CONTENTS

Australian Prescriber
Volume 24
Number 2
2001

EDITORIAL

Antibiotics in animals – much ado about something

John Turnidge, Professor, Microbiology and Infectious Diseases Department, Women's and Children's Hospital, Adelaide

Index words: antibiotic resistance, avoparcin, vancomycin.

(Aust Prescr 2001;24:26–7)

Much media attention has been focused on the use of antibiotics in animals, particularly the animals we eat, and the potential spread of resistance to bacteria which infect humans. Although the problem was recognised over 30 years ago[1], few countries acted upon it until recently. In the early 1990s a link was identified between the emergence of vancomycin-resistant *Enterococcus faecium* with the *vanA* gene (*vanA* EF) and the use of avoparcin, a vancomycin analogue, as a growth promoter in pig and poultry production.

Australian antibiotic use in farming, medicine and veterinary medicine is high. During 1992–7 an annual average of 399 tonnes or 56% of all antibiotics by weight was used in stockfeed. Humans consumed 251 tonnes or 36%, while 54 tonnes or 8% were used in veterinary therapeutics.[2]

A very wide range of antibiotics is used for many different reasons in animal husbandry, agriculture, and in veterinary practice. Common sense and a knowledge of bacterial genetics tell us that we need to monitor the emergence of resistance and only give antibiotics to animals when it is therapeutically rational and cost-effective to do so. Resistant bacteria can be generated in animals, transferred to humans and amplified to become a major human problem. These bacteria may either cause disease in humans or transfer their resistance genes to normal flora that may later become pathogenic. Good food hygiene will slow the transfer rate but will not eliminate the transfer of resistance. Antibiotics should therefore be given to animals only when necessary and for the shortest effective duration.

While short courses at therapeutic doses minimise resistance selection, a significant proportion of the antibiotics used in animals are given in feed at low doses over many weeks of the production cycle. Antibiotics are used in this way by the so-called intensive animal industries, especially meat poultry and pig production, where the animals are housed in close quarters in large numbers (just like hospitals!). Cross-infection is a problem, and antibiotics play an important role in suppressing infection and controlling stock loss, as well as in promoting the animals' growth.

These patterns of use generate maximum selective pressure for antibiotic resistance. This would not be a problem if the antibiotics used were from different classes and had a different mechanism of action from those used in humans. Unfortunately, a number of drugs used in this way belong to the same classes and select for cross-resistance to human antibiotics. Examples include avoparcin (a glycopeptide), virginiamycin (a streptogramin which selects for cross-resistance to the newly released drug quinupristin/dalfopristin) and certain macrolides.

Before calling for blanket decisions to prohibit all antibiotic use in animals, we need to understand the data suggesting that resistance has been transferred from animals to humans via the food chain. The data concerning resistance transfer are limited to a small number of organisms and antibiotics such as *vanA* EF and avoparcin, thermophilic *Campylobacter* species and fluoroquinolones, multi-drug resistant *Salmonella* species and aminoglycoside resistance in *E. coli*. Apart from these examples there is little information to show just how much resistance in human bacteria can be traced back to the use of antibiotics in animals.

Data in Australia are even more limited. For instance, although avoparcin has been widely used in Australia since the mid 1980s, and vancomycin-resistant enterococci (VRE) emerged in human isolates in Australia in 1994, the predominant type of VRE contain a different gene from that attributed to avoparcin use. One small study of animal samples in the Hunter Valley revealed only two strains of VRE, and their association with avoparcin use remains unclear.[3]

The concern for human medicine is that avoparcin and virginiamycin select for resistance to drugs that are reserved

In this issue...

The spectre of antibiotic resistance is probably contributing to the improved use of antibiotics in the community. Jonathan Dartnell tells us that educational approaches can also improve hospital prescribing, while John Turnidge discusses how agricultural antibiotics could contribute to the resistance problem.

Mental illnesses such as depression are also increasing, but many depressed patients need not be treated with potentially toxic drugs. John Tiller explains how doctors can use cognitive behaviour therapy to help patients with mental disorders.

Coeliac disease is also being recognised more frequently than previously, and Warwick Selby tells us how to confirm the diagnosis.

for infections caused by bacteria resistant to multiple other antibiotics ('last-line' drugs). After sustained pressure about this issue the European Union decided to suspend the use of avoparcin as an in-feed antibiotic. Subsequently it was withdrawn from the international market, including Australia. The Europeans have also suspended other in-feed drugs, including virginiamycin, tylosin, spiramycin and bacitracin.

What could or should be done about antibiotic use in animals? Australia has produced a blueprint for tackling this problem.[2] A number of recommendations have been made in the areas of regulation, surveillance and monitoring, infection prevention, education and research. One key recommendation is that of phasing out the long-term, low dose use of antibiotics that can generate resistance to 'last-line' human antibiotics.

The most important feature of the recommendations is that rational antibiotic use is the responsibility of **all** prescribers and users, medical practitioners and veterinarians, patients and farmers. Antibiotic use of any type and the antibiotic resistance it generates is a public health issue. The use of antibiotics in animals may be making a lesser contribution than inappropriate prescribing to resistance problems in humans. However, all users must endeavour to minimise resistance for the sake of healthy animals, food and humans.

E-mail: turnidgej@wch.sa.gov.au

REFERENCES

1. UK Joint Committee on the use of antibiotics in animal husbandry and veterinary medicine ('Swann Report'). London: Her Majesty's Stationery Office; 1969 Nov.
2. Joint Expert Technical Advisory Committee on Antimicrobial Resistance (JETACAR). The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans. Canberra: Commonwealth Department of Health and Aged Care and the Commonwealth Department of Agriculture, Fisheries and Forestry; 1999 Sept. http://www.health.gov.au/hfs/pubs/jetacar.htm
3. Butt H, Bell J, Ferguson J. Are vancomycin-resistant enterococci prevalent in Hunter region farm animals? Microbiology 1997;18:A115.

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.

Topical ciprofloxacin and antibiotic resistance

Editor, – A generation or so ago, I was taught that if one wanted to render antibiotics useless, due to resistance, as quickly as possible, apply them topically. Why is ciprofloxacin being marketed in this way? Should there not be a full re-evaluation of the use and misuse of all topical antibiotics? Is there any convincing evidence that any of them are a good idea?

Peter Rout

General Practitioner

Darlington, NSW

Professor J. Turnidge, Microbiology and Infectious Diseases, Women's and Children's Hospital, Adelaide, comments:

The concern expressed by Dr Rout about the topical use of ciprofloxacin is shared by many others. The standard teaching comes from the early experience with the use of topical antibiotics to treat infected burns, where resistance emerged rapidly. It is possible that the very high counts of bacteria in infected burns made the selection of resistance easier. Whether this problem occurs with all topical antibiotic use is not clear. The concentrations of topical antibiotics are often 1000 fold higher than the minimal inhibitory concentrations of the bacteria. Thus, in theory, there should be a lower risk of resistance selection than with systemic use.

However, there is another principle that must be taken into account. The rate of resistance selection is related to the total amount of antibiotic use in the community. We should prefer topical drugs which, when resistance is selected, do not jeopardise the valuable systemic antibiotics. Indeed, in the case of fluoroquinolones, strenuous efforts have been made to ensure that availability of the systemic drug is restricted to cases of proven need. Topical application should follow the same principle. Dr Rout will be pleased to know that the availability of topical ciprofloxacin (and other topical quinolones) has been taken up with national regulators. Although the outcome is not known, we hope that these drugs will be restricted to (rare) cases of proven need.

Treatment of panic disorder

Editor, – In writing about the 'Treatment of panic disorder' (Aust Prescr 2000;23:124–6) Professor Tiller provides the standard definition used in psychiatry. The definition ignores the most outstanding characteristic of panic disorder and panic attacks: over-breathing. Indeed, the Diagnostic and Statistical Manual (DSM) does not provide a diagnosis for hyperventilation disorder which is a common affliction in the community and certainly so among those with mental disorders.[1] Caught in this bind, Professor Tiller arrives at the task of management without any theoretical explanation of the measures he advocates.

I intend no criticism of the author. The fact that he deals with hyperventilation at all shows that he is well ahead of his academic colleagues and most working in the field. He has rediscovered the wheel earlier than they. The part that hyperventilation disorder played received full acknowledgment long ago[1] and the symptoms of cerebral hypoxia caused by cerebral vasoconstriction were explained in the 19th century. All that knowledge disappeared in the face of psychopharmacotherapy. Psychiatrists have discarded the simple clinical recognition of the deep breaths taken by the anxious patient, the revealing account of light-headedness, pins and needles in the periphery, pain in the left side of the chest, the lump in the throat, palpitations and panic. Instead of restoring normal breathing and confidence, doctors now take out the prescription pad and a reversible process becomes irreversible.

Advanced as he is in rediscovering the wheel, Professor Tiller still has not quite grasped the principles of restoring normal breathing. Normal breathing is not deep. It is abdominal (diaphragmatic) rather than thoracic. Few people have paper bags these days. A plastic bag does just as well and does not make the noise which the author finds socially unacceptable. Tying a piece of tubing into the neck makes it easier to use it as a re-breathing bag. The real reason for not using it is that in most cases correct diagnosis, reassurance and instruction in normal breathing is all that is needed.[2,3]

David S. Bell
Psychiatrist
Mosman, NSW

REFERENCES

1. Kerr WJ, Dalton JW, Gliebe PA. Some physical phenomena associated with the anxiety states and their relation to hyperventilation. Ann Int Med 1937;11:961-92.
2. Cluff RA. Chronic hyperventilation and its treatment by physiotherapy: discussion paper. J R Soc Med 1984;77:855-62.
3. Lum LC. Hyperventilation and anxiety state. J R Soc Med 1981;74:1-4.

Professor JWG Tiller, author of 'Treatment of panic disorder', comments:

Dr Bell is correct that the DSM does not emphasise over-breathing as a common characteristic of panic. This diagnostic classification tries to differentiate disorders, so it omits features such as over-breathing which may occur in several disorders. I used DSM IV as it is the most common diagnostic system used in Australian psychiatry. I did not attempt a treatise on respiration, notwithstanding my interest in this area.[1]

When faced with hyperventilation, in getting patients to focus on slow, deep breaths, I have not assumed what they might regard as 'normal breathing'. A slow respiratory rate is one element. If patients use slow shallow breathing they simply shift air predominantly in their dead space. They feel they are suffocating and their panic is reinforced. Hence the recommendation for slow, deep breathing as the first step in restoring normal breathing. The immediate response to hyperventilation may be exaggerated before 'normal' diaphragmatic breathing is re-established.

I would not argue on the popularity of different types of bag, paper, plastic or otherwise. Nevertheless, it would be a spectacular sight to see a patient in the middle of public transport tying a tube into the neck of a plastic bag and then breathing in and out. I would suggest that this would be somewhat attention-grabbing and embarrassing.

My paper focused on psychological interventions rather than pharmacological, as the former will suffice for most patients. However, pharmacotherapy can be uniquely efficacious for some disabled individuals. In my review, rather than rediscovering the wheel, I hope I have simply given it a further push in what may be generally the right direction.

