

Approved indication: prevention of human papillomavirus infection and associated genital disease

Australian Medicines Handbook section 20.1

Human papillomavirus is one of the most common sexually transmitted viral infections. While most of these infections are transient, some can persist and lead to the development of cervical cancer. In Australia there are approximately 800 new cases of cervical cancer each year. Cervical screening, which is regularly undertaken by 63% of Australian women, has reduced the mortality associated with cervical cancer due to the early identification and management of precancerous lesions.[1]

Over 40 different types of human papillomavirus have been identified that infect the genital mucosa. Human papillomavirus types 6 and 11 cause 90% of genital warts. In Australia, the most prevalent types found in invasive cervical cancer are types 16 and 18.[1]

A quadrivalent human papillomavirus vaccine has been approved in Australia for intramuscular injection in males and females aged 9–15 and in females aged 16–26. This is not a live virus, but contains virus-like particles derived from the major

capsid (L1) protein of human papillomavirus types 6, 11, 16 and 18. The vaccine is indicated for the prevention of cervical, vulvar and vaginal cancer, precancerous or dysplastic lesions, genital warts and infection caused by these viral types.

The safety and efficacy of the quadrivalent vaccine has been compared to placebo in one phase II trial and two phase III trials. These trials involved a total of approximately 18 000 women aged 16–26 with a history of normal cervical smears. Participants received three doses of either vaccine or placebo at 0, 2 and 6 months. Human papillomavirus infection and associated genital disease were monitored for up to 36 months after the initial vaccination.

The phase II trial enrolled 552 women from the USA, Europe and Brazil. The efficacy analysis was done on the per-protocol population, which was defined as women who did not have antibodies to vaccine-type human papillomavirus at the beginning of the trial and remained free of infection from vaccine-type human papillomavirus through to completion of the vaccination regimen. At 36 months after the initial dose, 94%, 96%, 100% and 76% of women given the vaccine were seropositive for human papillomavirus vaccine types 6, 11, 16 and 18 respectively. There were 4 cases of persistent vaccine-type human papillomavirus infection or associated genital disease in 235 vaccinated women compared with 36 cases in 233 women in the placebo group, representing a vaccine efficacy of 89%.[2]

The efficacy of the vaccine appears to be similar in the phase III trials, but as yet the results have not been published in full. In the per-protocol populations, the number of cases of cervical intraepithelial neoplasia or cervical adenocarcinoma *in situ* was reduced from 80 in 7628 women given the placebo to 4 in 7623 women given the vaccine. Likewise, there was only one case of genital warts, vulval intraepithelial neoplasia or vaginal intraepithelial neoplasia in the vaccine groups compared with 110 cases in the placebo groups. The vaccine did not prevent disease caused by other viral types that were not present in the vaccine.

Although this vaccine is indicated for boys aged 9–15, published evidence of its efficacy in males is lacking.

There were no vaccine-related serious adverse effects reported in the trials. However, there were more injection-site reactions (pain, redness and swelling) and fever in women given the vaccine compared to those given the placebo.

It is likely that this vaccine will reduce human papillomavirus infections, which will in turn reduce cervical cancer and other human papillomavirus-related genital conditions. Men and women are at risk from human papillomavirus infection for as long as they are sexually active. Longer follow-up studies will therefore be needed to assess the duration of efficacy for this quadrivalent vaccine, and to determine whether booster doses will be needed.

T T manufacturer provided some data

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Solifenacin succinate

Vesicare (Arrow Pharmaceuticals)

5 mg and 10 mg tablets

Approved indication: overactive bladder

Australian Medicines Handbook section 13.1.1

Patients with overactive bladders may have urgency and frequency. Some may develop urge incontinence. If these symptoms are troublesome and do not respond to non-drug treatment an anticholinergic drug may help (see 'Anticholinergic drugs for overactive bladder', Aust Prescr 2006;29:22–4).

Solifenacin is an anticholinergic drug with a high affinity for the M_3 muscarinic receptors in smooth muscle. It is well absorbed and can be taken once a day. Solifenacin is metabolised in the liver by cytochrome P450 3A4 so it may interact with other drugs which inhibit or induce this enzyme. Most of the metabolites are excreted in the urine. The half-life is 45–68 hours, but this is prolonged by renal or hepatic impairment.

In a randomised double-blind trial, once-daily solifenacin was compared with placebo in 907 patients with overactive bladder. After 12 weeks the mean number of daily micturitions had reduced, from a baseline rate of about 12 in 24 hours, by 2.4 with solifenacin 5 mg and by 2.8 with solifenacin 10 mg. This was a statistical advantage over the placebo group who had 1.6 fewer micturitions per day. The reduction in incontinence showed a similar pattern with 1.3 fewer episodes in the placebo group and 1.6 fewer episodes with solifenacin 5 mg or 10 mg.[1]

A pooled analysis of trials in patients over 65 years old showed some statistical advantages over placebo, but the absolute differences were small. Solifenacin 5 mg reduced incontinence by a median of 1 episode per day compared with 0.7 episodes with placebo and 1.5 episodes with solifenacin 10 mg. Patients taking placebo had one less micturition per day while those taking solifenacin 5 mg had two less micturitions. The median change with solifenacin 10 mg was 2.3 fewer micturitions per day.[2]

Despite its affinity for the M_3 receptor, solifenacin is not free of anticholinergic adverse effects. In the placebo-controlled trial, 23% of the patients taking solifenacin 10 mg developed a dry mouth compared with 7.7% of the solifenacin 5 mg group and

2.3% of the placebo group. Constipation and blurred vision were also more likely with solifenacin.[1] In the pooled analysis, dry mouth affected 29.7% of the elderly people taking solifenacin 10 mg, 13.5% of those taking solifenacin 5 mg and 4.5% of the placebo group. Constipation affected 17.2%, 8.9% and 4.3% respectively.[2]

Solifenacin can prolong the QT_c interval on the ECG. An ECG should be considered before starting treatment if there is a risk of QT_c prolongation.

