Australian Prescriber
Volume 26
Number 1
2003

EDITORIAL

Informing the consumer

Sarah Fogg, Consumer consultant, member of Pharmaceutical Health and Rational use of Medicines Committee (PHARM)

Index words: medication, communication, Consumer Medicine Information.

(Aust Prescr 2003;26:2–3)

Good communication between medical practitioners and consumers, and between pharmacists and consumers, is vital if the best health outcomes are to be achieved through the use of medicines. The provision of information to consumers about their medication is an important part of that communication.

Consumers have different decision-making styles and interest in health information. However, virtually all want to be informed about and make decisions about their medicines, to some degree. Some take a passive approach and choose to 'let the doctor decide', while others wish to be much more active, to receive detailed information about their treatment options and to share in the decision-making.

Other factors may also influence how actively or passively involved consumers wish to be, for example, what stage they are at in the continuum of care. The amount of information consumers want at diagnosis may be quite different to what they want when coping with their condition over the long term.

The risks of not informing consumers about their medications are that they may not adhere to treatment – if, for example, they do not understand what the medicine is for, or do not know what effects to expect or the potential benefits and harms. Poorly informed consumers may also take the medicine incorrectly, they may fail to recognise problems that occur and will be ill-equipped to act appropriately if problems do arise.

Conversely, well informed consumers are more likely to adhere to treatments and have better health outcomes. Errors are more likely to be avoided if consumers are well informed. Informing consumers also encourages them to become more self-reliant and confident in the management of their medications.[1]

In 1993 the National Health and Medical Research Council (NHMRC) published guidelines[2] for health professionals on providing information to consumers. Since then a number of tools have become available to make providing information to consumers about their medication easier. Consumer Medicine Information (CMI) for prescription medicines is the most significant. The information helps the consumer to understand what the medication is for, its benefits, adverse effects and risks. CMI also contains practical information about dosage, administration and contraindications, which consumers can refer to if needed.

CMI also has the advantage of being standard for a particular medication, irrespective of whether the consumer receives it from their pharmacist, their doctor or as a package insert. Practitioners can therefore be sure about what information their patients will be receiving.

CMI has to remain consistent with the product information and so is updated when any changes occur to the product information. In practice, companies differ in how thoroughly they test CMI on consumers and as a result CMI does vary in quality.

CMI is now available for virtually all prescription medicines. However, its distribution to consumers is still far from widespread. Encouraging consumers to ask for the CMI when their medication is dispensed would help. This may be more practical than printing it out for consumers at the surgery, although it is certainly available through prescribing software.

Of course, CMI has its limitations and will never be the complete answer to people's information needs. A significant proportion of the population has some or great difficulty with the written information encountered in everyday life.[3] People also vary in the extent to which they prefer receiving information verbally, in written form or a combination of the two. However, it is a mistake to assume that, for example, just because a person's spoken English is not good, that they have no use for CMIs in English. Research suggests that many people would prefer receiving a CMI about their medication in English rather than not receiving one at all.[4] They may be able to read

In this issue...

Now that the furore about hormone replacement therapy (HRT) has settled, Alastair MacLennan suggests how this treatment should be used in future. Perhaps some of the overenthusiastic use of HRT was driven by marketing. Sometimes marketing can be overenthusiastic and Melissa Sweet reports on a case where health professionals may have been deliberately misled.

If health professionals have misleading information, it will not help them to inform consumers about their treatment as Sarah Fogg would like. Hilda Bastian reminds us that consumers view the risks of treatment in different ways.

Patients who are debilitated are at risk of aspiration pneumonia. One of the strategies Simon O'Connor suggests for reducing the risk of aspiration is good oral hygiene which, Barbara Anne Taylor tells us, will also benefit patients with drug-induced gingival enlargement.

it at their own pace at home or they may have family members who can read it for them.

An often-voiced concern about CMI is that the information about the risk of harm does not indicate how frequently harm actually occurs and, as a result, consumers may be too scared to take their medication. The newer and better CMIs include such information. A good technique is to encourage consumers to come back with any queries they may have after reading the CMI. This then opens up opportunities to address any fears and correct any misunderstandings which may have prevented them taking the medicine.

CMI also does not contain information about how much a drug will cost. Failure to talk about costs may result in consumers not getting a prescription dispensed. If cost concerns are discussed there is then an opportunity to talk about cheaper options or the consequences of not going ahead with the treatment.

To make informed decisions about treatment consumers need comparative information about the pros and cons of the various options. CMI can help in this discussion to an extent, although an individual CMI only provides information about one particular medicine. It is also important that doctors explain when prescribing outside an approved indication, that the indication will not appear on the CMI, but information about adverse effects and interactions will still be relevant.

The internet is increasingly being used as a source of health information. In the USA up to 75% of internet users have used it to obtain health information and 41% of Americans say that material they found affected decisions about whether they should go to the doctor, how to treat an illness or how to question a doctor.[5] Australia may not be that different.

Doctors are right to be concerned about the quality of information available to consumers via the internet. Consumers may have difficulty distinguishing between good and poor quality information and independent versus promotional material. Doctors can play a key role in guiding consumers to good and reliable web sites relevant to Australian consumers. The Federal Government's health web site HealthInsite (www.healthinsite.gov.au) is a good starting point for health information that conforms to standards of quality and independence and is written for a consumer audience. The *Australian Prescriber* web site (www.australianprescriber.com) also has brief information for consumers on the topics of the main articles.

A new telephone medicine information service for consumers has just been set up by the National Prescribing Service. Staffed by pharmacists, Medicines Line operates Monday to Friday 9 a.m. to 6 p.m. AEST and offers an avenue through which consumers can get free reliable accurate information about their medication if they are unable, or unwilling, to ask their doctor or pharmacist. The Medicines Line number is 1300 888 763.

E-mail: sfogg@dot.net.au

REFERENCES

1. Coulter A. After Bristol: putting patients at the centre. Br Med J 2002;324:648-51.
2. National Health and Medical Research Council. General guidelines for medical practitioners on providing information to patients. Canberra: Australian Government Publishing Service; 1993. Currently being revised by the NHMRC. http://www.health.gov.au/nhmrc/
3. Australian Bureau of Statistics. Aspects of literacy: assessed skill levels, Australia, 1996. Catalogue No. 4228.0. Canberra: Australian Bureau of Statistics; 1996.
4. Lawrence A, Fogg S. 'In our country all medications had an instruction leaflet'. Older people from diverse linguistic and cultural backgrounds talk about Consumer Medicine Information and the quality use of medicines. Canberra: Australian Pensioners' and Superannuants' Federation; 1998.
5. Fox S, Rainie L. The online health care revolution: how the Web helps Americans take better care of themselves. Washington DC: The Pew Internet and American Life Project; 2000. http://www.pewinternet.org/reports/toc.asp?Report=26

Conflict of interest: none declared

Letters

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

Can we afford intensive management of diabetes?

Editor, – The article 'Can we afford intensive management of diabetes?' (Aust Prescr 2002;25:102–3) presents an altogether different view of the management of diabetes. In developing countries the practicality of intensive control may be limited. The prevalence of type 2 diabetes mellitus is more than 11% in the urban population of India and is increasing.[1] In this context the interpretation of data from the United Kingdom Prospective Diabetes Study (UKPDS)[2] assumes great importance.

The authors correctly pointed out that six patients need to be treated intensively for blood pressure over 10 years to prevent one patient developing any complication.[3] However, the number needed to treat (NNT) to prevent one case of microvascular disease is **not** 196 patients treated for 10 years. From our calculations the NNT to prevent one microvascular complication is 42. The NNT is the reciprocal of absolute risk reduction, and the absolute risk reduction is the difference in the event rates between the control group (P_C) and the treatment group (P_T). In the UKPDS, the corresponding values for microvascular complications were 225 out of 2729 patients in the intensive treatment group (P_T = 225/2729 = 0.082) and 121 out of 1138 in the conventional treatment group (P_C = 121/1138 = 0.106). Absolute risk reduction ($P_C - P_T$) is therefore 0.024. This gives an NNT of 42 (1/0.024).

We agree that controlling blood pressure is more important for the prevention of complications, but the relative merits of intensive control of diabetes are greater than the article would make us believe. We also agree with the author that the UK results may not be generalisable to other countries, especially developing countries. The increased pressure on resources caused by an intensive approach would mean stretching the healthcare system to the limit and diverting resources away from other illnesses like infections and malnutrition that still remain number one killers in poor countries.

Samir Malhotra
Assistant Professor
P. Pandi
Professor and Head
Department of Pharmacology
Post Graduate Institute of Medical Education and Research
Chandigarh City
India

REFERENCES

1. Ramchandran A, Snehalatha C, Latha E, Vijay V, Viswanathan N. Rising prevalence of NIDDM in an urban population in India. Diabetologia 1997;40:232-7.
2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study. Lancet 1998;352:837-53.
3. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. Br Med J 1998;317:703-13.

Ms B. Pekarsky, one of the authors of the article, comments:

We thank the authors for pointing out our error in the calculations. With regard to the generalisability of our conclusions, we agree that they are less relevant to the Indian situation, except to the extent that it is essential that the opportunity cost of an intervention that requires more intensive use of general practitioners' time is considered in the decision-making processes.

Top 10 drugs

These tables show the top 10 subsidised drugs in 2001-02. The tables do not include private prescriptions.

Table 1

Top 10 drugs by defined daily dose/thousand population/day*

Drug	*PBS/RPBS* †
1. atorvastatin	65.605
2. simvastatin	45.282
3. salbutamol	26.634
4. omeprazole	25.376
5. frusemide	23.768
6. ramipril	23.691
7. celecoxib	22.255
8. rofecoxib	20.667
9. irbesartan	19.179
10. amlodipine besylate	18.132

Table 2

Top 10 drugs by prescription counts

Drug	*PBS/RPBS* †
1. atorvastatin	5,512,101
2. simvastatin	5,138,175
3. paracetamol	4,850,202
4. omeprazole	4,160,725
5. celecoxib	3,850,345
6. salbutamol	3,591,854
7. codeine with paracetamol	2,931,715
8. ranitidine hydrochloride	2,882,721
9. atenolol	2,827,368
10. irbesartan	2,716,788

Table 3

Top 10 drugs by cost to government

Drug	*PBS/RPBS* † *DDD/1000/day* *	*PBS/RPBS scripts*	*Cost to government ($A)*
1. atorvastatin	65.605	5,512,101	287,876,894
2. simvastatin	45.282	5,138,175	286,570,094
3. omeprazole	25.376	4,160,725	192,954,689
4. olanzapine	3.151	634,682	132,686,315
5. salmeterol and fluticasone	0	1,948,027	121,027,026
6. celecoxib	22.255	3,850,345	110,969,962
7. pravastatin	12.981	1,757,528	97,574,529
8. insulin (human)	11.876	431,219	79,363,981
9. rofecoxib	20.667	2,549,886	76,327,930
10. pantoprazole	9.586	1,796,286	75,681,935

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people, in every thousand Australians, are taking the standard dose of a drug every day.

† PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

Source: Drug Utilisation Sub-Committee (DUSC): Drug Utilisation Database © Commonwealth of Australia

Delivering inhaled asthma therapy

M.C.F. Pain, Consultant Thoracic Physician, Royal Melbourne Hospital, Melbourne

SYNOPSIS

There is a wide range of devices for delivering inhaled therapy. Metered dose inhalers are commonly used, but the introduction of formulations without chlorofluorocarbons will require practitioners to reassess their patients' therapy. Nebulisers, pressurised devices and dry powder preparations are all effective. The most important issue is to ensure patients use their devices correctly and adhere to their treatment plan. Recent meta-analyses show that nebulisers, although convenient in acute attacks, have no sustained advantage over pressurised devices with or without spacers.

Index words: inhalers, nebulisers, spacers, devices.

(Aust Prescr 2003;26:5–7)

Introduction

Inhaled medication is the commonest form of therapy for acute and chronic asthma and for other conditions associated with airflow limitation (obstructive bronchitis, emphysema, cystic fibrosis). There are over 50 separate listings of inhaled medications in the respiratory drugs section of the current Schedule of Pharmaceutical Benefits (Table 1). The choice of inhalational device is as important as the choice of drug therapy.

Theoretical considerations

There is a strong logic in giving drugs which act on the bronchial tree by the inhaled route. The delivery is directly to the site of pathology and the large surface area available for absorption should lead to a rapid response. There is no need to obtain significant concentrations in the blood so the incidence or extent of unwanted adverse effects is reduced.

The fate of an inhaled medication within the respiratory tract is determined by complex physical factors. However, the most important relate to particle size and breathing patterns. Particles with a median mass diameter greater than 10 microns tend to be deposited in the upper respiratory tract and those smaller than 0.5 microns behave as gases and are exhaled. Deposition within the lower respiratory tract increasingly occurs as the particle size decreases from 4 to 2 microns.

Nebulisers

A pump/nebuliser system has several attractions:

- administration does not require close supervision
- co-ordinated breathing manoeuvres are unnecessary
- combinations of drugs may be given simultaneously
- it is suitable at extremes of age
- the dose delivered, among other factors, is a function of time.

Currently available models are surprisingly efficient and have an average output of 1–2 mL over 10 minutes with about 30–50% of the output being as a respirable aerosol.

Weighed against these attractions are the considerable cost compared with simpler devices, the wastage of nebulised drug during exhalation and the fact that delivery of larger doses does not translate into better therapeutic responses. This is because there is a dose-response relationship which reaches a plateau so that delivering a larger dose via a nebuliser will produce no further bronchodilatation. A recent meta-analysis (16 trials, 375 adults, 686 children) concluded that metered dose inhalers with holding chambers (spacers) produced outcomes at least equivalent to nebuliser delivery.[1]

While the actual nebuliser unit is not expensive (about $18 retail), the driving source, which is usually a small compressor unit, costs between $180 and $480. It requires minimal maintenance and a good quality device should last 5–10 years. The economics of the nebulised solutions are relevant. Single dose units, although convenient, are nearly three times more expensive than the multidose preparations.

Nebulisation is still necessary for preparations which are not available in other devices (for example, pentamidine prophylaxis against *Pneumocystis carinii*, mucolytics and rhDNase in cystic fibrosis). Most international guidelines dealing with the treatment of acute asthma in adults recommend a place for a nebulised short-acting beta agonist, using oxygen as the driving gas.[2] However, the current tendency is to use a pump/nebuliser system only when there are valid reasons for doing so rather than as a first-line approach to inhalational therapy.

Ultrasonic nebulisers have little if any place in asthma therapy. They are expensive and deliver an efficient aerosol which, because of the very fine particle size, can lead to difficulties with dose retention.

Metered dose inhalers

Metered dose inhalers have been enthusiastically accepted and perform well when compared with all other forms of administration.[3] They are very convenient and provide accurate doses which can be readily adjusted by changing the number of actuations. Using an inhaler requires some level of understanding and a major problem with their use is inappropriate technique. It is always good practice to show the patient how to use an inhaler and subsequently check their technique. The important points are:

- timing of activation (at the commencement of inspiration from functional residual capacity)

- inspiratory flow rate (full lung inflation in about two seconds)
- breath-holding time at the end of inspiration (at least three seconds and preferably up to 10 seconds).[4]

Pressurised inhalers with hydrofluoroalkanes as the propellant (Table 1) have been developed to comply with the Montreal Protocol (to reduce and phase out the use of chlorofluorocarbons (CFCs)). By 2005, there will be no inhalers containing CFCs. Several products were withdrawn during 2002.

It is important to realise that the CFC-free inhalers produce a finer particle size and hence lead to a more effective lung deposition. This means that the actual dose required is less for the same brochodilator effect and the product information should be read carefully. In practice the 'numbers of inhalations' between CFC and non-CFC preparations are roughly equivalent.

Breath-activated pressurised inhalers

Clever technology has seen the development of devices in which the pressurised inhaler is triggered by the reduction in pressure associated with the onset of inspiration. This avoids difficulties some patients have in co-ordinating manual triggering with early inspiration. These devices are more expensive and thus have prescribing restrictions in the Pharmaceutical Benefits Scheme (PBS).

Dry powder inhalers

Devices delivering drugs in a dry powder are an alternative to propellant driven inhalers. Patients initially tend to distrust the performance of these devices since they do not produce a visible aerosol and there is no sensation of having inhaled the minute amount of powder delivered. These devices appear to be just as convenient and efficient as the pressurised inhalers and they are reassuring for patients concerned about the environment.

Combination therapy

In the past, combination therapy in a single commercial product was viewed with some disdain, as fixed dose ratios do not allow individual tailoring of doses. To some extent this criticism has been outweighed by the likelihood of better adherence to a regimen if the number of inhalers is reduced. Preparations including a long-acting beta agonist and inhaled corticosteroid have been readily accepted although the various dose combinations require some juggling and their prescription under the PBS remains restricted. Combination therapy is not satisfactory in the management of an acute exacerbation.

Spacers

There are several commercially available spacers and some are specifically constructed to attach only to a specific

Table 1

Inhaled preparations currently listed on the Pharmaceutical Benefits Scheme for asthma

Device	*Advantages*	*Disadvantages*	*Products available*
Nebulising solution	No co-ordination required Suitable at extremes of age	Initial cost Equipment maintenance Wasteful drug use	Salbutamol sulfate Terbutaline sulfate Ipratropium bromide Budesonide Sodium cromoglycate
Dry powder preparation	Convenient	No sensation of inhaling active drug	Salbutamol sulfate Salmeterol xinafoate Eformoterol fumarate Terbutaline sulfate Budesonide Fluticasone propionate Sodium cromoglycate Eformoterol/budesonide Salmeterol/fluticasone
Pressurised inhaler	Convenient	Being phased out Co-ordination required	Salmeterol xinafoate Ipratropium bromide Sodium cromoglycate Salbutamol/ipratropium*
Pressurised inhaler CFC-free	More uniform lung deposition	Co-ordination required Dose adjustment considerations	Salbutamol sulfate Beclomethasone dipropionate Fluticasone propionate Sodium cromoglycate Salmeterol/fluticasone Nedocromil sodium
Breath-triggered pressurised inhaler	No co-ordination required	More expensive	Ipratropium bromide
Breath-triggered pressurised inhaler CFC-free	No co-ordination required More uniform lung deposition	More expensive Dose adjustment considerations	Beclomethasone dipropionate Salbutamol sulfate

* Repatriation Pharmaceutical Benefits Scheme only

inhaler. They are somewhat bulky and therefore tend to be used at home.

Spacers fulfil two functions. First, they allow the larger particles within the aerosol generated by an inhaler to rain out within the chamber. The inhaled portion has a higher proportion of finer particles which should improve deposition within the lungs and reduce oral deposition. This reduces the incidence of oral thrush, however mouth gargling with clean water after inhalation is still important. Second, the larger chambers, with a one-way valve at the mouthpiece, can retain an aerosol in suspension while the patient inhales that suspension without the need for special co-ordination. Spacers can be used for single breath actuation, but an alternative is to deliver the total dose (e.g. two activations) into the spacer and inspire from the spacer over several breaths. This is a great advantage in very young patients, the elderly and the unco-ordinated. As the medication becomes attached to the walls of the chamber, spacers need cleaning about every two weeks using warm soapy water. They should be left to dry out naturally to avoid accumulation of static charge by towelling.

Conclusions

Factors to consider in choosing a device to deliver asthma therapy include the patient's age, level of understanding and co-operation, and extent of co-ordination. A trial period with a device will often reveal problems with compliance or individual preferences. The wide variety of devices and preparations does not alter the eternal truth that the most important aspect of inhalational therapy for chronic respiratory diseases is to establish and maintain correct usage and faithful adherence to an overall plan of management. The actual drug chosen within a particular class of medication is of secondary importance.

E-mail: michael.pain@mh.org.au

REFERENCES

1. Cates CJ, Rowe BH, Bara A. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma (Cochrane Review). In: The Cochrane Library, Issue 4, 2002. Oxford: Update Software.
2. Asthma Management Handbook. South Melbourne: National Asthma Council Australia Ltd.; 2002.
3. Ram FS, Wright J, Brocklebank D, White JE. Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering β_2 agonists bronchodilators in asthma. Br Med J 2001;323:901-5.
4. Farr SJ, Rowe AM, Rubsamen R, Taylor G. Aerosol deposition in the human lung following administration from a microprocessor-controlled pressurised metered dose inhaler. Thorax 1995;50:639-44.

Conflict of interest: none declared

Patient Support Organisation: Asthma Australia. See details on page 21.

Self-test questions

The following statements are either true or false (answers on page 23)

1. Spacers should not be dried with a towel.
2. Beta agonist bronchodilators are more effective when delivered by nebuliser than when they are given by a metered dose inhaler through a spacer.

Online reporting of adverse drug reactions

Australian Prescriber readers are now able to report adverse drug reactions directly to the Adverse Drug Reactions Advisory Committee (ADRAC). A new computer system will also allow readers to request information from the database of adverse reactions.