REFERENCE

1. Tiller J, Pain M, Biddle N. Anxiety disorder and perception of inspiratory resistive loads. Chest 1987;91:547-51.

Editor, – The article on Panic disorder (Aust Prescr 2000;23:124–6) had its relevance enhanced by the subsequent commentary by comedian Garry McDonald, wherein reference was made to a book by Bronwyn Fox 'Anxiety attack: don't panic'. A footnote pointed out that this book was out of print.

However there is a more recent book by the same author on the same subject – 'Power over panic'[1] – with a foreword by Garry McDonald. I believe it would be a worthy substitute for the now unobtainable earlier book.

Anthony Martin
Endodontist
Sydney

REFERENCE

1. Fox B. Power over panic: freedom from panic/anxiety related disorders. Melbourne: Longman; 1998.

Ancestim

Editor, – Thank you for including the notes on ancestim (Stemgen) in the New drugs section (Aust Prescr 2000;23:137).

We wish to point out that the approved product information states that ancestim is indicated for use in combination with filgrastim only. There have been no clinical studies of the use of ancestim with a granulocyte colony stimulating factor other than filgrastim.

Jane Campbell
Senior Regulatory Affairs Specialist
Amgen Australia
Hawthorn, Vic.

The ethics of rational prescribing

Editor, – Regarding Dr Max Kamien's letter to the Editor (Aust Prescr 2000;23:96) and the response from the Pharmaceutical Society, it seems to me that industry marketing to physicians and pharmacists continues to play a greater part in prescribing than evidence. The 'evidence' used by industry to push new drugs in general and in this case COX-2 inhibitors specifically, is often far from clinically relevant. Statistical significance and clinical relevance are often totally unrelated.

Regarding the pharmacist pushing new drugs (of the same class) onto patients, there is a case in Canada that is possibly on its way to the courts. The doctor prescribed a well-tested non-steroidal anti-inflammatory drug and the pharmacist replaced it with the newer, so-called miracle drug, but the patient did not do well.

Dr Kamien's conclusion is absolutely on the mark. It is neither socially responsive nor ethical for pharmacists to push new drugs. Our patients deserve better.

Carl Whiteside
Department of Family Practice
University of British Columbia
Vancouver, Canada

Activities to improve hospital prescribing

Jonathan Dartnell, Production Manager, Therapeutic Guidelines Ltd., Melbourne

SYNOPSIS

Prescribing restrictions can effectively control drug use, but can also shift practice in unforeseen ways. Doctors must therefore be involved in any interventions to change their prescribing. Multifaceted interventions aimed at the barriers preventing good prescribing probably have the greatest chance of success. Interactive educational meetings are more influential than didactic meetings and one-to-one educational outreach visits are consistently effective. The implementation of guidelines should be supported with strategies such as systematic audit and feedback, active educational measures and mechanisms to ensure they are accessible at the point of prescribing.

Index words: drug information, drug utilisation, intervention studies.

(Aust Prescr 2001;24:29–31)

Introduction

While most prescribing occurs in the community, the quality use of medicines in hospitals should not be neglected. Doctors learn to prescribe in hospitals, and this has a great bearing on how they prescribe thereafter. Our major teaching hospitals care for the most complex patients, but their immediate therapeutic care is managed by our least experienced prescribers, albeit under the supervision of experienced clinicians. In contrast to community prescribing, there is little information available on drug use in hospitals due to a lack of co-ordination and poorly developed information systems. However, many detailed evaluations have shown that there are prescribing problems in Australian hospitals[1], for example, the overuse of cephalosporins (see page 32).

Characteristics of the drug use environment

Poor prescribing is not simply due to a lack of access to drug information or training of the prescriber.[2] A complex array of factors impact on prescribing and since therapeutic decision-making is loaded with uncertainties, the environment in which prescribing occurs has a powerful influence. Time pressures on the prescriber are great, resulting in hasty decision-making. Resources are limited, defining the boundaries of care and forcing priorities to be made. Prescribers have expectations of a drug's efficacy and adverse effects moulded by experience, peers and advertising, but these expectations may not be consistent with the evidence. Patients have expectations that cannot always be met, however, every patient has the right to understand treatment options and participate in decisions about what will happen to them. Commercial incentives are a reality and drive the pharmaceutical industry, which in turn is driving developments in health care.

Improving drug use

Improving drug use is not easy. Presenting prescribers with research and evidence, or identifying a problem rarely changes practice. However, there is a range of interventions that can be effective in changing prescribing but their success is dependent on the setting in which they are applied.[3,4] Multifaceted interventions aimed at the different barriers to change probably have the greatest chance of improving drug use although they are relatively expensive and can require repetition to maintain their impact, especially if there is a high turnover of staff (see example 1).

Example 1. Educational marketing and outreach

In one example, marketing techniques and educational outreach (academic detailing) were used to improve surgical antibiotic prophylaxis. The prescribers were visited by a pharmacist who explained the campaign, which involved posters, lectures and videotapes. As a result, prescribing in the six hospitals involved in the campaign improved significantly more than in six control hospitals.[5]

Education

Ideally medical students should be educated in the principles of good prescribing before they enter the hospital. On the wards, these principles should be reinforced with bedside teaching and examinations. The quality use of medicines needs to be recognised as an important part of medical education and intern training programs.

Junior medical staff make most of the prescribing decisions in hospitals and young interns prescribe largely by following the instructions of more senior residents and consultants.[6] Educational activities should be tailored to the different levels of therapeutic decision-making in teaching hospitals.

While they may be useful to disseminate information, didactic educational meetings such as lectures, alone, have little or no effect on practice.[7] The impact of training and education seems to be increased by:

- using interactive meetings (e.g. group problem solving, role playing, workshops)
- repeated sessions

- focusing on one clinical problem at a time
- training and practice at the work site
- using detailers and opinion leaders.

Opinion leaders are those who are named by their peers as trusted sources of information. The concept has been extensively utilised by the pharmaceutical industry for product promotion. When used to promote good practice, the impact of opinion leaders is variable and their role is not always clear.[8] In hospitals, in contrast to general practice, it can be relatively easy to identify opinion leaders and recruit them into campaigns. There will be problems if they have not been involved or if their opinion is inconsistent with campaign messages.

Academic detailing (educational outreach)

Face-to-face educational visits by trained personnel with individual health practitioners are consistently shown to be effective in changing behaviour and prescribing practice.[9] An economical and sustainable approach may be to train hospital staff to deliver the detailing during the course of their usual activities. In hospitals junior clinicians are important recipients of detailing but are sometimes overlooked (see example 1).

Feedback

Feedback provides clinicians with information comparing their practices or patient outcomes with other clinicians' or an external standard (e.g. a practice guideline). Feedback is successful when it is immediate, specific, able to identify those to whom it is directed, and when the desired change in behaviour or response is clear and unambiguous.[9] In hospitals, there is an excellent opportunity to combine the methods of educational outreach with audit and feedback to deliver concurrent prescriber feedback, a potentially powerful intervention method. This process uses the power of the face-to-face encounter of educational outreach, and also provides information to the prescriber on their management of specific cases[10] (see example 2).

Example 2. Concurrent prescriber feedback

Immediate feedback has been used to improve antibiotic prescribing. Following an educational program, prescribers were alerted within 24 hours if they had prescribed an unnecessary intravenous antibiotic. This rapid feedback resulted in significantly greater use of oral antibiotics.[10]

Guidelines

In general, effective implementation of guidelines requires support with strategies such as systematic audit and feedback and active educational measures.[3,4] Guidelines should take account of local circumstances and local consensus processes can be important. However, this must be matched with a sustainable and regular production process so the guidelines remain current. That may not be possible for guidelines at the local level.

Dissemination of guidelines alone is unlikely to lead to behaviour change. However, they may have a lasting impact when the target audience is already particularly receptive to change and the message is timely and delivered by a credible source in a clinically relevant way[11] (see example 3). Dissemination activities by themselves are also unlikely to lead to behaviour change, but raising awareness of the messages underpinning proposed changes is still important.[4]

Example 3. Guidelines, audit and feedback

In one example, prescribers were issued with guidelines after an audit of their anticoagulant prescribing. This intervention, coupled with a new order form for heparin prescriptions, increased the time the patients were in the therapeutic range and reduced the delay in starting warfarin therapy.[12]

For guidelines to be effective they need to be accessible at the time a decision is being made. In hospitals, pocket-sized materials have enjoyed some success. State departments of health are providing access to health information via web portals. However, computers are generally not yet at the patient bedside where most therapeutic decisions are made and there is limited access elsewhere in the hospital. Unfortunately, computerised prescribing developments in Australian public hospitals have lagged behind general practice. Frustrated clinicians are buying hand-held computers to access clinical information. We need to tap into this emerging phenomenon and evaluate its impact on practice.

'Computerised prescribing developments in Australian public hospitals have lagged behind general practice'

Routine reminders, forms and required consultations

Manual or computerised prompts to perform a specific clinical action are effective.[4] Simple interventions such as altering order forms to reflect preferred dosing intervals for antibiotics have been successful in improving use. Many hospitals limit the use of particular drugs until a nominated senior clinician has been consulted, however this can be onerous. Prescribing restrictions are a proven measure for controlling antibiotic use, but can shift practice in unforeseen ways and require efficient systems and a supportive framework to function smoothly.[4] Even without computer-based prescribing, interactive web modules could be developed as an alternative means to implement prescribing restrictions.

Sustainability of interventions to improve prescribing

A single round of interventions does not generally achieve a sustained impact on practice. The impact of co-ordinated educational and persuasive interventions such as the dissemination of printed guidelines, supported with promotional campaigning and academic detailing, may be expected to last up to 12 months (see example 1). By that time, staff turnover, other campaigns, pharmaceutical product promotion and fading memories will cause a shift in priorities and practice

behaviour, and a loss of motivation. Interventions that change the process of drug use and decision making (such as the use of forms, prescribing restrictions, routine reminders and decision support systems) should have a more sustained impact, but even these require resources to maintain and update.

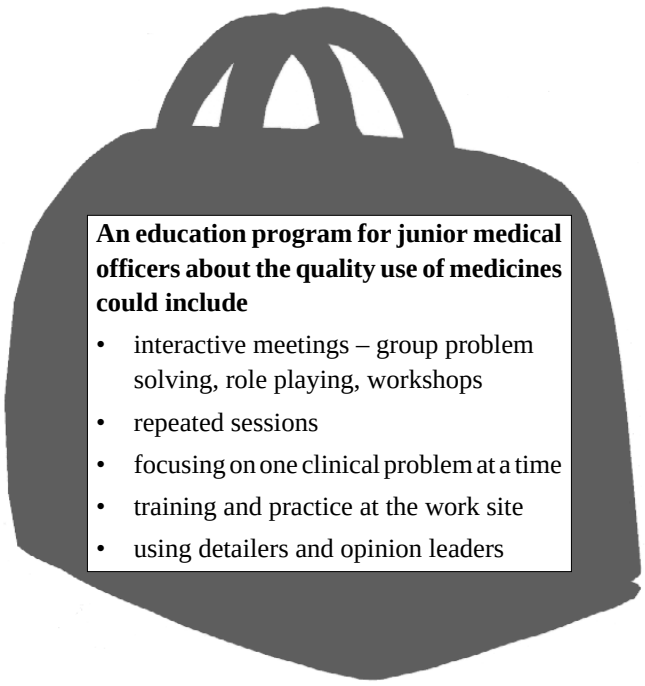
Quality improvement, drug usage evaluation, and drug and therapeutic committees

Given the number, range and persistence of drug use problems, there is a compelling case for the support and development of programs that are dedicated to improving the quality use of medicines. Drug usage evaluation programs[13] identify, observe and explain patterns of practice then implement activities to improve drug use, and then verify the effects of interventions. To work, these programs need clinicians' involvement, individual practitioner feedback and a supportive organisational culture, in particular an authoritative and credible drug and therapeutics committee.