Tolterodine is another recently approved drug for overactive bladder. It has been compared with solifenacin in 1200 patients over 12 weeks. The results were not analysed by the dose of solifenacin (5 mg or 10 mg), but overall there was no difference in the frequency of micturition. Solifenacin reduced daily micturitions by 2.45 compared to a reduction of 2.24 with tolterodine. Incontinence episodes per 24 hours reduced by a mean of 1.6 with solifenacin and 1.1 with tolterodine. Adverse events were slightly more frequent with solifenacin.[3]

Solifenacin will reduce urgency and this may improve the patient's quality of life. However, the efficacy is modest and the patient may have to endure adverse effects to obtain the benefit.

T T manufacturer provided some data

References *

1. Cardozo L, Lisec M, Millard R, van Vierssen Trip O, Kuzmin I, Drogendijk TE, et al. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. J Urol 2004;172:1919-24.
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Tigecycline

Tygacil (Wyeth)

vials containing 50 mg lyophilised powder for reconstitution

Approved indication: complicated skin and soft tissue infections and complicated intra-abdominal infections

Australian Medicines Handbook section 5.1.11

Tigecycline is structurally related to the tetracycline class of antibiotics and is a derivative of minocycline. It has broad spectrum *in vitro* activity against Gram-positive, Gram-negative and anaerobic organisms and also tetracycline-resistant bacteria. Coverage includes multiresistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci. Tigecycline has poor activity against *Pseudomonas* species.

Tigecycline is not absorbed from the gut so it must be administered by slow intravenous infusion. It is extensively distributed in the body and has a serum half-life of 40 hours. The tissue half-life is not known. Tigecycline is not extensively metabolised and so most of the drug is excreted unchanged in the urine and faeces.

The safety and efficacy of tigecycline were evaluated for the treatment of skin and skin-structure infections from pooled data of two trials totalling 1116 hospitalised adults. Soft tissue infections, abscesses and infected ulcers were the most common type of infections in these patients. In both trials, tigecycline (100 mg intravenously followed by 50 mg every 12 hours) was compared to a combination of vancomycin and aztreonam for 5–14 days of therapy. Microbiological data were available for 540 patients and clinical data were available for 833 patients. Cure rates for tigecycline and vancomycin/aztreonam were similar in both sets of data, with approximately 86% of tigecycline recipients responding to treatment compared to approximately 88% of vancomycin/aztreonam recipients. Both treatments were equally effective in patients with underlying comorbidities such as diabetes mellitus and peripheral vascular disease.[1]

The safety and efficacy of tigecycline were also evaluated for the treatment of complicated intra-abdominal infections, such as complicated appendicitis, from pooled data of two studies totalling 1642 hospitalised adults. Patients received tigecycline or a combination of imipenem and cilastatin for 5–14 days. Of the 685 patients with clinically evaluable data, a total of 594 responded to tigecycline, compared to the 607 of the 697 patients with clinically evaluable data in the comparator group. Similar levels of drug efficacy were reflected in the 1025 patients who were microbiologically evaluable.[2]

Although tigecycline has *in vitro* activity to multidrug resistant bacteria, there were limited data in these trials to support its use in patients with these infections. However, tigecycline was effective at eradicating MRSA in 25 out of 32 patients with complicated skin infections.[1]

There were two reports of bacterial resistance to tigecycline in the intra-abdominal infection pooled analysis. Both patients infected with these resistant isolates failed to respond to tigecycline treatment.[2]

In all four trials, there were slightly more drug-related adverse events reported by tigecycline recipients (986 of 1383 patients) than by patients receiving the comparator treatments (927 of 1375 patients). The most common events in the tigecycline-treated patients were nausea and vomiting. Nausea was experienced by 394 of the patients given tigecycline and 202 patients in the comparator group. Vomiting occurred in 268 patients taking tigecycline and 138 patients taking the comparator treatments. Overall there were 30 deaths in the tigecycline groups and 18 deaths in the control groups. One

death of a tigecycline recipient, after septic shock, was possibly related to the study drug.

Tigecycline is not recommended for pregnant women or children. Tetracycline class effects, such as photosensitivity, may also occur in patients taking tigecycline.

Tigecycline provides an alternative antibiotic therapy for the treatment of serious infections in hospitalised adults. However, its effectiveness in treating multidrug resistant infections remains to be fully evaluated. Advice from an infectious disease specialist or bacteriologist should be sought before using tigecycline.

T T T manufacturer provided all requested information

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1. Ellis-Grosse EJ, Babinchak T, Dartois N, Rose G, Loh E. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. Clin Infect Dis 2005;41:S341-53.
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The T-score (T) is explained in 'Two-way transparency', Aust Prescr 2005;28:103.

* 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 Agency for the Evaluation of Medicinal Products (www.emea.eu.int)

Correction

Epoetin beta (New drugs, Aust Prescr 2006;29:112–5)
The brand name for epoetin beta is NeoRecormon.

Answers to self-test questions

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

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