Health professionals who are likely to use the new service regularly can become 'registered reporters'. Those who just wish to report reactions occasionally can do so as 'unregistered reporters'.

To access the service, people can connect to the web site of the Therapeutic Goods Administration (www.health.gov.au/tga). They can then click on the 'Online Services' button and follow the links.

The Adverse Drug Reactions Advisory Committee is planning further electronic developments. From later this year it should be possible for general practitioners to submit reports of adverse reactions if they use prescribing software on their practice computers.

For health professionals who do not use computers, reports can still be mailed using the 'blue card'. Copies of the blue card are distributed with *Australian Prescriber* four times a year.

Hormone replacement therapy: where to now?

Alastair H. MacLennan, Professor of Obstetrics and Gynaecology, The University of Adelaide, Adelaide

SYNOPSIS

The Women's Health Initiative Study was stopped because of safety concerns about hormone replacement therapy with oestrogen and progestogen. There was an increase in breast cancer, however this was not greater than the increase reported in observational studies. Although there was an increase in vascular events, many of the women in the study had pre-existing risk factors for cardiovascular disease. No long-term trials of combined hormone replacement therapy are continuing, so the balance between benefit and harm will remain uncertain. Hormone replacement therapy can still be prescribed for menopausal symptoms and for osteoporosis prevention, but the need for continued use should be reviewed annually.

Index words: menopause, breast cancer, heart disease.

(Aust Prescr 2003;26:8–10)

Introduction

The premature cessation of one arm of the ongoing US Women's Health Initiative study (WHI) undoubtedly caused more media alarm than scientific alarm.[1] This study is very important, as it was one of only two studies of long-term hormone replacement therapy (HRT). Although the combined oestrogen and progestogen arm was stopped the dietary and oestrogen-only arms continue. The combined HRT arm was stopped because the predetermined stopping point (a small but statistically significant increase in detected breast cancer) was reached. In addition, there was an increase in stroke and thromboembolism, and a trend to an increase in heart disease (Fig. 1).

Although breast cancer increased (by 8 cases per 10 000 women years) there was no overall difference in cancer rates or mortality between the placebo and combined HRT groups. This was because HRT was associated with a reduction in bowel and uterine cancers. The results observed in the WHI study were of similar magnitude as those seen in the systematic reanalysis of observational studies[2] of women taking combined oestrogen and progestogen (Table 1). The early cessation of this arm of the study at 5.2 years prevents the assessment of later benefits and risks.

Cardiovascular disease

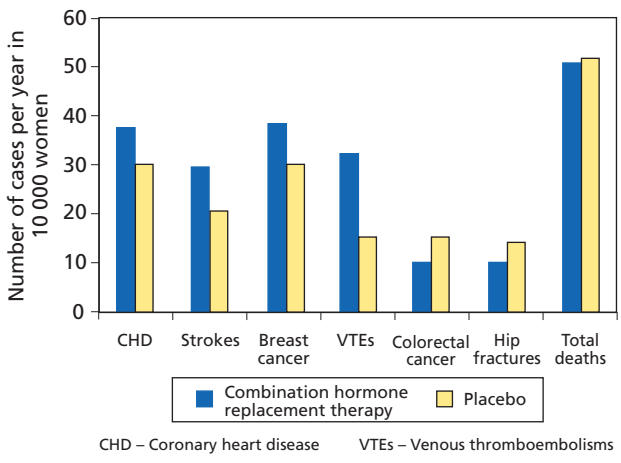
The reported results of WHI to date are little different from the published results of randomised trials looking at the secondary prevention of heart disease. Most women enrolled in the WHI study were overweight, 80% were between 60 and 79 years old, half had smoked and some had hypertension and increased concentrations of cholesterol. These cardiovascular risk factors suggest that many in the study could have had established atherosclerosis.

Recent studies suggest HRT may inhibit the process of atherosclerosis in healthy arteries soon after menopause [3], and observational studies in younger women starting HRT suggest a potential cardiovascular benefit.[4] However, HRT may have a deleterious effect by destabilising plaques in the atherosclerotic arteries of older women. Secondary prevention studies such as HERS [5] confirm an early increase in adverse cardiovascular events when HRT is first prescribed after a cardiac event.

To improve the power of the study for cardiac events the WHI enrolled many older women, with cardiovascular risk factors, up to the age of 79 years. To what extent the effect of combined HRT seen in the WHI population applies to women commencing HRT at perimenopause remains debatable. The cardiovascular results of WHI are going to remain controversial until healthier and younger postmenopausal women are studied in a long-term trial. When counselling older women one could show the results of WHI (Fig. 1). A summary of the statistically significant results of major outcomes (Fig. 2) may help simplify counselling in younger women around the menopause.

Fig. 1

Event rates in the Women's Health Initiative Study



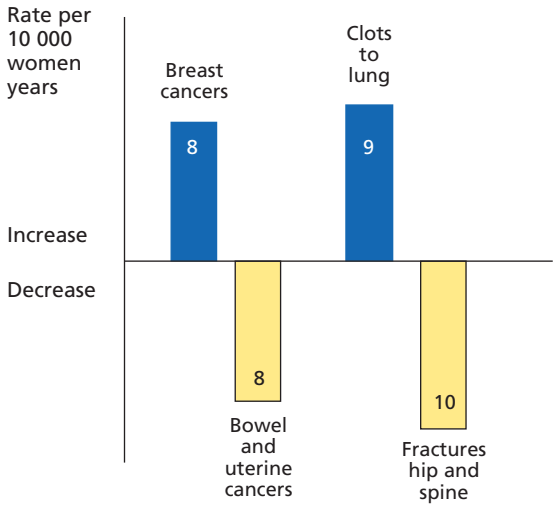
Adapted from US WHI Study, 2002 [1]

Unresolved issues

A long-term randomised trial can study only a few therapeutic regimens. Only conjugated equine oestrogens and medroxyprogesterone acetate were being tested in the long-term HRT trials, WHI and WISDOM (Women's International Study of long Duration Oestrogen after Menopause). No other HRT regimens are being tested. It is therefore impossible to know if HRT by non-oral routes, other oestrogens, other progestogens or other drugs such as tibolone have different effects. It would be wise to counsel that the outcomes for other combined HRT products may be similar to those reported by the WHI.

Fig. 2

Summary of significant risks and benefits after 5 years of HRT*



* Although increased stroke and heart attacks were seen in the US WHI population, this population had many pre-existing risk factors for these problems. The effect of HRT on the blood vessels of younger, healthier women around menopause requires further study.

Adapted from US WHI Study, 2002 [1]

To date, oestrogen-only HRT does not have the same risk profile as combined oestrogen and progestogen and the oestrogen-only arm of the WHI study continues. Most importantly the WHI study does not give the overall harm:benefit ratio for long-term HRT as many outcomes were not measured. These include quality of life, menopausal symptom control, cognitive function, dementia, urogenital health, arthritis, other cancers and the effects of HRT on other body parts, e.g. eyes, teeth, skin. All these outcomes and a better understanding of the effects of HRT on the cardiovascular system are still greatly needed. WISDOM (the UK, Australian and New Zealand 15-year trial of HRT) was looking at these outcomes, but the study has been discontinued.[6] It is unlikely that we shall ever have good evidence to assess the risks, benefits and costs of long-term HRT.

It is important to emphasise that short-term trials of HRT show clear evidence of benefit for menopausal symptoms, especially vasomotor symptoms. These studies also show adverse effects which include start-up bleeding, breast tenderness and the uncommon but early risk of thromboembolism. The risk of breast cancer does not significantly increase until after five years of first use of combined HRT. The most pessimistic increase in breast cancer in all studies to date is one extra-detected breast cancer per 100 women after 10 years of use, but without an increase in breast cancer mortality. In women who have had a premature menopause and who require earlier HRT their risk at age 55 is approximately that of women commencing HRT at age 50. Long-term use in these women up to age 55 is appropriate.

Table 1

Comparison of outcomes from the Women's Health Initiative and observational studies *

Outcome after 5 years of combined hormone replacement therapy	*Relative risk (± CI) † in systematic reviews of observational studies*	*Hazard ratio (± adjusted CI) in WHI study at 5.2 years ‡*
Cancer		
Invasive breast[2]	1.35 (1.21–1.49)§ 1.53‡	1.26 (0.83–1.92)
Endometrial[7]	0.80 (0.6–1.2)	0.83 (0.29–2.32)
Colorectal[8]	0.72 (0.53–0.96)	0.63 (0.32–1.24)
Total	–	1.03 (0.86–1.22)
Fractures		
Hip[9]	0.60 (0.4–0.91)	0.66 (0.33–1.33)
Vertebral[10]	0.67 (0.45–0.98)	0.66 (0.32–1.34)
Total	–	0.76 (0.63–0.92)
Cardiovascular disease		
Stroke[11]	1.45 (1.10–1.92)	1.41 (0.86–2.31)
Thromboembolism[12]	2.14 (1.64–2.81)	2.11 (1.26–3.55)
Coronary heart disease		1.29 (0.85–1.97)
Observational studies[4]	0.66 (0.53–0.84)	
HERS# overall[5]	0.99 (0.8–1.22)	
HERS# mortality	1.24 (0.87–1.75)	
Total mortality	–	0.98 (0.70–1.37)

* Observational studies and randomised controlled trials cannot be directly compared but it is reassuring to see the magnitude of effect is similar in this case.
† Confidence interval
‡ Combined oestrogen and progestogen regimens
§ All regimens of hormone replacement therapy
# The Heart and Estrogen/Progestin Replacement Study (HERS) was a randomised placebo-controlled trial.

What to do now

It is not appropriate to prescribe HRT without an indication. The following points act as a guide to good practice.

- The main indication for HRT is for the control of menopausal symptoms and where quality of life is improved on HRT.
- Always counsel about the mixed risks and benefits of HRT and document this counselling. Supplementary written and video counselling is available from the Australasian Menopause Society web site (www.menopause.org.au).
- Oral HRT is still the route of choice. Women with a uterus require combined HRT, giving the progestogen cyclically over perimenopause and continuously after menopause. Women with a uterus should not receive oestrogen alone.
- In women who only have urogenital symptoms local vaginal oestrogens can be used.
- In women at risk of osteoporotic fractures, discuss and tailor the individual evidence-based therapies such as HRT, selective oestrogen receptor modulators or bisphosphonates, together with lifestyle advice.
- HRT is not advocated for the treatment or prevention of cardiovascular disease.
- Women on HRT should be reviewed yearly to determine optimal therapy and time for cessation of treatment.
- After 4–5 years of therapy it is appropriate to offer a trial off HRT. The dose can be reduced over 1–2 months before cessation.
- In women who have a return of disabling symptoms, HRT can be re-introduced for further treatment periods at the lowest effective dose and at any time of their lives.
- Women who are aware of the currently known mixed benefits and risks of long-term therapy and who have found that they have a better quality of life on HRT can be prescribed long-term HRT.