In current hospital administration structures, the committee is ideal for overseeing drug usage evaluation as well as being a major stimulus to improve the quality use of medicines.[14] Most hospitals with a pharmacy service have a committee, but its role may be more oriented towards regulatory rather than improvement activities and it may lack broad and credible representation from clinicians. Prescribers must be engaged in any process aimed at changing their prescribing, to reduce the perception of outsider interference and challenges which threaten professional judgements, decision-making and patient care.[15]

Conclusion

To encourage the quality use of medicines, prescribers need to be aware of the issues and believe or be persuaded, that they are important. Prescribers need to know what to do, and have confidence and familiarity in doing the right thing. They need to be able to recognise when they have to act, and how they should act. The system should make doing the right thing easy.



An education program for junior medical officers about the quality use of medicines could include

- interactive meetings – group problem solving, role playing, workshops
- repeated sessions
- focusing on one clinical problem at a time
- training and practice at the work site
- using detailers and opinion leaders

REFERENCES

1. Quality use of medicines mapping project. Canberra: Commonwealth Department of Health and Aged Care; 1998. http://www.qummap.health.gov.au/
2. International conference on improving use of medicines. Essent Drugs Monit 1997;23:6-12.
3. Le Grand A, Hogerzeil HV, Haaijer-Ruskamp FM. Intervention research in rational use of drugs: a review. Health Policy Plan 1999;14:89-102.
4. NHS Centre for Reviews and Dissemination. Getting evidence into practice. Eff Health Care 1999;5:1-16. http://www.york.ac.uk/inst/crd/ehc51.htm
5. Landgren FT, Harvey KJ, Mashford ML, Moulds RF, Guthrie B, Hemming M. Changing antibiotic prescribing by educational marketing. Med J Aust 1988;149:595-9.
6. Moulds RFW. From knowledge to action: improving drug prescribing [editorial]. Med J Aust 1996;165:299-300.
7. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. Br Med J 1998;317:465-8.
8. Thompson O'Brien MA, Oxman AD, Haynes RB, Davis DA, Freemantle N, Harvey EL. Local opinion leaders: effects on professional practice and health care outcomes (Cochrane Review). In: The Cochrane Library. Oxford: Update Software; Issue 1, 2001.
9. Thomson MA, Oxman AD, Davis DA, Haynes RB, Freemantle N, Harvey EL. Educational outreach visits: effects on professional practice and health care outcomes (Cochrane Review). In: The Cochrane Library. Oxford: Update Software; Issue 1, 2001.
10. Seto WH, Ching TY, Kou M, Chiang SC, Lauder IJ, Kumana CR. Hospital antibiotic prescribing successfully modified by 'immediate concurrent feedback'. Br J Clin Pharmacol 1996;41:229-34.
11. Lomas J. Words without action? The production, dissemination, and impact of consensus recommendations. Annu Rev Public Health 1991;12:41-65.
12. Dartnell JG, Allen B, McGrath KM, Moulds RF. Prescriber guidelines improve initiation of anticoagulation [published erratum appears in Med J Aust 1995;162:197]. Med J Aust 1995;162:70-3.
13. Dartnell JGA, Kirsa SW. DUE – an essential tool to achieve QUM [editorial]. Aust J Hosp Pharm 2000;30:251-2.
14. Day R, Brown S, Weekes L. Drug committees – the key to quality use of medicines? Aust J Hosp Pharm 1996;26:622-3.
15. Greco PJ, Eisenberg JM. Changing physicians' practices. N Engl J Med 1993;329:1271-3.

E-mail: jdartnell@tg.com.au

How education influences prescribing at John Hunter Hospital

Jennifer MacDonald, Deputy Director, Pharmacy, and John Ferguson, Microbiology and Infectious Diseases, John Hunter Hospital, Newcastle, NSW

The problem

The overuse of broad spectrum antibiotics, including the 'third generation' cephalosporins such as cefotaxime or ceftriaxone, has been linked to the emergence of multiresistant organisms.[1] These include vancomycin resistant enterococci (VRE), methicillin resistant *Staphylococcus aureus* (MRSA) and an increase in the incidence of opportunistic pathogens such as *Clostridium difficile*.[2] Such an increase in nosocomial *C. difficile* was noted in John Hunter Hospital, a tertiary referral centre, towards the end of 1997. If not clinically warranted these cephalosporins are often a more expensive option for treatment than alternatives.

The strategy

Educational initiatives designed to alter prescribing habits can be more effective and better accepted in many settings than a totally proscriptive approach.

The strategy used at the John Hunter Hospital involved a multifaceted approach. A working party, looking specifically at the use of anti-infective drugs, was formed to encourage compliance with the prescribing guidelines published in the Antibiotic Guidelines[3] and those developed specifically for our hospital environment. Other interventions included:

- individual detailing of prescribers when inappropriate use was identified by ward pharmacists
- educational presentations to clinical units such as Emergency, Intensive Care and Respiratory Medicine
- the development and promotion of a consensus guideline which reduced the role of cephalosporins in management of community- and hospital-acquired pneumonia
- publicity of the hospital's anti-infective guidelines through the drug bulletin and on the intranet
- education sessions aimed at junior medical officers and interns
- presentations during grand rounds and Quality Week.

The results

Antibiotic usage relative to hospital activity confirmed the success in changing prescribing habits.

The use of third generation cephalosporins dropped markedly from an average of 40.9 DDD*/1000 patient days in 1997 to 27.9 for 1998–2000 (September) (incidence rate ratio 0.68, 95% CI 0.66–0.70).

In 1997 the average number of nosocomial *C. difficile* infections was 9.8 cases per 10^5 patient days. For the period 1998 to 2000 (September) the average fell to 4.0 cases per 10^5 patient days (incidence rate ratio 0.41, 95% CI 0.21–0.80).

Whilst this reduction may be due to many causes, the more appropriate use of broad spectrum anti-infective drugs may be a contributory factor.

In the 12 month period from January 1998, when the first education intervention commenced, the decreased use of cephalosporins was reflected in a greater than $55 000 saving over the previous year. This reduction has been sustained over the three years since the first intervention by a continuing education and awareness process. A drug utilisation review cycle has been established involving twice yearly auditing of third generation cephalosporin prescribing, feedback and education. There has been a consistent improvement in the level of 'appropriate' prescribing of third generation cephalosporins as assessed by the infectious diseases team, with each audit.

* DDD = defined daily doses

ACKNOWLEDGEMENT

The authors wish to acknowledge the Hunter Infection Prevention and Control Unit for providing information on *Clostridium difficile*.

REFERENCES

1. Gaynes R, Monnet D. The contribution of antibiotic use on the frequency of antibiotic resistance in hospitals [review]. Ciba Foundation Symposium 1997;207:47–60.
2. Zadik PM, Moore AP. Antimicrobial associations of an outbreak of diarrhoea due to *Clostridium difficile*. J Hosp Infect 1998;39:189–93.
3. Writing Group for Therapeutic Guidelines: Antibiotic. Therapeutic Guidelines: Antibiotic. Version 11. Melbourne: Therapeutic Guidelines Limited; 2000.

E-mail: jmacdonald@hunter.health.nsw.gov.au
john.ferguson@hunter.health.nsw.gov.au

Cognitive behaviour therapy in medical practice

John W.G. Tiller, Associate Professor and Reader, Department of Psychiatry, University of Melbourne, Royal Melbourne Hospital, and Albert Road Clinic, Melbourne

SYNOPSIS

Cognitive behaviour therapy is a psychological treatment which is suitable for many patients with psychiatric problems or psychological reactions to physical illnesses. It can enhance the effects of drug treatment. The principles of the therapy are educating the patient, teaching basic relaxation and breathing control skills, and developing skills to identify, challenge and change maladaptive thoughts, feelings, perceptions and behaviour. It is a treatment readily used by medical practitioners.

Index words: anxiety, depression, hyperventilation.

(Aust Prescr 2001;24:xx)

Introduction

Cognitive behaviour therapy (CBT) can be usefully and easily applied in any area of medical practice. There is evidence to show that CBT is better than placebo for insomnia, depression, panic disorder, agoraphobia, specific phobia, social anxiety disorder and pain. In some cases, it is better than drug therapy and may be less expensive. For other patients the combination of CBT with drug therapy may be effective.

Many doctors use elements of CBT even though they may not recognise that they are doing so. Understanding CBT is important, as it is possible to unwittingly reinforce negative or adverse responses. For example, encouraging avoidance of a feared situation to give temporary relief of anxiety may result in the patient having to repeatedly avoid that situation, thereby maintaining or exacerbating their problem.

Components of CBT

The basic processes of CBT are to:

- educate the patient
- teach basic skills for anxiety control with relaxation and breathing (hyperventilation) control
- identify, challenge and change maladaptive thoughts, feelings, perceptions and behaviour.

Treatment aims for decreased avoidance, more realistic thinking and more adaptive responses (emotional, physiological and behavioural).

Education

Doctors may incorrectly assume that patients know about their illnesses. Patients may have misconceptions about the diagnosis, the treatment and the prognosis. For example, patients with panic symptoms may believe they have a severe cardiac condition. This can increase anxiety and cause tachycardia, reinforcing fears of cardiac disease. Brief education about their illness will counter inaccurate appraisals of symptoms, minimise secondary anxiety and lead to more rational responses to symptoms.

The patient should be an active partner in their education and not simply a passive recipient of information.

Anxiety reduction techniques

Relaxation

Many people get tense with their illness, or in reaction to it. This tension may result in headache or muscle aches and pains, particularly in the neck, shoulder and lower back.

Stress-reduction books and tapes offer a range of relaxation techniques. They typically start with a person sitting quietly and then clenching their fists and then relaxing, extending their wrists and then relaxing, flexing the elbow and then relaxing, and so forth. While usually started in a quiet setting, once learnt the technique can be applied in a subtle and abbreviated fashion anywhere. This can prevent the development of excessive and uncontrollable tension. Relaxation techniques do not address the cognitive aspects of anxiety; a person can seem to be physically relaxed, while their worrying thoughts continue unabated.