E-mail: alastair.maclennan@adelaide.edu.au

REFERENCES

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33. (randomised trial)
2. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047-59.
3. Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis, and vascular function. Cardiovasc Res 2002;53:605-19.
4. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. Annu Rev Public Health 1998;19:55-72.
5. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605-13. (randomised trial)
6. Vikkers M, Meade T, Darbyshire J. WISDOM: history and early demise – was it inevitable? Climacteric 2002;5:317-25.
7. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol 1995;85:304-13.
8. Grodstein F, Martinez ME, Platz EA, Giovannucci E, Colditz GA, Kautzky M, et al. Postmenopausal hormone use and risk for colorectal cancer and adenoma. Ann Intern Med 1998;128:705-12.
9. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. JAMA 2001;285:2891-7.
10. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials. BMC Musculoskelet Disord 2001;2:7. http://www.biomedcentral.com/1471-2474/2/7
11. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med 2000;133:933-41.
12. Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2002;136:680-90.

Professor MacLennan was a WISDOM investigator.

Self-test questions

The following statements are either true or false (answers on page 23)

3. The risk of breast cancer reported in the Women's Health Initiative study, of combined hormone replacement therapy, was significantly greater than the risk reported in previous observational studies.
4. Hormone replacement therapy should no longer be prescribed for the relief of menopausal symptoms.

Australian Prescriber wallchart

Copies of the wallchart 'Medical management of severe anaphylactoid and anaphylactic reactions' which was published with Vol. 24 No. 5 of 2001, are available for surgeries, clinics, hospitals and consulting rooms while stocks last.

To order copies contact the Australian Prescriber Mailing Service (see inside back cover for details).

Management of drug-induced gingival enlargement

Barbara Anne Taylor, Department of Periodontics, United Dental Hospital of Sydney, Sydney

SYNOPSIS

Healthy gums are pale pink or pigmented, and wrap tightly around the neck of the teeth. Gingival enlargement is an unwanted adverse effect of some drugs such as cyclosporin, phenytoin and calcium channel antagonists. This can be a cosmetic problem, interfere with eating and speech, impede effective tooth cleaning or force the teeth out of alignment. Gingival enlargement can be managed locally and systemically with a combination of medical and dental treatment. Co-operative teamwork and good communication between the patient, their doctor and their dentist are essential.

Index words: periodontal disease, cyclosporin, phenytoin, calcium channel antagonists.

(Aust Prescr 2003;26:11–3)

Periodontal disease

The periodontal diseases are a family of chronic inflammatory diseases that involve the periodontium – the bone and soft tissues that support the teeth in the jaws. They are the most common infection in humans. These diseases are caused by bacterial plaque that grows on the teeth and the immune response to that chronic infection.

Gingivitis and periodontitis are the two main periodontal diseases and may be present concurrently. Gingivitis is inflammation of the gingival margin. It affects approximately 45% of the adult population in Australia and is characterised by redness and swelling or oedema of the gingival margin around the neck of the teeth. Periodontitis is a more severe condition. It afflicts 15–20% of the adult dentate population and causes loss of the bone supporting the teeth. Signs of periodontitis include, in addition to signs of gingivitis, recession of the gums, tooth looseness, changes in tooth alignment, and halitosis. The commonest sign of either gingivitis or periodontitis is bleeding gums which can be provoked by toothbrushing, flossing, and eating hard foods, but can also be spontaneous. The absence of bleeding does not necessarily indicate the absence of periodontal disease, particulary in smokers.

Periodontal practice today is largely evidence-based. It aims to reduce inflammation by cleaning the teeth to remove plaque, and by using various treatment modalities to prevent or limit further plaque accumulation. A patient's management of their plaque control is central to successful periodontal treatment, but the response to treatment will also be influenced by factors such as genetic susceptibility to periodontal disease and background systemic disease.

Drug-induced gingival enlargement

Drug-induced gingival enlargement was first observed in patients who were taking phenytoin for epilepsy, with approximately 50% having gingival overgrowth. Cyclosporin is an immunosuppressant which has been reported to cause gingival enlargement in 25–80% of patients.[1,2] The calcium channel antagonists can also cause gingival enlargement. The dihydropyridines (e.g. nifedipine, felodipine, amlodipine) tend to be more commonly associated with gingival enlargement than the other sub-groups of calcium channel antagonists. Prescription of calcium channel blockers is relatively common, making it difficult to determine the true incidence of drug-induced gingival enlargement. Some of the variation in incidence of gingival enlargement can be attributed to differences between study populations and methods of classifying its severity.

Clinical presentation

Gingival enlargement usually develops in a susceptible individual within a few months of starting the medication. Drug-induced gingival enlargement consists of soft tissue growth that begins between the teeth and increases in all directions. As the tissue enlarges it develops a characteristically thickened and lobulated appearance. It may partially or completely cover the tooth surfaces, including the occlusal (chewing) surfaces, as well as extending the other way, into the sulcus. The epithelial surface is usually smooth and fibrotic, but can be nodular in cyclosporin-induced enlargement. If there is underlying periodontal disease then the tissues may be inflamed, red or purplish in colour, and highly vascularised, with a tendency to bleed profusely (Fig. 1).

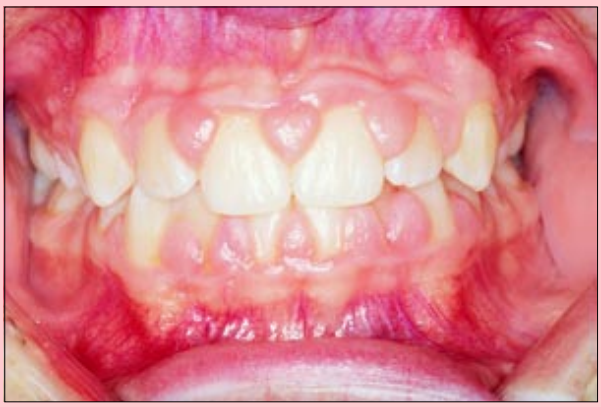
Gingival enlargement tends to be more severe in areas where plaque accumulates, such as at the edges of fillings and around orthodontic appliances. It is rarely seen in edentulous areas. Gingival enlargement impedes effective plaque control and regularly traps plaque or food, producing halitosis or suppuration. There is a tendency for gingival enlargement to be distributed symmetrically and for the anterior teeth to be more severely affected than the posterior teeth.

Clinical parameters such as the standard of oral hygiene, drug dosage, and serum and salivary levels have some relationship to the incidence of gingival enlargement. Generally, a higher dose and poorer plaque control – or more plaque retentive sites – are more likely to be associated with gingival enlargement. However, there is no direct relationship and these factors do not fully explain the incidence or the characteristics of the lesion.

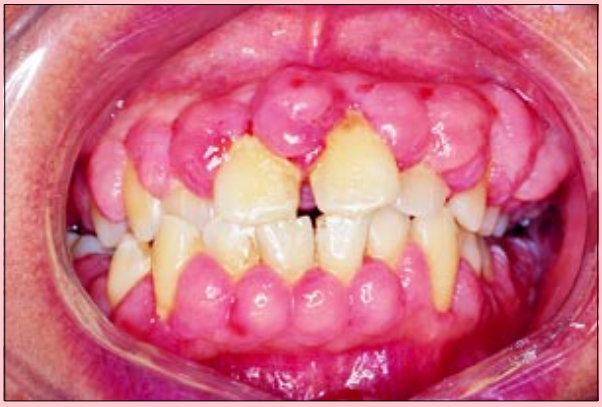
Fig. 1

Gingival enlargement

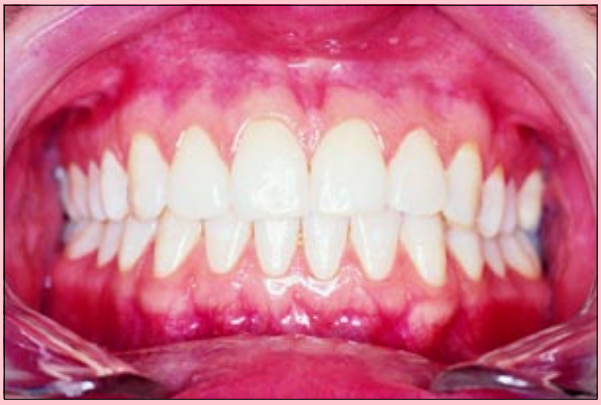
a. Mild-moderate: gingival enlargement induced by cyclosporin and diltiazem



b. Severe: gingival enlargement induced by cyclosporin, nifedipine, amlodipine



c. Healthy gingival tissue



Management of gingival enlargement

In addition to plaque control and medical management, periodontal surgical treatment and multidisciplinary dental care are key strategies in managing gingival enlargement.

Mild gingival enlargement may only require local management as improvement in oral hygiene, together with professional cleaning of the teeth, can lead to resolution of inflammation and reduction in gingival enlargement. Treatment planning becomes more complex where there is periodontitis plus gingival enlargement that is a cosmetic or functional problem. Periodontitis can be treated using conventional clinical care, but the gingival enlargement may require changes to the medication regimen, periodontal surgery to remove excess tissue, or a combination of the two.

Plaque control

Effective plaque control can reduce and prevent gingival enlargement. Most people clean their teeth, but not particularly effectively. It is important that the dental professional encourages improved tooth cleaning in a supportive and positive manner, as well as providing information about the role of dental plaque in promoting gingival overgrowth. Mild gingival enlargement will often diminish with removal of plaque and calculus deposits. Even moderate gingival enlargement may reduce enough to avoid surgical intervention.

Attempts at improving oral hygiene are of limited benefit in severe gingival enlargement – surgical gingival resection is indicated. Chlorhexidine 0.1% should be rinsed two or three times daily for the first few postoperative days, with careful mechanical cleaning introduced gradually as it becomes more comfortable. Areas that are not included in the surgery can be cleaned as usual. The efficacy of chlorhexidine may be reduced by toothpaste because of a chemical interaction. The interval between toothbrushing and rinsing should therefore be at least 30 minutes.[3]

Many patients who take drugs that induce gingival enlargement will have some gingival growth between the teeth and thickening of the gums. It follows then that when they brush their teeth they risk either traumatising the soft tissue or inadequate cleaning of the crown of the tooth close to the gingival margin. Flossing is difficult and using interproximal brushes and woodsticks is often out of the question when gingival enlargement is present.

Plaque can be removed by cleaning each tooth separately, holding the brush in line with the long axis of the tooth. The narrower dimension of the head of the brush then fits in between the papillae (the part of the gum between the teeth). Another option is to use an electric toothbrush with a round head to clean the teeth in the same longitudinal fashion. Cleaning plaque from between the teeth can also be carried out if the patient is shown how to gently slide dental floss or tape along the tooth surfaces and under the edge of the gum. Thorough cleaning by brushing and flossing should be carried out at least once daily.

Medical management

Many cases of gingival enlargement will respond to local treatment, but consideration should be given to altering the medication if gingival enlargement covers more than about a third of the tooth surface. When possible, reducing the dose or changing to another drug may bring about partial or complete regression of the lesion. Most patients will observe an alteration in the soft tissues within a few days. If a person continues taking the same gingival enlargement-inducing medication then they should be warned of the possibility of gingival

enlargement recurring despite periodontal treatment.

Several alternatives to phenytoin are available, but they may not be as well tolerated or they may not control seizures as well. Some patients can switch to a lower dose of phenytoin combined with another anticonvulsant.

If a patient develops gingival enlargement as a result of taking a particular calcium antagonist, they will usually also develop it in response to other calcium antagonists. Alternative classes of antihypertensive medication may be suitable for patients who are being treated for hypertension.

The dose of cyclosporin may be reduced in the course of medical treatment, and can also be reduced in some cases where patients are on a maintenance dose, with no adverse effects. Once the gingival enlargement is drawn to the treating physician's attention, it may be possible to maintain a patient on a lower dose.

Changing from cyclosporin to tacrolimus can be considered if significant gingival enlargement recurs after excision. Tacrolimus has a different toxicity profile and is not associated with gingival enlargement. It has the same interactions with diltiazem, which could still be used, producing a residual but diminished gingival enlargement.

Conclusion

Gingival enlargement is an under-recognised adverse effect of cyclosporin, phenytoin, and the calcium channel antagonists. Medical practitioners and pharmacists are ideally placed to advise patients of the possibility of this effect and emphasise the importance of maintaining good oral hygiene as a preventive measure. Doctors can identify the problem by looking in the patient's mouth and can then refer the patient for dental management if necessary.

E-mail: barbara.taylor@email.cs.nsw.gov.au

REFERENCES

1. Daley TD, Wysocki GP, Day C. Clinical and pharmacologic correlations in cyclosporine-induced gingival hyperplasia. Oral Surg Oral Med Oral Pathol 1986;62:417-21.
2. Friskopp J, Klintmalm G. Gingival enlargement. A comparison between cyclosporine and azathioprine treated renal allograft recipients. Swed Dent J 1986;10:85-92.
3. Barkvoll P, Rolla G, Svendsen K. Interaction between chlorhexidine digluconate and sodium lauryl sulfate in vivo. J Clin Periodontol 1989;16:593-5.

FURTHER READING

Hallmon WW, Rossmann JA. The role of drugs in the pathogenesis of gingival overgrowth. A collective review of current concepts. Periodontol 2000 1999;21:176-96.

Seymour RA, Heasman PA. Drugs and the periodontium. J Clin Periodontol 1988;15:1-16.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 23)

5. Among the calcium channel antagonists, gingival enlargement is most frequently associated with dihydropyridines.
6. Gingival hypertrophy occurs in less than 5% of patients treated with phenytoin.

The painting on the cover

Australian Prescriber's international readership is growing. To identify the journal as distinctively Australian, the cover features an Australian Aboriginal painting. Jennifer Summerfield, the Aboriginal artist, from the centre of Australia, created the painting in 1998 for National Medicines Week. The central icon is of a gathering of people sitting around a fire, talking. Jennifer's story follows:

I'm Jennifer Summerfield. I am a Pitjantjatjara woman. I live at Umuwa on the Anangu Pitjantjatjara Lands in the north west of South Australia. I work as an Anangu Health Worker for Nganampa Health Council. I am the artist who did the painting for National Medicines Week.

This painting is about using medicine properly, especially for older people. Store your tablets in a cool place or in your bag away from kids and other old people. Take your medication at the right time with the pictures of the sun showing in the morning, at midday and in the evening. Don't throw your medicines on the ground. If you don't take your tablets you may be blind or never walk again. This is what the painting is about.

The older people in the middle of the painting are keeping their medicine safe in a bag. The people in each corner have not taken their medicines and have become blind or crippled. There is the sun to tell them to take their medicine, in the morning, at midday and in the evening. People at the middle top of the painting are taking their medicines. People down the bottom of the painting sometimes take their medicine and sometimes throw it away. Then young kids can find that medicine and take it and become sick. The two black paintings show that when people don't take their medicine properly, they die. Around the outside of the painting are a few bush medicines.

Aspiration pneumonia and pneumonitis

Simon O'Connor, Chest Physician, Tamworth, New South Wales

SYNOPSIS

The two major aspiration syndromes are bacterial pneumonia and chemical pneumonitis. They have distinct features but may overlap. For chemical pneumonitis, supportive care is the mainstay of treatment while bacterial infection requires antibiotics. The choice of antibiotic is confused by conflicting evidence about the organisms responsible for infection, the poor yield from cultures in clinical practice and the lack of data comparing antibiotic regimens. Preventive strategies may help to reduce aspiration in vulnerable patients.

Index words: respiratory tract infection, antibiotics, corticosteroids.

(Aust Prescr 2003;26:14–7)

Introduction

Aspiration of oropharyngeal or gastric contents is a common, but often unrecognised cause of pneumonia. Focusing the management of pneumonia on the distinction between community- and hospital-acquired disease means that clinicians may not appreciate that aspiration can be a significant factor in both presentations.

Classification

Aspiration can occur in healthy individuals without sequelae. The development of infection depends on other factors such as the size of the inoculum, virulence of the organisms and the state of host defences such as glottic closure, cough reflex and immune status. Pneumonia may arise following 'micro' aspiration of virulent micro-organisms. However, the term aspiration pneumonia is reserved for pneumonia arising when the size of the inoculum is large and/or host defences fail.

Aspiration can be divided into two broad categories. This has important management implications. Aspiration of oropharyngeal contents, for example due to swallowing difficulty, will cause bacterial pneumonia with mouth organisms predominating. Aspiration of gastric contents will cause a chemical pneumonitis (e.g. Mendelson's syndrome) because the gastric contents are usually sterile, but their acidity results in the rapid development of inflammation in the lungs. There may be overlap between pneumonia and pneumonitis, but it is usually possible to make the distinction and tailor treatment accordingly.

Other aspiration syndromes include airway obstruction due to a foreign body and exogenous lipoid pneumonia.

Epidemiology

Table1 lists common causes of aspiration. Patients with stroke or a critical illness requiring intensive care usually have several of these risk factors and make up a large proportion of cases. Poor dental hygiene, especially in elderly or debilitated patients, results in colonisation of the mouth with potentially pathogenic organisms and/or increased bacterial load. This increases the risk of infection should aspiration occur.

Clinical features

The history, examination and chest X-ray help to differentiate between pneumonia and pneumonitis.

Aspiration pneumonia

The clinical features are often indistinguishable from other causes of pneumonia, for example cough, chest pain, dyspnoea, fever and consolidation on chest X-ray. The presence of aspiration may be obvious, for example patients with motor

Table 1

Conditions that predispose to aspiration

Altered level of consciousness
- stroke
- seizures
- intoxication (alcohol and other drugs)
- head trauma
- anaesthesia

Mechanical disruption of usual defences
- nasogastric tube
- endotracheal intubation
- tracheostomy
- upper gastrointestinal endoscopy
- bronchoscopy

Neuromuscular disease
- multiple sclerosis
- Parkinson's disease
- myasthenia gravis
- bulbar or pseudobulbar palsy

Gastro-oesophageal disorders
- incompetent cardiac sphincter
- oesophageal stricture
- neoplasm
- gastric outlet obstruction
- protracted vomiting

Other
- recumbent position
- general debility

neurone disease who cough when swallowing. However, aspiration is usually not witnessed and detecting it requires a high degree of suspicion. Some patients will have a relatively sudden onset typical of infection with common organisms such as *Streptococcus pneumoniae*. However, compared with other causes of pneumonia, aspiration pneumonia tends to have a more indolent course, evolving over days to weeks rather than hours. Patients may present with late complications such as weight loss, anaemia, lung abscess or empyema.

Chest X-ray usually shows consolidation in the lung segments which were dependent at the time of aspiration. If the patient was supine the posterior segments of upper or apical segments of lower lobes are involved. The basal segments of lower lobes are involved if the patient was upright. The subsequent course on X-ray is similar to pneumonia from other causes. Without treatment, patients have a higher incidence of cavitation and abscess formation.

Aspiration of gastric contents

In contrast to the aspiration of oropharyngeal secretions, aspiration of gastric contents is more likely to be witnessed or inferred. The original description of Mendelson's syndrome involved obstetric patients undergoing ether anaesthesia. Witnessed aspiration was followed by respiratory distress and cyanosis within two hours. The women's X-rays showed infiltrates in one or both lower lobes. Despite the severity of the illness, all the patients had recovered within 36 hours and there was radiographic resolution within seven days.

Subsequent studies of aspiration pneumonitis have shown a more fulminant clinical course resulting in the adult respiratory distress syndrome. The different clinical course probably reflects different study populations. The original patients were young, previously healthy women, while later studies often involved elderly, debilitated patients or those burdened with serious comorbid conditions.

Microbiology

There is conflicting information about the range of organisms responsible for aspiration pneumonia. The role of anaerobic organisms from the mouth seemed to be established in the 1970s and 80s using transtracheal and pleural aspiration to obtain specimens from the lower respiratory tract, avoiding the problem of contamination of expectorated sputum by normal mouth flora. The organisms include *Peptostreptococcus, Fusobacterium* and *Bacteroides*.

The use of protected brush specimens obtained via a bronchoscope in more recent times has yielded a different range of organisms, the identity of which depends on where the infection is acquired. *Streptococcus pneumoniae* predominates in community-acquired cases, *Staphylococcus aureus* and Gram negative organisms predominate in hospital-acquired cases. Anaerobic organisms have been conspicuously absent in these series.[1]

There are a number of reasons for these contradictory results. In the studies that isolated anaerobes, the specimens were usually obtained late in the course of the illness after complications such as empyema or lung abscess had developed. Many of the patients were alcoholics and had foul sputum. They presumably represent only part of the spectrum of aspiration pneumonia. The studies that isolated aerobic bacteria were performed at an earlier stage of the illness, usually before antibiotics were used, and were taken from a wider range of patients with aspiration pneumonia.