Breathing control

Hyperventilation is a normal physiological response to a threat. Other symptoms of fear are typically a dry mouth, shortness of breath or feelings of suffocation, tachycardia, chest discomfort, pressure or tightness and dizziness. Symptoms due to the alkalosis caused by hyperventilation include light-headedness, numbness and tingling, and in more marked cases tetany with spasms, which usually start in the hands.

If their symptoms occur, patients should breathe slowly with deep even relaxed breaths in five-second cycles. They also need to recognise the fear and how their breathing responds to that fear.

Getting patients to hyperventilate in your office can often reproduce some of their symptoms. As this hyperventilation occurs in a 'safe' controlled setting and without the cues that trigger an attack, a panic/anxiety attack may not follow. That does not mean hyperventilation is not an influence in other

settings. By practising breathing control patients can learn that they can influence their symptoms.

This induction of symptoms in a controlled graded fashion followed by response prevention or response management is a classical intervention. To gain mastery, patients must be prepared to take modest risks.

There is no evidence that breathing in and out of a paper bag is efficacious, probably because it is mostly used long after the event which caused the hyperventilation. Asking patients to monitor and control their respiration is effective and not as socially embarrassing for them as breathing in and out of a paper bag in public.

Cognitive therapy

The patient can learn to identify, challenge, gradually modify, and change maladaptive, automatic thoughts, feelings, perceptions and behaviour. Five processes are described.

Collaborative empiricism

The doctor and patient jointly evolve an understanding of the problems and the goals of the treatment, providing feedback and demystifying therapy. For example the patient may regard symptoms, such as back pain, as out of their control, or that they must rest lest their back 'break'. The patient can be taught to take control of their pain through guided activity and the gradual experience of some relief.

Socratic dialogue

A progressive question and answer process assists in the identification of maladaptive thoughts and assumptions. The dialogue examines the meaning of events for the patient, assessing the consequences of maintaining maladaptive thoughts and behaviours, and developing more useful ways of dealing with the identified problems. A patient with a pathology result indicating neoplasia may believe they will rapidly die a horrible painful death. The reality may be quite the contrary. The doctor can relieve anxiety and avoid unnecessary consultations by a careful explanation of the illness, its treatment and the recovery process.

Guided discovery

The patient modifies their maladaptive beliefs and behaviours through a series of graded tasks developed with their doctor. These tasks are usually set weekly, for around 12 weeks. For example, the thought that life is hopeless (so why bother with anything) can be challenged and gradually changed to a more realistic and positive view, giving the patient a sense of purpose.

Identification of automatic (core) negative thoughts

CBT challenges the patient's automatic (core) negative thoughts and helps them to learn to challenge these thoughts themselves. These thoughts, feelings and perceptions may occur 'out of the blue', or for example, in response to a certain feared situation such as travelling on public transport or in a lift.

People may fear the same situation for different reasons. For example the experience of anxiety and the desire to leave a supermarket may have different causes. Those with social anxiety disorder may fear embarrassment or humiliation while exposed to the scrutiny of others. Those with panic disorder might fear the check-out queue because they feel unable to escape easily if they get a panic attack, and patients with depression may be irritable and feel that they cannot endure the wait in the queue. The same avoidance behaviour may therefore require different solutions for different diagnoses.

There can be characteristic distorted perceptions. A depressed patient may feel that others can see they are a bad person, even though others may have no such attitudes. Other depressed patients may not feel bad, but may expect they will fail in any activity they undertake. Patients with social anxiety disorder may place excessively high expectations on their social performance. They may feel that everyone's eyes are on them in a social situation, when the reality is that most people are unaware of their presence.

Automatic or 'core' thoughts and feelings often include false assumptions. For example the patient with social anxiety disorder might feel that they **will** embarrass or humiliate themselves. Their fear may be baseless, or based on some event in the past. This automatic thought might be better reconceptualised as a new circumstance in which they **may** embarrass or humiliate themselves, rather than they **will** do so. There is a possibility, but not an inevitability, of humiliation.

'R' strategy

The 'R' strategy is to relabel, re-attribute, refocus, record and revalue elements of the patient's problem.

To **relabel** an aspect of their obsessive-compulsive disorder (OCD) a person with obsessions about cleanliness should not say to themselves, 'I think my hands are dirty, or feel my hands are dirty,' but instead say 'I am having an obsession that my hands are dirty'.

A patient who feels that they must be a bad person, because they developed cancer, could **re-attribute** their symptoms by saying (then thinking and feeling), 'It is being ill with cancer that makes me feel bad'.

Refocus is a very important shift, which helps the patient train themselves to respond in new ways to their automatic thoughts, feelings, perceptions and behaviours. They can be taught to resist urges, to hold their anxiety, and habituate. Habituation is the reduction in the anxiety when the patient is placed in an anxiety-provoking situation and remains there. The fear or anxiety reaction diminishes during such exposure. If patients experience fear and want to avoid or leave an anxiety-provoking situation, they should hold off acting for fifteen minutes or so. They can then re-evaluate the situation, their thoughts, feelings and responses, and assess and **record** them. This helps mastering the task they felt previously unable to approach.

To **revalue** means to take on the role of an impartial spectator, a person we carry around inside us who is aware of all of our feeling states and circumstances. The patient, when wanting to do an anxiety-provoking task, can call up their own impartial spectator and watch themselves in action. This is to move

from an internal personal battle to a more externalised conflict. This is a shift from an internal 'me against myself' conflict to an external situation 'who is in charge here, me or my illness'.

Behaviour therapy

Establishing a problem list and hierarchy (see Box 1)

The patient needs to make a list of problems or situations they have avoided or might avoid. Each problem is then subdivided into a hierarchy ranging from tasks easily mastered to those achieved only with great difficulty. The patient and doctor can work through some of these situations. At first this can be done in the patient's imagination. They can think of a situation which causes minimal anxiety. They then think of a setting in which they face that situation and overcome it. This desensitisation in imagination is a precursor to getting into those situations and controlling them in practice. The person must have confidence in this process and be prepared to take risks. These are emotional 'risks' and should not expose the patient to danger. Gradual exposure leads to habituation. The fear diminishes, anxiety lessens and avoidant behaviour may be overcome.

The more the patient identifies, challenges and modifies their thoughts, feelings and behaviour, the easier mastery will become. What initially may seem a very challenging task will soon become routine as it is mastered and the patient moves on to more difficult tasks.

Exposure and response prevention (see Box 2)

Exposure with response prevention leading to habituation and extinction of the anxiety and fear may be explained to the patient as 'getting used' to the feared situation or thought. This is part of common experience in learning new skills. For example, a child might feel that learning to ride a bicycle is impossible, but once they can ride, with much worry and anxiety, they have learnt a skill that remains for a lifetime.

Another, effective way to deal with anxieties is by flooding. This involves putting the person into the feared situation and have them remain there for however long it takes for their anxiety to subside. That can be emotionally distressing for a patient and is generally unnecessary, as a series of graded tasks agreed on by the patient and doctor, can achieve a satisfactory outcome with less distress.

Some feelings are reinforced by patient experiences. For example a typical journey in a lift is under a minute. If a sufferer gets into a lift they will leave the lift when their anxiety has built to a peak rather than when lessening. There is reinforcement that travel in lifts causes increasing anxiety up to a peak. If, however, they can be encouraged to stay longer in the lift (riding up and down), until their anxiety starts to settle, they begin to get a feeling of mastery over their problem. Progressively one can increase the period of time they spend in a lift. The important element is that the sufferer experiences their anxiety decreasing in the feared setting, rather than increasing.

Patient evaluation of thoughts and behaviour (see Box 3)

The patient can rate the severity of their thoughts, anxieties and behaviours, then re-rate them after challenge and reappraisal. Most patients can understand and apply a 0-10 scale for a particular symptom. Patients can rate their subjective anxiety and distress, the extent to which they hold beliefs and are coping, and the ease with which they can elicit a relaxation response.

What if the patient gets stuck?

Occasionally a patient says everything is too difficult. The tendency is for both patient and practitioner to focus on the problem that is blocking progress. They should not dwell on this problem, but move to consider the next item in the hierarchy. Mastery of the next item may make the earlier problem irrelevant or eventually lead to it being overcome. If treatment reaches an impasse, it is worth considering additional help. Most psychiatrists and clinical psychologists are specifically trained in CBT and can provide further expert advice.

Patient motivation and self-efficacy

Motivation can be helped by a sense of self-efficacy, which challenges the irrational notion that problems can **never** be overcome. Work out alternatives with patients that elicit adaptive responses. For example, patients can learn to recognise and to control their anxiety with methods like relaxation, and hyperventilation control. This means that when they think about or test out some anxiety-provoking situation, they do not automatically have to panic, avoid the circumstance, or resort to medication. Patients should understand that transient increases in anxiety and distress are inevitable as they gain mastery over their difficulties.

Costs

CBT does not need multiple extended consultations. In medical practice CBT can be done sequentially over a number of relatively brief, for example ten minute, treatment sessions.

Medicines and CBT

Some people master their problems without drugs, while others benefit from having medicines with CBT.

Benzodiazepines can impede CBT. The rapid reduction in anxiety reduces the motivation to change and the patient may not achieve mastery, especially at higher doses. However, if a patient is very anxious, a small dose of a benzodiazepine can help with the first steps in taking risks, facing their fears and gaining mastery over symptoms.

For depression, panic disorder, obsessive-compulsive disorder, generalised anxiety disorder and social anxiety disorder antidepressants can be effective with CBT.

For those with schizophrenia, the use of an antipsychotic drug will usually improve their condition enough to enable them to benefit from CBT for other elements of their illness.

An outline ofCBTin practice

Initial appointment (Table 1)

For some patients the 'initial' evaluation will be spread over two or three visits. General practitioners are usually familiar with the patient's problems and can often complete the initial

Table 1

Suggested approach for cognitive behaviour therapy: first appointment

Evaluation

- take detailed history
- perform physical examination
- make the diagnosis, or diagnoses and rate severity of symptoms and the disorder
- consider possible antecedents, especially alcohol, caffeine and illicit drugs

Delineation of core therapeutic issues

- identify problems, automatic thoughts, feelings, perceptions and behaviours that are troublesome to the patient
- define the patient's disabilities, what they cannot do and want to overcome

Education

- provide education, and outline CBT as one element of treatment
- explain physical symptoms that represent an emotional disorder
- reassure that the disorder is real and can be treated
- explain you will not conduct investigations unless clearly indicated on history or examination

Teach basic skills and self-evaluation

- begin hyperventilation control and relaxation techniques
- encourage the patient to develop a hierarchy of problem issues, and rate their severity
- explain how to self-monitor
- consider concomitant pharmacotherapy, if indicated

evaluation quickly. The evaluation should include a physical examination so that any general medical illnesses can be managed appropriately.

After the evaluation give the patient some initial education, including an estimate of how long it will take to respond (usually 6–8 weeks). They can be asked to compile a list of their problems (Box 1). If patients are given any exposure tasks they can record their responses (Box 2). To help them monitor their feelings they can fill in another chart (Box 3).

For patients with mild depression or anxiety, CBT may be useful alone. If the disorder is severe, drug treatment may be started at this session.