Identifying organism(s) responsible for pneumonia is often attempted but not achieved in clinical practice for a number of reasons. These include contamination of sputum specimens with oropharyngeal flora, previous treatment with antibiotics and the difficulties using invasive techniques (such as bronchoscopy, transtracheal and transthoracic and pleural aspiration) that are more reliable at isolating pathogens. Anaerobic pathogens are difficult to identify even with good laboratory expertise.

Management

All patients need supportive care[2] as well as specific treatment.

Aspiration (chemical) pneumonitis

The airway should be cleared of fluids and particulate matter as soon as possible after the aspiration of gastric contents is witnessed. Endotracheal intubation should be considered for those who are unable to protect their airway. Although it is common practice, there is no evidence that prophylactic use of antibiotics improves outcomes and, theoretically, this may make things worse by selecting out resistant organisms. Conversely, there may be difficulty distinguishing between purely chemical pneumonitis and bacterial infection. In clinical studies, up to 25% of patients develop superimposed bacterial infection during the course of chemical pneumonitis.

A reasonable compromise is to withhold antibiotics where the diagnosis is clear. Empirical antibiotic treatment should be considered if there is no improvement after 48 hours. If the pneumonitis cannot be distinguished from bacterial pneumonia or if patients have conditions known to be associated with colonisation of gastric contents (for example small bowel obstruction, or being in intensive care) immediate empirical antibiotic treatment is appropriate.

Corticosteroids have been used, with varying degrees of enthusiasm, for decades in the management of aspiration pneumonitis, but there are limited data to support this practice. Studies in humans are generally unsuccessful and sometimes the outcomes are worse for those treated with corticosteroids. Large randomised controlled trials of high dose corticosteroids for adult respiratory distress syndrome (of which chemical pneumonitis is a subset) showed no benefit.[3] As a result, this treatment is not recommended.

Bacterial aspiration pneumonia

In contrast to chemical pneumonitis, antibiotics are the most important component in the treatment of aspiration pneumonia. Early empirical treatment is required for cases that are severe enough to warrant hospitalisation. Waiting for the results of

culture is unwise and will disappoint because of the low yield. Where practical, samples of blood, sputum and pleural fluid should be taken for culture before antibiotic use. If antibiotics have already been used, cultures may still be helpful in severe cases with a large organism load.

Which antibiotic?

The choice of antibiotic is influenced by the clinical setting (community- versus hospital-acquired), culture results, previous antibiotic use, and disease characteristics. The recommendations of *Therapeutic Guidelines: Antibiotic*[4] for empirical therapy (see box) emphasise the importance of anaerobic infection and minimise the role of aerobic organisms. I believe the emphasis should be tilted to at least giving equal importance to aerobic infection.

Antibiotic regimens which only aim at anaerobic infection are indicated if there is evidence of anaerobic infection (for example lung abscess or empyema with putrid sputum) and reasonable confidence there is no aerobic infection. Metronidazole used alone results in a significant treatment failure rate and should be used with another drug, usually penicillin.[5,6] If penicillin allergy is a problem, clindamycin alone is adequate. I prefer clindamycin for intravenous treatment as it is more effective than penicillin alone and comparable to the combination of penicillin and metronidazole. Clindamycin is more convenient to administer and overall is as well tolerated, although its adverse effect profile differs from that of penicillin and metronidazole. Amoxycillin-clavulanate alone is also effective. For oral therapy, I prefer either amoxycillin-clavulanate or clindamycin alone over penicillin with metronidazole for similar reasons.

The value of other drugs commonly prescribed to treat pneumonia has not been systematically studied in anaerobic infection. It is likely that some of these, for example macrolides, second and third generation cephalosporins, may be ineffective as they lack activity against some anaerobes including the *Bacteroides* group. Drugs such as ciprofloxacin, aminoglycosides and trimethoprim-sulfamethoxazole have poor activity against all anaerobes.

Imipenem, meropenem or any combination beta lactam/beta lactamase inhibitor (e.g. ticarcillin and clavulanate or piperacillin and tazobactam) are effective against virtually all anaerobic bacteria and should be effective against anaerobic pulmonary infection. They are attractive if there is concern about aerobic Gram negative infection or infection due to the commonly recognised respiratory pathogens (*Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus* and *Moraxella* species) as well as anaerobic infection. *Therapeutic Guidelines: Antibiotic* recommends adding gentamicin to penicillin/metronidazole or clindamycin where Gram negative infection is suspected. I prefer to use one of the regimens mentioned above as they are generally easier to administer, less toxic and do not require measurement of drug concentrations.

Depending on the clinical setting, anaerobic infection may be relatively uncommon compared with aspiration pneumonia due to aerobic organisms. These especially include *Streptococcus pneumoniae* and *Haemophilus influenzae* in community-acquired cases, and *Staphylococcus aureus*, aerobic enteric Gram negative organisms and *Pseudomonas aeruginosa* in hospital-acquired cases or where there has been previous antibiotic use. There is an array of antibiotic regimens for hospital-acquired pneumonia (which is largely caused by aspiration).[4,7]

Which route?

The decision to use intravenous rather than oral therapy will depend on a number of factors. More severe illness requires more aggressive treatment and greater certainty that adequate doses of antibiotic are delivered to the lungs. In these cases, especially if there is doubt about gastrointestinal absorption, intravenous therapy is required. In less severe illness, oral therapy will often suffice. Switching from intravenous to oral therapy will be determined by the individual patient's progress. In those who respond rapidly, oral therapy can often be introduced within 2–3 days.

***Therapeutic Guidelines: Antibiotic*[4] recommendations for aspiration pneumonia**

For severe aspiration or lung abscess:
benzylpenicillin 1.2 g intravenously 4–6 hourly + metronidazole 500 mg intravenously 12 hourly

If hypersensitive to penicillin:
use clindamycin 600 mg intravenously eight hourly as a single drug

If Gram negative pneumonia is suspected:
add gentamicin 4–6 mg/kg intravenously daily; alternatively, as a single agent use ticarcillin + clavulanate 3.1 g intravenously six hourly OR piperacillin + tazobactam 4.5 g intravenously eight hourly

Other interventions for aspiration syndromes

A semirecumbent, as opposed to supine, body position reduces the frequency of nosocomial pneumonia in patients receiving mechanical ventilation presumably by minimising gastro-oesophageal reflux and subsequent aspiration.[8] A systematic approach to improving oral care in nursing home patients has also been shown to reduce the rate of pneumonia, presumably by reducing the oral organism load in these patients who have a high rate of aspiration.[9]

Assessment of cough and gag reflexes is an unreliable method to identify stroke and other patients at risk of aspiration. A more comprehensive evaluation of swallowing, usually by a speech pathologist, is required. This may include a videofluoroscopic swallowing study and/or endoscopic evaluation. In patients at risk, behavioural, dietary and medical interventions may reduce risk. For swallowing dysfunction, a soft diet is often used along with feeding strategies, for example keeping chin tucked, small bite size.

There are contradictory aspects to the issue of tube feeding and aspiration pneumonia. It is reasonable, but unproven, to believe that tube feeding will reduce the risk of aspiration pneumonia in some patients with swallowing difficulties.

The contradiction lies in the role of tube feeding in causing aspiration pneumonia. Feeding tubes offer no protection from aspiration of oral secretions (and nasogastric tubes may make it worse). Aspiration of gastric contents can still occur and aspiration pneumonia remains a common cause of morbidity and death in patients fed this way. Percutaneous endoscopically-placed gastrostomy tubes are not superior to nasogastric tubes when it comes to preventing aspiration pneumonia. However, for long-term use they are more convenient and more acceptable to patients who cannot be adequately fed by conventional means. Tube feeding may be recommended for patients who continue to aspirate despite other preventive strategies (the bulk of these are stroke patients). This decision will also rest on patient preference, prognosis and other indications for tube feeding, such as nutritional maintenance.

Conclusion

Pulmonary aspiration is a significant cause of morbidity and mortality in a wide range of patients. Identifying and differentiating between the various aspiration syndromes is largely a clinical/epidemiological skill. Treatment is usually empirical, and therefore adequate differentiation between types of aspiration is needed to achieve best outcomes. Preventive strategies have recently been shown to reduce the rate of aspiration syndromes.

E-mail: simonoconnor@optusnet.com.au

REFERENCES

1. Marik PE, Careau P. The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia: a prospective study. Chest 1999;115:178-83. (randomised trial)
2. Kollef MH, Schuster DP. The acute respiratory distress syndrome. N Engl J Med 1995;332:27-37.
3. Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 1987;317:1565-70. (randomised trial)
4. Writing Group for Therapeutic Guidelines: Antibiotic. Therapeutic guidelines: Antibiotic. 11th ed. Melbourne: Therapeutic Guidelines Limited; 2000.
5. Perlino CA. Metronidazole vs clindamycin treatment of anerobic pulmonary infection. Failure of metronidazole therapy. Arch Intern Med 1981;141:1424-7.
6. Sanders CV, Hanna BJ, Lewis AC. Metronidazole in the treatment of anaerobic infections. Am Rev Respir Dis 1979;120:337-43.
7. Hospital-acquired pneumonia in adults: diagnosis, assesment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995 [review]. Am J Respir Crit Care Med 1996;153:1711-25.
8. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet 1999;354: 1851-8. (randomised trial)
9. Yoneyama T, Yoshida M, Ohrui T, Mukaiyama H, Okamoto H, Hoshiba K, et al. Oral care reduces pneumonia in older patients in nursing homes. J Am Geriatr Soc 2002;50:430-3. (randomised trial)

FURTHER READING

Marik PE. Aspiration pneumonitis and aspiration pneumonia. N Engl J Med 2001;344:665-71.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 23)

7. Patients with aspiration pneumonitis should be given a bolus dose of corticosteroids as soon as possible after the aspiration.
8. Aspiration pneumonia does not occur in patients who are tube fed.

Electronically tested

Australian Prescriber was one of the first medical journals in the world to make its full text freely available on the internet. Many thousands of people from around the world visit the web site (www.australianprescriber.com) and some of them participated in a recent survey.

Most of the participants were health professionals from Australia, but at least one third were from overseas. More than half the participants had visited the site before and found it was useful when they were looking for information about a specific therapy or condition. The most popular topics on the *Australian Prescriber* web site are deep vein thrombosis and infections.

The participants made lots of useful suggestions for improving the site. However, the web site already includes some of the features that people were looking for.

The web site has both an index and a search function. While the index will list articles where the subject, for example, hypertension, was an important part of the article, the search function will identify every article containing that word. The index is more specific, but is currently only updated annually when the paper index is published. (The Editorial Executive Committee will look at the possibility of updating the index more frequently in future.)

Although the survey is now completed readers are always welcome to send suggestions for improving the electronic or print forms of *Australian Prescriber*.

Gabapentin documents raise concerns about off-label promotion and prescribing

Melissa Sweet, Health and Medical Writer, Sweet Communication, Sydney

SYNOPSIS

Anticonvulsant medications have been widely used for off-label indications. Court documents recently released in the USA suggest that some of the off-label use of the anticonvulsant gabapentin was driven by deceptive and illegal marketing practices. Reliable evidence is not available to support many of the off-label uses of gabapentin. Off-label use of medications can be beneficial, but clinicians and patients should be aware of the quality of evidence available to support such usage.

Index words: pharmaceutical industry, advertising.

(Aust Prescr 2003;26:18–9)

Since its approval in the USA in late 1993 as an add-on treatment for partial seizures, gabapentin (Neurontin) has become the world's top-selling anticonvulsant, according to the web site of its manufacturer, Pfizer. The company also says that gabapentin has one of the fastest-growing markets of any drug and that it is one of the key products expected to drive its manufacturer's future profits.

In Australia, gabapentin is approved as add-on therapy for partial epilepsy and for neuropathic pain, but only subsidised by the Pharmaceutical Benefits Scheme (PBS) for patients with epilepsy whose seizures are not controlled by other drugs. Health Insurance Commission data show that scripts dispensed for gabapentin under the Pharmaceutical Benefits Scheme increased by 320% between 1996–97 and 2001–02 (from 15 340 to 64 686). By comparison, PBS scripts for a comparable anticonvulsant, lamotrogine, increased by 81% over the same period, while vigabatrin scripts dropped by 58%.

Anticonvulsants have a long history of off-label use; carbamazepine and valproate were widely used, for example, as alternative and adjunctive treatments to lithium for mood disorders, before they received regulatory approval. Literature searches show that there has also been widespread interest in off-label use of gabapentin, including for mood disorders, aggressive behaviour associated with dementia, treatment of drug and alcohol addiction, low back pain, postoperative pain, muscle cramps, and hot flushes associated with tamoxifen therapy. Some of these indications are being studied in clinical trials.[1]

Evidence has recently emerged suggesting that at least some of the off-label use of gabapentin in the USA was driven by deceptive and illegal marketing practices.[2,3] Court documents allege that Parke-Davis, a subsidiary of Warner-Lambert which merged with Pfizer in 2000, systematically promoted gabapentin for off-label uses for which there was not good evidence.

Dr David Franklin, a former employee of Warner-Lambert, has filed a lawsuit in the District Court for the District of Massachusetts against the company. It alleges that the company's sales representatives encouraged doctors to prescribe gabapentin for unapproved indications, including bipolar disorder, attention deficit disorder, restless leg syndrome, migraine, and drug and alcohol withdrawal seizures. Strategies for influencing prescribers included:

- funding dinners, conferences and medical education seminars where presentations were made on off-label uses
- providing educational grants to gabapentin advocates
- paying doctors honoraria for use of their names on ghost-written scientific articles
- establishing a Speakers Bureau to make payments to doctors who promoted gabapentin.

It has been described as 'the most complete and well documented case of off-label promotion to ever come into public view'.[3]

Meanwhile, Pfizer was reprimanded by the Association of the British Pharmaceutical Industry earlier this year, after being found in breach of the industry's code of conduct. The Prescription Medicines Code of Practice Authority found that Pfizer had been promoting off-licence indications for products, including gabapentin.[4]

Pfizer stresses that promotion of off-label indications is against company policy and that it is unaware of any such promotion of gabapentin having occurred in Australia. The industry body Medicines Australia has not received any complaints alleging off-label promotion of gabapentin.

However, there is some anecdotal evidence of off-label promotion of gabapentin in Australia. An Australian psychiatrist says he attended a conference in Sydney, organised by Parke-Davis, where an American speaker gave a presentation endorsing gabapentin's use in bipolar disorder and other psychiatric conditions, despite a lack of evidence from randomised trials.[5,6]

Off-label prescribing can be a double-edged sword for clinicians and patients. It may be clinically appropriate, for example, if

there is reliable evidence of benefit. It is also important to distinguish between lack of evidence of benefit and evidence of lack of benefit; sometimes no studies may have been done in a population, such as the elderly or children, who might benefit from off-label prescribing. Sometimes there may be little financial incentive for companies to conduct trials for an indication which is widely accepted but not approved by drug regulatory authorities.

The gabapentin story is a reminder, however, of the need for caution, especially when the evidence is unreliable or being promoted by vested interests. Much of the enthusiasm for gabapentin's off-label uses appears to have been driven by case reports, uncontrolled studies and other unreliable forms of evidence. A recent review of prophylactic migraine treatments noted that gabapentin had been suggested to be effective despite a lack of rigorous, reliable data.[7] A Cochrane review said anticonvulsants are used widely in chronic pain, although surprisingly few trials show analgesic effectiveness.[8] It also raised questions about the increasing use of gabapentin in neuropathic pain.

Given the uncertainties that can surround off-label prescribing, there is an extra imperative to carefully weigh the potential benefits and harms involved, and to ensure these are openly canvassed, where possible and appropriate, with patients and their families.

E-mail: sweetcom@tig.com.au

REFERENCES

1. Oncology/Hematology Associates of Central Illinois. http://www.ohaci.com/palm/trials/misc_cancer_control_trials/N00CB_trials.htm
2. Neurontin (Gabapentin) – The illegal corporate creation of a blockbuster drug. Worst Pills, Best Pills 2002;8:36-8. http://www.citizen.org/
3. Update on the illegal promotion of Gabapentin (Neurontin). Worst Pills, Best Pills 2002;8:68-71. http://www.citizen.org/
4. Dinsdale P. Pfizer gets a public dressing down over promoting unlicensed drugs. Br Med J 2002;324:753.
5. Frye MA, Ketter TA, Kimbrell TA, Dunn RT, Speer AM, Osuch EA, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. J Clin Psychopharmacol 2000;20:607-14.
6. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. Bipolar Disord 2000;2(3 Pt 2):249-55.
7. Krymchantowski AV, Bigal ME, Moreira PF. New and emerging prophylactic agents for migraine [review]. CNS Drugs 2002;16:611-34.
8. Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.

Conflict of interest: none declared

Greed and gabapentin

Editorial comment

Some of the recent corporate collapses show that the relentless pursuit of profit can have disastrous consequences. Although the pharmaceutical industry aims to help patients it may not be immune from questionable corporate practices.

The New York Times has reported an accusation that rules were broken in the promotion of gabapentin.[1] 'Worst Pills, Best Pills', an American drug bulletin, has been keeping its readers and other members of the International Society of Drug Bulletins (including *Australian Prescriber*) informed of the case.[2]

Allegedly, the manufacturer concocted uses for gabapentin to boost profits. Despite a lack of independent supporting evidence, the company is said to have aggressively promoted these 'off-label' indications to doctors. The promotional strategy is alleged to have involved payments to opinion leaders and the placement of ghost-written articles in medical journals.

These strategies appear to have worked well as sales of gabapentin reached US$1.3 billion in 2000. 'Worst Pills, Best Pills' reports that as much as 78% of these sales were for uses without evidence that gabapentin was safe and effective.[2]

Although these allegations are yet to be tested in court, and the manufacturer involved has now been taken over by another company, the Editorial Executive Committee of *Australian Prescriber* believes readers will be interested in how big business might influence prescribing. As gabapentin is an extraordinary case, the Editorial Executive Committee has asked well-known medical journalist Melissa Sweet to provide more details.

Could it happen here? The code of conduct for the Australian pharmaceutical industry prohibits claims which are not consistent with the product information approved by the Therapeutic Goods Administration. Although the code offers some protection, similar rules in the USA did not prevent the gabapentin controversy. To strengthen the code it is important that health professionals contact Medicines Australia* if they have evidence of drugs being promoted for unapproved indications.

REFERENCES

1. Petersen M. Whistle-blower says marketers broke the rules to push a drug. New York Times 2002 March 14; Section C, Page 1 (col. 5).
2. Neurontin (Gabapentin) – The illegal corporate creation of a blockbuster drug. Worst Pills, Best Pills 2002;8:36-8.

* Medicines Australia
Level 1, 16 Napier Close DEAKIN ACT 2600
Phone (02) 6282 6888
Fax (02) 6282 6299
www.medicinesaustralia.com.au

Variation in perceptions of risk between doctors and patients: risks look different when they are close to home

Hilda Bastian, Cochrane Consumer Network, The Cochrane Collaboration, Melbourne

SYNOPSIS

There are no simple 'one size fits all' instructions to guide health professionals in communicating with their patients about risks. Patients – as individuals, and as a group – may see risks very differently to the medical profession. Understanding that things have a certain perspective to health professionals, and that other things may be closer to home for the patient, could help the health professionals better 'speak their patient's language' of risk. Helping patients get a balanced, multidimensional picture of their risks may not lead to the decisions the health professional expects, but should assist people to make decisions in accordance with their values and priorities.

Index words: consumer, adverse effects.

(Aust Prescr 2003;26:20–1)

There is a large and growing literature about how to try and affect people's perceptions and understanding of risk.[1] Despite this, people often forget just how differently individuals see risks (some of us are simply far more 'risk averse' than others). Your perceptions may quickly change if it is you, facing a real-life decision. Radical treatments that look unacceptably risky to a healthy person (such as bone marrow transplantation), can look very different to a person with advanced cancer who is running out of options. Yet, far too much of the evidence in this area is based on studies of people saying what they **think** they would do in a hypothetical situation. Extrapolating the recommendations of these studies into real life is risky.

Health professionals and patients often view risks differently. For example, doctors have expertise, but this also means that their view of health risks may be out of proportion. What is more, doctors are so used to adverse effects of medicines, or the indignities, inconvenience and discomfort of tests and procedures, that they can fail to appreciate what these mean to the average person. Perceptions of what is 'trivial' or 'mild discomfort' can be vastly different to people on opposite sides of the prescription pad (never mind the scalpel). For a doctor who wants a healthy person to take a drug to prevent a serious outcome (such as a stroke), the image of the person with a stroke may loom very large. For the patient, though, this outcome could be far more hypothetical. Meanwhile the risks and inconvenience of taking warfarin every day are immediate and real. Sometimes, people are simply more willing to hope for luck with life's many gambles, than take a chance on something that might turn out to be poison for them. Others see 'doing nothing' as inherently risky.