Second appointment (Table 2)

This may be two or three days, or one to two weeks after the first appointment, but is better sooner than later. If the patient was given some tasks at the first appointment, their charts can be reviewed to assess progress.

The patient will inevitably have further additions to their story. They may have dealt with some issues and some symptoms will have already changed. For example, a patient may have a fear of public transport. They may have said 'I don't like to use it' in a non-specific way. They may rate the severity as 9/10. Discussion and exploration of the issue may elicit that they fear having a panic attack in a setting like public transport where they cannot escape. Defining the issue may itself reduce the self-rating of severity as the known is often less fearful than the unknown. Working at panic control may further reduce anxiety as escape becomes unnecessary.

Table 2

Suggested approach for cognitive behaviour therapy: second appointment

- reappraise the patient and any changes and additions to their story
- continue education about the illness, and the therapeutic process
- continue hyperventilation control and relaxation techniques
- work with the patient on their hierarchy – delineate specific problems, how the patient perceives these problems and their severity
- set initial exposure tasks
- encourage positive self-statements to settle anxieties
- reassure that CBT management skills take time, but can help
- rate the severity of symptoms on the patient's charts
- address any medication issues

Third and subsequent appointments (Table 3)

The charts help both doctor and patients see what progress has been made by the third visit. Depending on the patient's progress new tasks can be set.

Subsequent appointments involve reviews and reinforcements. If medication has been prescribed the duration of treatment should be adequate, for example 6–12 months for depression. Remember that benzodiazepines may impede CBT and raise issues of tolerance, dependence and discontinuation. Changes are normally effected over about twelve or so appointments. Some patients can achieve change more quickly, while others take much longer.

End of therapy

Once the patient's symptoms are under reasonable control without disability, or the ongoing disability is minimised as much as is practical, the initial period of CBT can cease.

The patient should be encouraged to maintain their CBT activities, skills and behaviours to help sustain their improvement. Review and booster sessions can be scheduled at three, six and twelve months, or as appropriate, after the initial treatment course. Medicines should also be continued as long as is normally indicated for relapse prevention. CBT can be especially effective in reducing the occurrence, severity and disability of relapses that may otherwise occur after stopping pharmacotherapy.

How to respond to relapses

The patient should be encouraged to contact you if there is any appreciable relapse. Early intervention for a relapse can result in rapid recovery, whereas a prolonged period of relapse can necessitate an extended repetition of therapy. Any severe return of symptoms should prompt the patient to contact their doctor for further treatment, as should a lesser return of symptoms if there is persisting or recurring disability which lasts, for example, more than four days.

Conclusion

CBT is a useful, effective, practical and economic treatment for use by doctors in all areas of medicine. It is progressive

Table 3

Suggested approach for cognitive behaviour therapy: third and subsequent appointments

Third appointment

- reinforce relaxation and hyperventilation control
- review the patient's hierarchy and set further tasks to evaluate and work on
- work with the patient to develop and practise more adaptive thinking and behavioural patterns
- encourage progress and help over difficulties
- rate the severity of symptoms on the patient's personalised schedule
- revise targets as progress occurs

Subsequent appointments

- review and reinforce progress
- ensure adequate medication, if medicine is indicated
- involve spouse, partner, or other family member if that may help
- set further tasks if prior tasks have been dealt with adequately
- plan coping strategies that can be implemented during these additional tasks
- rate improvements
- repeat this process over subsequent sessions until there is reasonable symptom improvement
- discuss relapse prevention

treatment over time, which can be effected in a series of relatively brief appointments. The patient does the majority of the work in their own time. The doctor's role is to help delineate the problem, identify the targets for intervention, then assist the patient in successful mastery of these targets.

The doctor also has an important role in advising and prescribing relevant concurrent pharmacotherapy, if necessary. In particular, it is important that the doctor is aware of those medicines that may assist the therapeutic process and those that may impede CBT. It should be regarded as a mainstream treatment that can be usefully applied by all doctors in the evaluation and the treatment of their patients.

NOTE

Examples of problem charts and self-monitoring charts can be printed for use. Click here.

ACKNOWLEDGEMENT

The author wishes to acknowledge the assistance of Dr M Kyrios in reviewing and commenting on this paper.

FURTHER READING

Andrews G, Crino R, Hunt C, Lampe L, Page A. The treatment of anxiety disorders. Cambridge: Cambridge University Press; 1996.

Hawton K, Salkovskis PM, Kirk J, Clark DM. Cognitive behaviour therapy for psychiatric problems: a practical guide. Oxford: Oxford University Press; 1989.

Bourne EJ. The anxiety and phobia workbook. 2nd ed. Oakland (CA): New Harbinger Publications Inc.; 1995.

Corsini RJ, Wedding D, McMahon JW. Current psychotherapies. 4th ed. Itasca (IL): F. E. Peacock Publishers; 1989.

Greenberger D, Padesky CA. Mind over mood: change how you feel by changing the way you think. New York (NY): The Guilford Press; 1995.

Self-test questions

The following statements are either true or false (answers on page 47)

1. Cognitive behaviour therapy eliminates the need for drugs for anxiety disorders.
2. Cognitive behaviour therapy treatment is only for use by clinical psychologists, not medical practitioners.

DIAGNOSTIC TESTS

Gluten enteropathy

Warwick Selby, Senior Visiting Gastroenterologist, Royal Prince Alfred Hospital, and Clinical Associate Professor, Department of Medicine, University of Sydney, Sydney

SYNOPSIS

The presentation of coeliac disease is changing, and typical malabsorption is now uncommon. Patients are more likely to present with non-specific symptoms or with iron and/or folate deficiency. The diagnosis still depends upon finding villous atrophy in the small intestine by endoscopic biopsy of the distal duodenum. The mucosal changes should improve after the patient has followed a gluten-free diet for at least six months.

IgA antibodies to gliadin, endomysium and/or tissue transglutaminase are detectable in most untreated patients. Antibody testing should not be used alone to make the diagnosis, because of the possibility of false positive results. This testing is used in patients where the clinical index of suspicion is low, in those with one of the disorders associated with coeliac disease or for screening relatives. Everyone with detectable antibodies requires a small bowel biopsy. Patients in whom the clinical index of suspicion of the disease is high should undergo biopsy regardless of the results of antibody testing. There is no place for an empirical trial of a gluten-free diet if coeliac disease is suspected.

Index words: coeliac disease.

(Aust Prescr 2001;24:38–40)

Introduction

Gluten enteropathy, or coeliac disease, results from an abnormal immune response to gliadin, a component of dietary gluten, found in wheat, barley, rye and possibly oats. This causes villous atrophy of the small bowel mucosa, which in turn leads to malabsorption and a predisposition to gastrointestinal malignancy, particularly carcinoma of the oropharynx and oesophagus, and small bowel lymphoma. The disease may present in either children or adults, but it is uncommon in adolescence and its manifestations may disappear at this age.

Coeliac disease is largely a disorder of Caucasians. In Australia it affects approximately 1 in 2000 people. Subclinical, or 'silent', coeliac disease, detected by antibody screening, may be up to ten times more frequent.

Pathogenesis

Patients with coeliac disease typically have the HLA-B8, DR3, DQ2 or DQ8 haplotype. This genetic background explains the occurrence of coeliac disease in 10% of first-degree relatives, 30% of HLA-identical siblings and 70% of monozygotic twins. However, approximately 20% of the general population have the same HLA alleles but do not develop coeliac disease.

When gliadin enters the small bowel mucosa, it undergoes enzymatic deamidation by tissue transglutaminase (tTG), an extracellular enzyme found in the connective tissue of the small bowel. In susceptible people, the gliadin-tTG complex becomes antigenic, producing a local immune response. This leads to the characteristic villous atrophy of coeliac disease. As part of this immune reaction antibodies to tTG are produced and are recognised as endomysial antibodies.

Clinical features

The classic presentation of a patient with abdominal distension, steatorrhoea, weight loss, bruising and other obvious features of malabsorption is now uncommon. Adults are more likely to seek help for milder, non-specific symptoms such as diarrhoea, flatulence and bloating, or fatigue.[1] Isolated iron and/or folate deficiency anaemia are also common forms of presentation.[2]

The clinical features have also changed in children. Coeliac disease should be suspected in children with growth or pubertal failure, recurrent abdominal pain, iron and/or folate deficiency or malaise. It can also lead to irritability and poor school performance.

Coeliac disease can also present with non-gastrointestinal problems. Apart from anaemia, it can cause recurrent mouth ulcers and, in women, delayed menarche, infertility or repeated miscarriage. Most adults with coeliac disease will have significant osteopaenia at the time of presentation. Conversely, approximately 5% of adults diagnosed with osteoporosis will be found to have underlying coeliac disease as the cause.

A number of other disorders are associated with underlying coeliac disease (Table 1).[3] At least 75% of patients with dermatitis herpetiformis have the typical villous atrophy on small bowel biopsy. Most of the others have more subtle mucosal changes. Coeliac disease is significantly more common in patients with type 1 diabetes, autoimmune thyroid disease, IgA deficiency and Down's syndrome. More unusual associations are with hyposplenism, and cryptogenic neurological illness, in particular epilepsy and ataxia (leading to the term 'gluten ataxia').

Diagnostic tests (Table 2)

The most important factor for the early diagnosis of coeliac disease is a high index of suspicion, keeping in mind the variable clinical features and known associated disorders.

Table 1

Disorders associated with coeliac disease

Dermatitis herpetiformis
IgA deficiency
Hyposplenism
Type 1 diabetes mellitus
Autoimmune thyroiditis
Atrophic gastritis
Down's syndrome
Epilepsy
Ataxia
Peripheral neuropathy
Autoimmune liver disease
Primary biliary cirrhosis
Alopecia areata

Histology

The definitive diagnosis in adults and children is the finding of villous atrophy in a biopsy of the small bowel mucosa. Nowadays, biopsies are generally taken from the distal duodenum during upper gastrointestinal endoscopy. At least three, and preferably more, samples should be taken because of the patchiness of the changes seen in some patients. Characteristic changes include flattening or loss of villi, hyperplasia of mucosal crypts and increased numbers of lymphocytes in the epithelium.

If coeliac disease is a possibility, duodenal biopsies should be taken in patients undergoing endoscopy for unexplained iron deficiency anaemia.

Antibody testing

Serological testing can aid in the diagnosis of coeliac disease. However, it is less sensitive and specific than small bowel biopsy and cannot be relied on alone to make the diagnosis. The role of serological testing is in screening relatives and selecting which patients to biopsy when the clinical suspicion is low, for example patients with irritable bowel syndrome, chronic fatigue syndrome, or one of the disorders associated with coeliac disease. If the clinical suspicion of coeliac disease is high, for example in patients with malabsorption or iron deficiency, then biopsy should be done in all cases so antibody testing is unnecessary for diagnosis. All patients with dermatitis herpetiformis should also have a small bowel biopsy.