Some things hold true in certain circumstances, but not in others. For example, presenting data in the most dramatic way to evoke a desired reaction may work for someone scared of having a heart attack ('This will halve your risk'), but may have no effect on a parent intending to circumcise their newborn. A dramatic presentation is also less likely to work well when people have a fair working knowledge of something. Risk framing, as it is called, may not work as effectively with menopause, as it does for stroke. Severity of the problem matters too – fear of cancer or a stroke may outweigh most benefits of a treatment.

Just how afraid people are of a particular outcome also matters. It is clearly easier to activate people's desire to reduce risk when we are talking about cancer or HIV/AIDS, than it is to motivate people about measles. Too great an attempt by the health professions to use information to affect people's behaviour can backfire as well. Lack of openness about risks of treatments (including childhood immunisation) leaves fertile ground for others to raise fears, sow distrust and blind people to the risk of doing nothing.

There may well be a saturation point that differs between the community and the health professions. When health is your business, it can be easier to keep track of all the information. Take dietary advice for pregnancy: by the time the awareness campaigns of everything from the dangers of soft cheese and the need for more folate have rolled their way through (and you have morning sickness anyway), it can all get just a bit too hard. The community, healthier than it has ever been, seems to have been made more afraid than ever before of risks. While a doctor can more easily adjust their perspective if something turns out not to be a real risk (a false positive from a test result or a grey zone answer – raised but not 'high' cholesterol, for example), it is not always so simple for the patient. Further, while doctors understand the concept of risk as it applies to screening tests, the rest of us often see a test as a diagnosis. People's entire lives and health can be damaged by what a doctor thought was just a caution and explanation of risk, but which the patient sees as being labelled with a disease.[2,3]

We need to develop a more balanced and sophisticated approach to the communication of risk, one that takes patients' fears and concerns more seriously. The goal really is balance and perspective, so that the patient can make a decision in keeping with their values and priorities. This requires presenting a multidimensional picture. There is no 'one size fits all' approach to communicating about risk.

E-mail:hilda.bastian@cochraneconsumer.com

REFERENCES

1. Edwards A, Bastian H. Risk communication – making evidence part of patient choices. In: Edwards A, Elwyn G, editors. Evidence-based patient choice: inevitable or impossible? Oxford: Oxford University Press; 2001.
2. Bloom JR, Monterossa S. Hypertension labeling and sense of well-being. Am J Public Health 1981;71:1228-32.
3. McDonald IG, Daly J, Jelinek VM, Panetta F, Gutman JM. Opening Pandora's box: the unpredictability of reassurance by a normal test result. Br Med J 1996;313:329-32.

Conflict of interest: none declared

This article is the second in a series on risk. See also 'Perceptions of risk – a legal perspective' by J. McPhee in Vol. 25 No. 5, October 2002.

Patient support organisation

Asthma Australia

Asthma Australia is an association of all the Asthma Foundations throughout Australia. Asthma Australia aims to eliminate asthma as a major cause of ill health and disruption within the community. The Asthma Foundations provide asthma education, information, research, community advocacy and support to people with asthma and their carers.

Contacts

National office
Level 3, 63 Stead Street
SOUTH MELBOURNE VIC 3205
Phone: (03) 9696 7861; Freecall 1800 645 130
Fax: (03) 9696 7397
E-mail: national@asthma.org.au
Web site: www.asthmaaustralia.org.au

Asthma New South Wales
Unit 1/82-86 Pacific Highway
ST LEONARDS NSW 2065
Phone: (02) 9906 3233
Fax: (02) 9906 4493
E-mail: ask@asthmansw.org.au
Web site: www.asthmansw.org.au

Asthma Northern Territory
PO Box 40456
CASUARINA NT 0811
Phone: (08) 8922 8817
Fax: (08) 8922 8616
E-mail: asthmant@mpx.com.au

Asthma Queensland
51 Ballow Street
FORTITUDE VALLEY QLD 4006
Phone: (07) 3252 7677
Fax: (07) 3257 1080
E-mail: admin@asthmaqld.org.au
Web site: www.asthmaqld.org.au

Asthma South Australia
329 Payneham Road
ROYSTON PARK SA 5070
Phone: (08) 8362 6272
Fax: (08) 8362 2818
E-mail: info@asthmasa.org.au
Web site: www.asthmasa.org.au

Asthma Tasmania
Mailbox 5 McDougall Building
Ellerslie Road
BATTERY POINT TAS 7004
Phone: (03) 6223 7725
Fax: (03) 6224 2509
E-mail: asthmatas@bigpond.com
Web site: www.asthmatas.org.au

Asthma Victoria
69 Flemington Road
NORTH MELBOURNE VIC 3051
Phone: (03) 9326 7088
Fax: (03) 9326 7055
E-mail: afv@asthma.org.au
Web site: www.asthma.org.au

Asthma Western Australia
36 Ord Street
WEST PERTH WA 6005
Phone: (08) 9481 1234
Fax: (08) 9481 1292
E-mail: ask@asthmawa.org.au
Web site: www.asthmawa.org.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 Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Bimatoprost

Lumigan (Allergan Australia)

0.3 mg/mL in 3 mL, 5 mL and 10 mL bottles

Approved indication: glaucoma

Australian Medicines Handbook section 11.2.5

Prostaglandin $F_{2\alpha}$ agonists are effective drugs for reducing intra-ocular pressure. Bimatoprost has a similar structure and like the prostaglandin $F_{2\alpha}$ agonists it increases the outflow of aqueous humour (see 'New drugs for glaucoma' Aust Prescr 2002;25:142-6).

Patients instil one drop each evening. Intra-ocular pressure starts to fall after four hours and is lowest after 8–12 hours. The pressure falls by about 8 mmHg and the effect is sustained for at least 24 hours. Little bimatoprost is absorbed into the systemic circulation.

In a three-month comparative study once-daily bimatoprost reduced intra-ocular pressure by a mean of 9.16 mmHg. This was a significantly greater reduction than the 6.74 mmHg seen with twice-daily doses of timolol 0.5%.[1]

Another study compared bimatoprost with latanoprost for three months. Both drugs reduced intra-ocular pressure, but 53% of the patients taking bimatoprost achieved a target pressure of 17 mmHg or less compared with 43% of the latanoprost group.[2]

Bimatoprost causes more adverse effects than timolol. There is a higher incidence of conjunctival hyperaemia, itchy eyes and growth of eyelashes. Bimatoprost also causes more hyperaemia than latanoprost. Some patients develop increased iris pigmentation. Approximately 7% of patients stopped taking bimatoprost in the clinical trials because of adverse events.

There have been no specific drug interaction studies of bimatoprost, but it can be used as adjunctive therapy in patients whose intra-ocular pressure is not controlled by topical beta blockers.

Bimatoprost is at least as effective as latanoprost, but may be less well tolerated. Longer-term studies are needed to see if the benefits of bimatoprost are sustained.

REFERENCES

1. Brandt JD, VanDenburgh AM, Chen K, Whitcup SM. Comparison of once- or twice-daily bimatoprost with twice-daily timolol in patients with elevated IOP. Ophthalmology 2001;108:1023-32.
2. Gandolfi S, Simmons ST, Sturm R, Chen K. Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. Adv Ther 2001;18:110-21.

Tiotropium bromide

Spiriva (Boehringer Ingelheim)

capsules containing 22.5 microgram as powder for inhalation

Approved indication: chronic obstructive pulmonary disease

Australian Medicines Handbook section 19.1.2

Ipratropium is an anticholinergic bronchodilator which is inhaled three or four times a day. Tiotropium has a similar mechanism of action, but only needs to be inhaled once a day.

Compared to ipratropium, tiotropium dissociates more slowly from M_1 and M_3 muscarinic receptors. Its bronchodilator effect begins within 30 minutes but can last for more than 24 hours.

In a placebo-controlled trial, 279 patients with stable chronic obstructive pulmonary disease inhaled tiotropium powder every morning for 13 weeks. Respiratory function tests (see 'Basic tests of respiratory function' Aust Prescr 2000;23:10–2) showed significant increases in forced expired volume in one second (FEV_1), forced vital capacity (FVC) and peak expiratory flow rate. The FEV_1 and FVC increased within 30 minutes of the first dose. After one week of treatment, the FEV_1 and FVC 24 hours after a dose were 10–13% greater than before treatment. The patients needed to use significantly less salbutamol than the 191 patients in the placebo group.[1]

Another study randomised 191 patients to use tiotropium powder once a day and 97 to use an ipratropium inhaler four times a day for 13 weeks. The increases in mean FEV_1 and FVC were significantly greater with tiotropium than with ipratropium. Trough values (one hour before the next dose) of FEV_1 and FVC were significantly larger with tiotropium than with ipratropium.[2]

The most common adverse effect of tiotropium is a dry mouth. This affects nearly 15% of patients.[2]

Tiotropium seems to be more potent than ipratropium, but the clinical advantage is unclear. The difference between the peak expiratory flow rates narrowed over the course of the comparative study.[2] At the end of the study the difference was approximately 10 L/minute which is not significant. Although patients taking tiotropium used significantly less salbutamol, the mean difference was less than one puff per day.[2]

REFERENCES

1. US Tiotropium Study Group. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD. Chest 2000;118:1294-302.
2. Dutch Tiotropium Study Group. A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. Thorax 2000;55:289-94.

NEW COMBINATION

Peginterferon alfa-2b with ribavirin

Pegatron Combination Therapy (Schering Plough) composite packs containing vials of either 50, 80, 100, 120 or 150 microgram peginterferon alfa-2b powder for injection, and 200 mg ribavirin capsules (See 'New drugs: Peginterferon alfa-2b' Aust Prescr 2002;25:121–2)

NEW PROPRIETARY BRAND

Ciprofloxacin hydrochloride

Ciprofloxacin-BC (Biochemie)

250 mg, 500 mg and 750 mg tablets

Answers to self-test questions

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

☐ Send me the following back issue/s

.....

Editorial office

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

Telephone: (02) 6282 6755

Facsimile: (02) 6282 6855

Postal: The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
AUSTRALIA

E-mail: info@australianprescriber.com

Web site: www.australianprescriber.com

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
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
Telephone (02) 6282 6755

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

Published by the
National Prescribing Service