The two most commonly used investigations test for antigliadin antibody (AGA) and endomysial antibody (EMA). These are IgA antibodies. Testing for IgG antibodies is of little value since the sensitivity and specificity are only approximately 50%. More specific tests for antibody to tTG have also been developed and are likely to replace the other tests when they become more widely available.[4]

Over 90% of patients with coeliac disease will have detectable IgA AGA before diagnosis, while on a normal diet. Conversely, 80–90% of people with IgA AGA will have coeliac disease; the other 10–20% have a false positive result and a normal small bowel biopsy. Some will have other gastrointestinal disorders, such as Crohn's disease.

Endomysial and tTG antibodies have the greatest sensitivity and specificity for coeliac disease. IgA EMA is found in 95–100% of patients. False positives are much less common than with IgA AGA, being found in only 1% of subjects tested. EMA is detected by means of immunohistochemistry, using tissues which contain large amounts of tTG.

Tissue transglutaminase is now recognised as the antigen of endomysial antibody. Direct measurement of antibody to tTG can now be done by immunoassay without the need for animal tissue. As expected, the sensitivity and specificity of anti-tTG are the same as those of EMA.

Three to five percent of patients with coeliac disease have IgA deficiency. In these patients the IgA antibody tests will be negative. The total serum IgA concentration should therefore also be measured at the same time as antibody tests.

The need for biopsy

Antibody testing alone is still not recommended for the diagnosis of coeliac disease even though the combination of IgA AGA and EMA/tTG antibody will detect most patients. This is because at least 1 in 100 subjects with detectable antibody will be committed to a strict lifelong gluten-free diet without having the disorder. Moreover, if a patient starts a gluten-free diet without having a biopsy the diagnosis may subsequently be very difficult to confirm if there is any doubt. Finally, biopsy confirms the diagnosis for each patient and

Table 2

Diagnostic tests for coeliac disease

Test	*Indication*	*Comment*
Small bowel biopsy	• Essential for diagnosis in all patients	• Repeat biopsy after at least six months on gluten-free diet
Antibody testing	• Low index of suspicion • Associated disorder • Screening relatives • Dietary compliance	• Antibody tests alone not sufficient for diagnosis • Endomysial and/or transglutaminase antibodies most sensitive and specific • IgA antigliadin antibody of less value • IgG antigliadin antibody not specific for coeliac disease
Tests for malabsorption	• Raise suspicion of coeliac disease	• Not sufficient for diagnosis
HLA-phenotype	• No value in diagnosis	• Found in 20% of general population
Trial of gluten-free diet	• NO PLACE IN DIAGNOSIS OR TREATMENT	• Diet needs to be lifelong • Non-coeliac gluten intolerance

aids in ensuring the compliance that is required to avoid the nutritional consequences and the risk of malignancy.

Diagnosis by diet

There is absolutely no place for giving patients with suspected coeliac disease an empirical therapeutic trial of a gluten-free diet. Some people with a normal small bowel develop symptoms such as bloating and diarrhoea from the fermentation of wheat starch. This is referred to as non-coeliac gluten intolerance. They will improve after removal of gluten. Their symptoms recur if they are rechallenged but most are unwilling to do this if it is decided to rule out coeliac disease. The time to investigate someone for coeliac disease is at the time when the suspicion is first raised, and before prescribing a gluten-free diet.

Diagnosis of coeliac disease in children

The principles of diagnosis in children are the same as in adults. A general anaesthetic may be required for endoscopic biopsy. Children have a high frequency of transient IgA deficiency, meaning that IgA antibody tests are less reliable and measurement of total IgA is important. The serological and histological changes of coeliac disease might not occur until children have had gluten in their diet for at least two years. It is therefore important to ask about the amount and duration of gluten intake and whether this has been normal or restricted. Negative serological or other investigations done before two years of age should be repeated at a later time if coeliac disease is still suspected.

Confirmation of diagnosis

In children and adults the diagnosis of coeliac disease should be confirmed by a repeat small bowel biopsy after at least six months on a gluten-free diet. Symptom resolution alone is not a reliable guide to histological improvement. In the majority, the mucosa will have returned to normal. In some there may be persistent villous atrophy, although this is usually mild and improved compared with the pre-treatment appearance.

In the past, it was recommended that all children with coeliac disease undergo gluten challenge and biopsy as final confirmation of the diagnosis. However, recent guidelines recommend that this only be done in selected children where there is doubt about the initial diagnosis on clinical or histological grounds.[5]

Additional investigations

The determination of HLA phenotype is of little value in diagnosis or screening because of its frequency in the general population, despite the strong association of the HLA-B8, DR3, DQ2/DQ8 haplotype with coeliac disease.

Tests for nutritional deficiencies, such as iron, folate, calcium and vitamin D, may give a clue as to the possibility of malabsorption and the need for diagnostic testing but do not help in the diagnosis. They also give a guide to nutritional therapy. The same is true of measurement of bone mineral density. Specific tests for malabsorption, such as the d-xylose test, are no longer used.

Conclusion

Coeliac disease is more common than previously thought.[1] A high index of suspicion is important. Diagnosis still depends on the demonstration of villous atrophy on small bowel biopsy, with repeat biopsy after at least six months on a gluten-free diet. Antibody tests alone are not sufficient for diagnosis, but are useful in screening. All patients with detectable antibodies should undergo biopsy.

E-mail: warwicks@mail.med.usyd.edu.au

REFERENCES

1. Feighery C. Coeliac disease [review]. Br Med J 1999;319:236-9.
2. Barr GD, Grehan MJ. Coeliac disease [review]. Med J Aust 1998;169: 109-14.
3. Duggan JM. Recent developments in our understanding of adult coeliac disease [review]. Med J Aust 1997;166:312-5.
4. Sulkanen S, Halttunen T, Laurila K, Kolho KL, Korponay-Szabo IR, Sarnesto A, et al. Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. Gastroenterology 1998;115:1322-8.
5. Revised criteria for diagnosis of coeliac disease. Report of working group of European Society of Pediatric Gastroenterology and Nutrition [review]. Arch Dis Child 1990;65:909-11.

Self-test questions

The following statements are either true or false (answers on page 47)

3. Before children with suspected coeliac disease are subjected to endoscopy, they should be given a trial of a gluten-free diet.
4. Coeliac disease can be excluded if the patient has no IgG antigliadin antibodies.

Patient support organisations

The Coeliac Society of Australia

The Coeliac Society of Australia supports people who have been diagnosed with coeliac disease, and their families. It also supports sufferers of dermatitis herpetiformis and those medically diagnosed as requiring a gluten-free diet.

The State and Territory societies (see opposite) give advice and information about the gluten-free diet, ingredients and where to buy them, recipes and cooking, overseas travel, educational material, and research into coeliac disease. The Society works with food authorities and manufacturers to promote standards and labelling of food products.

Support groups have been set up throughout the States and Territories. Coeliac Awareness Week is held each year in March.

Contacts

Web site: www.coeliac.org.au

ACT and New South Wales

PO Box 703, Chatswood NSW 2057
Tel: (02) 9411 4100
Fax: (02) 9413 1296

Queensland

Level 1, Local Government House
25 Evelyn Street, Newstead QLD 4006
PO Box 2110, Fortitude Valley BC 4006
Tel: (07) 3854 0123
Fax: (07) 3854 0121
E-mail: coelqld@xenon.net

South Australia and Northern Territory

Unit 5, 88 Glynburn Road, Hectorville SA 5073
Tel: (08) 8365 1488
Fax: (08) 8365 1265

Tasmania

PO Box 159, Launceston TAS 7250
Tel: (03) 6427 2844
Fax: (03) 6427 3248

Victoria

11 Barlyn Road, Mt Waverley VIC 3149
PO Box 89, Holmesglen VIC 3148
Tel: (03) 9808 5566
Fax: (03) 9808 9922

Western Australia

Anzac Cottage, 38 Kalgoorlie Street
Mt Hawthorn WA 6016
PO Box 245, Mt Hawthorn WA 6016
Tel: (08) 9444 9200
Fax: (08) 9444 9255

Your questions to the PBAC

Bisphosphonates

A recent case highlighted the problems with authority prescriptions for bisphosphonates. A man with steroid-induced osteoporosis is at risk of fractures, but is unable to be prescribed bisphosphonates under the current conditions of the Pharmaceutical Benefits Scheme (PBS). In this case bone densitometry showed clearly that the patient had very low bone density.

The consultant has decided to use alendronate to improve this patient's prognosis. My question to the Pharmaceutical Benefits Advisory Committee is why is it necessary to wait until the patient inevitably cracks some bones before therapy can commence. A private prescription is quite expensive – about $90 for one month of treatment with alendronate 10 mg.

I was informed by the PBS Hotline that alendronate is not subsidised for male patients, however calcium/etidronate or calcitriol are available. Nevertheless the authority conditions for these drugs require the patient to have had a fracture.

It seems to me that on one hand the PBS is moving in the right direction in terms of preventative medicine. We now have few restrictions on COX-2 inhibitors which should reduce the gut ulceration caused by non-steroidal anti-inflammatory drugs. Yet we are not moving as fast with the bisphosphonates.

Phil Day

Pharmacist

Queen Elizabeth II Hospital

Brisbane

PBAC response:

Under current legislation, the PBAC can only recommend that a preparation be listed as a pharmaceutical benefit for those conditions in which use has been shown to be effective, safe and of reasonable cost-effectiveness. This ensures that the money the community spends in subsidising the PBS represents good value.

The subsidy of drugs used for the treatment of osteoporosis, such as alendronate sodium, disodium etidronate/calcium carbonate, calcitriol, and raloxifene, is limited to patients with osteoporosis who have experienced a fracture due to minimal trauma. This is because this is the only patient group in which cost-effectiveness has been demonstrated. To date, no manufacturer or other applicant has presented data to substantiate that these drugs are cost-effective in preventing osteoporotic fractures. Since the PBAC's decisions are evidence based, it cannot recommend a change to listing in the absence of the necessary supporting cost-effectiveness data.

Furthermore, the PBAC is aware of the importance of prevention of disease. It takes into account many factors in assessing the cost-effectiveness of a medication proposed for PBS listing. These include costs of hospitalisation or other medical treatments that may be required if the medication is not available, as well as less tangible factors such as patients' quality of life. If these preparations were to be listed for the primary prevention of fractures, the PBAC has decided (based on the evidence presented) that the benefits would be relatively small compared to the considerable cost of therapy.

Under the legislation on which the PBS is based, there is no provision for exceptions to be made to suit individual circumstances, even when the use of the drug may be beneficial, or where significant financial hardship is being incurred.

While I appreciate that this means the cost of alendronate will need to be borne as a private prescription, the Commonwealth Government has no control over the prices of non-PBS medicines.

APMA Code of Conduct

The Australian Pharmaceutical Manufacturers' Association Code of Conduct[1] provides guidelines for the ethical marketing and promotion of prescription pharmaceutical products in Australia. It complements the legal requirements of the Therapeutic Goods Regulations and the Therapeutic Goods Administration. The Code provides guidelines for promotional tools such as advertising, product starter packs (samples), mailings, gifts, trade displays, travel, sponsorship, entertainment, and the behaviour and training of medical representatives. It also covers relationships with health professionals, and most recently, information on the internet.

Compliance with the Code is a condition of APMA membership, and the Association's members represent more than 90% of pharmaceutical companies. The Code, established in 1960, is regularly revised.

The Code depends on a complaints process.[2] An independent Code of Conduct Committee considers complaints to determine whether a breach of the Code has occurred, and if so, the appropriate sanction that should be imposed. The most severe sanction is expulsion from the APMA, but this has never been used.[2] Pharmaceutical companies can appeal against the decision of the Committee.

The Committee comprises representatives from organisations such as the Therapeutic Goods Administration, Consumers' Health Forum, a patient support organisation – currently the Arthritis Foundation of Australia, the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, the Royal Australian College of General Practitioners and the Australian Medical Association.

Table 1

Breaches of the Code of Conduct July 1999 – June 2000

Company	*Breaches*	*Drug – brand name*	*Drug – generic name*	*Sanction imposed by Code of Conduct Committee*
Alcon	1	Betoptic S	betaxolol	Corrective letter to be sent to specialists
Boehringer Ingelheim	1	Persantin	dipyridamole	$5000 fine; withdrawal of promotional material
Bristol-Myers Squibb	4	Pravachol	pravastatin	$12500 fine for repeat of previous breach; withdrawal of material
		Serzone	nefazodone	$5000 fine
		Iscover	clopidogrel	Withdrawal of promotional material
Eli Lilly	1	Evista	raloxifene	Withdrawal of promotional material
Galderma	1	Loceryl	amorolfine	Withdrawal of promotional material
Glaxo Wellcome	2	Relenza	zanamivir	Withdrawal of advertising
		Pritor	telmisartan	Warning against future breach of Code; review of internal procedure
Merck Sharp & Dohme	4	Zocor	simvastatin	None
		Fosamax	alendronate	$5000 fine; withdrawal of advertising. Further $10 000 fine for repeat of previous breach
		Vioxx	rofecoxib	$10 000 fine
Mundipharma	1	Oxycontin	oxycodone	Material not to be used again
Novartis	1	Lamisil	terbinafine	Withdrawal of material
Novo Nordisk	2	Kliogest	norethisterone/ oestradiol	$5000 fine; material not to be used again
		Kliovance	norethisterone/ oestradiol	Cessation of activity; corrective letter to be sent to prescribers
Pfizer	2	Zoloft	sertraline	$10 000 fine; withdrawal of material. Further $25 000 fine (including $10 000 fine for repeat breach); withdrawal of material
Pfizer/Searle	1	Celebrex	celecoxib	$10 000 fine; withdrawal of promotional material
Pharmacia & Upjohn	2	Fragmin	dalteparin	Withdrawal of promotional material
		Caverject	alprostadil	Action to ensure use of correct font size in advertisements
Rhone-Poulenc Rorer	1	Clexane	enoxaparin	$15 000 fine; withdrawal of promotional material
Roche	1	Rocaltrol	calcitriol	$7500 fine; withdrawal of advertising
Sanofi-Synthelabo	1	Plavix	clopidogrel	Withdrawal of material
Searle	1	Lomotil	atropine/ diphenoxylate	Withdrawal of material; corrective advertisement placed
Wyeth	1	Premarin and Premia	conjugated oestrogens	Withdrawal of material

Breaches of the Code (Table 1)

In the interests of transparency, the Code includes a requirement for regular publication of Code breaches in medical journals. This information includes the names of companies who have had complaints brought against them, a summary of the complaints and sanctions imposed.

In 1999–2000 44 complaints were received. (Six of these were subsequently withdrawn, one was referred elsewhere and three were returned to the complainant.) Of the 34 complaints evaluated by the Committee, 28 were found to be in breach of the Code. There was a variety of problems dealt with by the Committee (see box).

Two complaints were found not to be breaches of the Code, but prompted the APMA to consider modifications to the Code:

- a complaint about using a telemarketing campaign to advise prescribers of a change in the availability of Losec
- a complaint about sending letters to patients encouraging them to lobby their Members of Parliament to support the listing of Aricept on the Pharmaceutical Benefits Scheme.

Examples of Code breaches

Oxycontin

Statements in the promotional material overstated the attributes of oxycontin and promised more than the product could reasonably be expected to deliver. One statement was probably misleading because it implied that oxycontin is first-line therapy (contrary to the approved indications). Statements used in an unqualified manner may have encouraged excess usage of oxycontin and were therefore inappropriate and misleading.

Kliovance

Healthcare professionals were invited to participate in a project that was not clearly identified as market research. Offering payment for their participation in a Product Familiarisation Programme and giving them a three month free supply of Kliovance was not permitted under the Code.

REFERENCES

1. Australian Pharmaceutical Manufacturers Association. Code of Conduct of the Australian Pharmaceutical Manufacturers Association. 13th ed. Sydney: Australian Pharmaceutical Manufacturers Association Inc.; 2000.
2. Roughead EE. The Australian Pharmaceutical Manufacturers Association Code of Conduct: guiding the promotion of prescription medicines. Aust Prescr 1999;22:78-80.

NOTE

The APMA Code of Conduct is available from:

Australian Pharmaceutical Manufacturers Association
Level 7, 88 Walker Street
North Sydney NSW 2060
Tel: (02) 9922 2699
Fax: (02) 9959 4860
http://www.apma.com.au

New drugs

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

Brinzolamide

Azopt (Alcon)

10 mg/mL in 5 mL dispensers

Approved indication: raised intraocular pressure

Australian Medicines Handbook Section 11.2.7

Conditions such as open-angle glaucoma cause increases in intraocular pressure which can result in blindness. The intraocular pressure can be reduced by drugs which decrease the production, or increase the outflow, of aqueous humour. Carbonic anhydrase inhibitors reduce the production of aqueous humour and can be given topically. Dorzolamide was the first topical member of the class to be approved in Australia.

Brinzolamide is structurally similar to dorzolamide. It has a high affinity for carbonic anhydrase-II, the predominant form of the enzyme in the eye. After brinzolamide is instilled into the eye, some drug is absorbed into the circulation. It is mainly distributed to the red blood cells. As the half-life of brinzolamide in whole blood is 111 days, it takes 6–9 months for the drug concentrations to reach a steady state. These concentrations are not great enough to interfere with the normal functions of carbonic anhydrase in the body.

During short-term clinical trials a twice-daily dose of brinzolamide 1% has reduced intraocular pressure by approximately 3–5 mmHg. In an 18-month study the mean reductions in intraocular pressure were 2.7–3.9 mmHg with brinzolamide and 4.7–5.6 mmHg with timolol 0.5% (a topical beta blocker).[1] Another study compared brinzolamide 1% with dorzolamide 2%, and timolol 0.5% for three months. All three drugs had similar effects on intraocular pressure and there were no significant differences in the efficacy of the two carbonic anhydrase inhibitors.[2] Adding brinzolamide to treatment with timolol can produce further reductions in intraocular pressure.

Most of the adverse effects of brinzolamide are related to the instillation of the drops. Patients may develop blurring of vision, and sore or painful eyes. They may also complain of a bitter taste.

Although brinzolamide has been used as monotherapy, the carbonic anhydrase inhibitors are second-line drugs. A three-times daily dose was used in some clinical trials, but 76% of patients will respond adequately to a twice-daily dose of brinzolamide.[2] This may give the drug an advantage over dorzolamide which is instilled three times a day. Another

advantage is that brinzolamide instillation causes significantly less discomfort.[2]

REFERENCES

1. Brinzolamide Long-Term Therapy Study Group. The long-term safety and efficacy of brinzolamide 1.0% (Azopt) in patients with primary open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2000;129: 136-43.
2. Brinzolamide Primary Therapy Study Group. Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. Am J Ophthalmol 1998;126:400-8.

Etonogestrel

Implanon (Organon)

68 mg implants

Approved indication: contraception

Australian Medicines Handbook Section 17.1.4

The approval of etonogestrel implants adds to the choice of progestogen-only methods of contraception. Etonogestrel is a metabolite of desogestrel which is used in some combined contraceptive pills.

The implant is 40 mm long and has a diameter of 2 mm. It is loaded inside a stainless steel applicator. After anaesthetising the area, the implant is inserted under the skin of the inner side of the upper arm. The inserting is done in the first five days of the menstrual cycle if the woman is not using the contraceptive pill. Women changing from a progestogen-only pill can have the implant at any stage of the cycle.

While etonogestrel does affect the cervical mucus, its main contraceptive effect is the inhibition of ovulation. Inhibitory concentrations of etonogestrel are reached within one day of insertion. One implant will release these concentrations of etonogestrel for at least two years. It should be removed after three years. The effect of etonogestrel quickly wears off after the implant is removed. This may be useful when managing adverse effects.

In clinical trials no pregnancies have occurred. The main problems have been the adverse effects associated with progestogens. The menstrual pattern is likely to change, some women will have irregular bleeding, others will have amenorrhoea. These changes often prompt women to ask for the implant to be removed. Other adverse effects include breast pain, acne and weight gain.

Prescribers who intend to offer etonogestrel as a contraceptive option should ensure they are instructed in how to insert and remove the implant.

Infliximab

Remicade (Schering-Plough)

vials containing 100 mg as lyophilised powder

Approved indication: Crohn's disease

Australian Medicines Handbook Section 14.1.4

Crohn's disease causes chronic inflammation in the gastrointestinal tract. With time it tends to respond less well to treatment and many patients will develop complications such as a fistula. The cause of the disease is unknown, but an immune mechanism may be involved. Patients with Crohn's disease produce increased amounts of tumour necrosis factor alpha (TNF-alpha). This factor may be responsible for inducing the mucosal inflammation.

Animal studies found that inflammation can be reduced by antibodies to TNF-alpha. Infliximab is a monoclonal antibody which neutralises TNF-alpha in humans. It was studied in a randomised controlled trial of 108 patients with moderate to severe Crohn's disease. Four weeks after a single infusion, 65% of the patients given infliximab had a clinical response compared with only 17% of the patients given a placebo. The disease went into remission in 33% of the infliximab group but only 4% of the placebo group.[1]

Another study investigated 94 patients with abdominal or perianal fistulas. These patients were given an infusion of infliximab or a placebo. This infusion was repeated two weeks and six weeks later. The number of draining fistulas decreased by half in 62% of the infliximab group compared with 26% of the placebo group. In 46% of the infliximab group the fistulas healed, while only 13% of the placebo group had an absence of any draining fistulas.[2]

Infliximab is a human form of a mouse monoclonal antibody produced using recombinant techniques. Approximately 16% of patients will have a reaction to its infusion. They may develop urticaria, fevers and chills. Some patients experience falls or rises in blood pressure so it is important that they are observed during and after the two hour infusion. Patients who develop antichimeric antibodies are more likely to have infusion reactions. These antibodies could also alter the pharmacokinetics of infliximab. The half-life of infliximab is normally about 10 days and it takes up to six months for serum concentrations to become undetectable.

Approximately 5% of patients withdrew from clinical trials of infliximab because of adverse events. Apart from infusion reactions adverse effects include headache, nausea, vomiting and abdominal pain. The patients given infliximab developed more infections than patients given a placebo. Although infliximab does not cause a generalised suppression of the immune system, caution is needed particularly if the patient has been taking immunosuppressive drugs for their Crohn's disease. It is unclear if infliximab increases the risks of developing lymphoproliferative disorders. Some patients will develop autoantibodies and cases of a lupus-like syndrome have been reported.

More information is needed on the long-term effectiveness of infliximab. In the short-term study the proportion of patients with a clinical response after 12 weeks had declined and the number of patients in remission was not significantly different from placebo.[1] If symptoms recur the treatment can be repeated within 14 weeks. Readministration after this period is currently not recommended because of the risk of delayed hypersensitivity reactions.

Recombinant products tend to be expensive. Infliximab is therefore reserved for patients who have not responded to conventional therapies for moderate to severe Crohn's disease.

REFERENCES

1. Crohn's disease cA2 Study Group. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. N Engl J Med 1997;337:1029-35.
2. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398-405.

Oseltamivir phosphate

Tamiflu (Roche)

75 mg capsules

Approved indication: influenza

Australian Medicines Handbook Section 5.3.2

Oseltamivir is the second neuraminidase inhibitor to receive Australian approval for the treatment of influenza. Unlike its predecessor, zanamivir, oseltamivir is taken by mouth.

After absorption oseltamivir is converted to its active form, oseltamivir carboxylate. The plasma concentrations of this metabolite reach a peak within three hours and then decline with a half-life of 6–10 hours. Oseltamivir carboxylate is excreted in the urine, so the dose should be reduced if renal function is impaired.

In a clinical trial, twice-daily doses of 75 mg or 150 mg were compared with a placebo. The 629 adults involved in the trial had presented within 36 hours of developing a febrile respiratory illness. Laboratory testing confirmed the presence of influenza virus (mostly influenza A) in 374 cases. In these cases oseltamivir reduced the duration of illness by more than 30%.[1]

Patients given oseltamivir are more likely to experience gastrointestinal upsets than those given a placebo. In clinical trials 12% of patients suffered vomiting and a further 11% complained of nausea. There is potential for the influenza virus to develop resistance.

Although patients treated with oseltamivir recover significantly faster than those given a placebo, the difference is only about one day. Treating 1000 patients reduces illness by 254 hours. However, patients given 75 mg twice a day were able to resume their normal activities 2–3 days sooner than those given a placebo. Giving a higher dose does not make patients recover more quickly.[1] As few elderly or debilitated people were included in the clinical trials, the best strategy for those at risk is still immunisation to prevent influenza. Little information is available about the efficacy of oseltamivir in influenza B.

REFERENCE

1. Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza. JAMA 2000;283:1016-24.

Rabeprazole

Pariet (Janssen-Cilag)

10 mg and 20 mg enteric-coated tablets

Approved indications: peptic ulcer, gastro-oesophageal reflux disease

Australian Medicines Handbook Section 12.1.4

Rabeprazole is the fourth proton pump inhibitor to be approved in Australia. The other members of the class are omeprazole, lansoprazole and pantoprazole. These drugs are potent inhibitors of acid secretion.[1]

The suppression of acid secretion begins within an hour of taking rabeprazole and lasts for up to 48 hours. This duration of action is much greater than the one hour half-life. The drug is metabolised by the cytochrome P450 system (CYP3A4 and CYP2C19) with most of the metabolites appearing in the urine.

Rabeprazole has been compared with omeprazole for each of its approved indications. Although many patients with duodenal ulcer will require treatment for *Helicobacter pylori*, the proton pump inhibitors can also be effective. After four weeks of treatment rabeprazole and omeprazole had healed more than 90% of the patients. Similar results were found after treating patients with gastric ulcers for six weeks, and patients with erosive or ulcerative gastro-oesophageal reflux disease for eight weeks. If patients with gastro-oesophageal reflux take rabeprazole or omeprazole for a year only about 5% will have a relapse.

Like other proton pump inhibitors rabeprazole is well tolerated. The commonest complaints in clinical trials included diarrhoea, headache and nausea. There have been reports of erythema and bullous skin reactions.

The product information states that rabeprazole does not have clinically significant interactions with other drugs metabolised by cytochrome P450. Rabeprazole does, however, interact with digoxin and ketoconazole.

Although rabeprazole may reduce the pain of peptic ulcer more than omeprazole, it has no clear advantage. The cost of rabeprazole may determine if it is widely prescribed.

REFERENCE

1. Yeomans ND. Drugs that inhibit acid secretion. Aust Prescr 2000;23:57-9.

Tenecteplase

Metalyse (Boehringer Ingelheim)

vials containing 8000 IU and 10 000 IU

Approved indication: thrombolysis

Australian Medicines Handbook Section 7.3

For more than a decade, patients with acute myocardial infarctions have been treated with infusions of thrombolytic drugs such streptokinase. The aim of treatment is to restore the blood flow through the coronary artery related to the infarct. Research has aimed at developing drugs which restore more blood flow and do not require a prolonged infusion.

Alteplase is a genetically engineered plasminogen activator. (The activation of plasminogen produces plasmin which breaks down the fibrin in the thrombosis.) Tenecteplase has a similar structure to alteplase and is also produced by genetic engineering. The differences in structure give tenecteplase better fibrin specificity and a longer half-life than alteplase.

Tenecteplase can be given by a single bolus injection. This will improve the blood flow through the infarct-related artery in most patients within 90 minutes. The elimination is biphasic

with a terminal half-life of approximately two hours. Clearance is by hepatic metabolism.

A large study involving nearly 17 000 patients has compared a bolus of tenecteplase with a 90 minute infusion of alteplase. All the patients were meant to be treated within six hours of developing the symptoms of acute myocardial infarction. They were also given aspirin and heparin. After 30 days a similar proportion of each treatment group had died. The mortality rate for tenecteplase was 6.18% and it was 6.15% for alteplase.[1]

Fibrinolytic drugs increase the risk of stroke. In the comparative trial 1.78% of the patients given tenecteplase had a stroke compared with 1.66% of the alteplase group. While the frequency of intracranial bleeding was the same for both drugs, tenecteplase caused significantly fewer non-cerebral haemorrhages. Only 4.3% of the tenecteplase group needed a blood transfusion compared with 5.5% of the alteplase group.[1]

Despite the reduced need for transfusion, haemorrhage is still a common complication. More than 26% of the tenecteplase group had a bleeding complication. Tenecteplase is contraindicated in patients with an increased risk of bleeding. This includes patients with severe hypertension, peptic ulcers within the last three months, those who are taking warfarin and those who have had recent surgery or trauma, including cardiac resuscitation.

Although most patients in the clinical trial were treated soon after their infarction, tenecteplase has been approved for use up to 12 hours later. This matches the indication for alteplase. While tenecteplase seems to have a few advantages over alteplase, its relative cost-effectiveness will determine if it becomes the preferred treatment option.

REFERENCE

1. ASSENT-2 investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet 1999;354:716-22.

NEW DELIVERY SYSTEMS

Levonorgestrel

Mirena (Schering)

intrauterine device containing 52 mg levonorgestrel

Approved indications: contraception, menorrhagia, hormone replacement therapy

Australian Medicines Handbook Section 17.1.2

This product is a T-shaped intrauterine device with a cylinder of levonorgestrel around the long arm. The levonorgestrel is covered by a membrane which controls the release of the drug. At first the release rate is 20 microgram per day. The device contains enough levonorgestrel to last for five years.

The actions of levonorgestrel in the uterine cavity have a contraceptive effect (see 'Progestogen-only methods of contraception' Aust Prescr 1999;22:6–8). Contraceptive protection is immediate because the product also acts as an intrauterine contraceptive device. The contraception is highly effective with a pregnancy rate of 0.16 per 100 women years, however 37% of these pregnancies are ectopic.

If there are no organic causes, the device can be used to treat menorrhagia. For some women it is preferable to hysterectomy.[1] The device's ability to prevent endometrial hyperplasia also enables it to be used to provide the progestogenic component in regimens of continuous hormone replacement therapy.

Some of the levonorgestrel is absorbed into the circulation and may inhibit ovulation. While there are other general effects such as acne, breast tenderness and weight changes, most adverse reactions affect the urogenital system. The menstrual pattern changes with spotting being a particular problem in the first few months after insertion. Increased bleeding or pain may be symptoms that the device is being expelled. The expulsion rate over five years is 2–6 per 100. Without the device in place, fertility soon returns. Conception occurs within a year in 80% of the women who have the device removed in order to become pregnant.

Pelvic infection may occur less frequently than with other intrauterine devices, but pelvic inflammatory disease is still a contraindication. The device should be removed if a pelvic infection does not rapidly respond to antibiotics.

While a levonorgestrel-releasing device may have some advantages it is not suitable for all women. It should not be the first choice for contraception in young nulliparous women. The device may also be unsuitable for postmenopausal women if atrophic changes have narrowed the cervical canal.

REFERENCE

1. Lahteenmaki P, Haukkamaa M, Puolakka J, Riikonen U, Sainio S, Suvisaari J, et al. Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy. Br Med J 1998;316:1122-6.

NEW FORMULATIONS

Clostridium botulinum type A toxin-haemagglutinin complex

Dysport (Ipsen)

500 IPSEN Units lyophilised powder

(Dysport is not therapeutically equivalent to the other botulinum toxin preparation currently available on the Australian market.)

Flurbiprofen

Strepfen (Boots Healthcare)

8.75 mg lozenges

Oxycodone hydrochloride

OxyNorm (Mundipharma)

5 mg capsules

NEW STRENGTHS

Cerivastatin sodium

Lipobay (Bayer)

400 microgram tablets

Oestradiol

Climara 25 (Schering)

1.97 mg transdermal patches

Climara 75 (Schering)

5.69 mg transdermal patches

NEW PROPRIETARY BRANDS

Enalapril maleate

Alphapril (Alphapharm)

5 mg, 10 mg and 20 mg tablets

Lisinopril

Lisodur (Alphapharm)

5 mg, 10 mg and 20 mg tablets

Mometasone furoate

Allermax (Schering-Plough)

50 microgram per actuation aqueous nasal spray

Oestradiol valerate/cyproterone acetate

Climen 28 (Schering)

packs containing 16 oestradiol valerate 2 mg tablets and 12 oestradiol valerate 2mg/cyproterone acetate 1 mg tablets

Salbutamol

Epaq Inhaler (Arrow)

100 microgram per dose

Answers to self-test questions

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

Australian Prescriber mailing list

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

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

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

NAME: .....

ADDRESS: .....

.....

.....

.....

PROFESSION: .....

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

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

Tick ☑ whichever of the following apply:

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

☐ Place me on the mailing list

☐ Delete me from the mailing list

My reference number is .....

☐ Change my address

My reference number is .....

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

☐ Send me the following back issue/s

.....

Editorial office

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

Telephone: (02) 6289 7038

Facsimile: (02) 6289 8641

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

E-mail: info@australianprescriber.com

Web site: www.australianprescriber.com

Supporting the
NPS
National Prescribing Service

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

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

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

Published by the Commonwealth
Department of Health and Aged Care