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EDITORIAL

Why are global drug prices so high... and other questions

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Index words: cost of drugs, drug industry.

(Aust Prescr 2003;26:26–7)

Why are drug prices so high in much of the world? Why isn't there an AIDS vaccine? Why don't we have effective antimalarials anymore? Why was there a shortage of noradrenaline in the UK last year?

The answers to these questions are pretty simple. We do not have the drugs we need, at the prices we want, because we have very little control over what drug companies do or do not do. Over the last 30 years we have largely relinquished control of drug development, supply and pricing decisions to the private sector, whose interests lie in maximising profits and growth, not in identifying and filling health needs. In most Western countries, the impact of this change has been ameliorated by health insurance systems, government subsidies or expensive carrots (like the Orphan Drug Act in the USA). However, this is not the case in developing countries, where governments are often too poor to shield patients from the brunt of industry production and pricing strategies.

Pharmaceutical industry strategies make commercial sense, but, particularly in developing countries, they can also conflict with what is best for public health. In response to shareholder pressure, drug companies have increasingly narrowed their research to focus on money-spinner drugs and diseases. The 10 best-selling drugs worldwide are for depression (4), cholesterol (2), hypertension (2), heartburn/ulcers (1) and hayfever (1).[1] The chief executive officer of the UK pharmaceutical company Amersham put the case bluntly: 'When I took on the biological business, two-thirds of our research was on tropical disease. I couldn't see how, virtuous as it was, that was going to deliver the revenue flows for the company. I was quite rigorous about cutting back on this research.'[2] The result of this trend is that in developing countries patients with malaria or sleeping sickness have little prospect of seeing new drugs developed for them unless there is government intervention.

Maximising profits also means getting rid of non-competitive products, irrespective of the health needs they may address. Companies faced with the need to improve the bottom line will, and have, simply stopped production of low-profit drugs like noradrenaline or isoprenaline, oily chloramphenicol for epidemics of bacterial meningitis, or eflornithine for sleeping sickness.

The real key to drug industry profit, however, is the ability to maintain high prices over long periods of time. Hence the enormous resources expended by the industry on lobbying governments to support measures that protect prices, reduce competition (which exerts downward pressure on prices) and extend patent monopolies.

The drug industry's greatest coup was the passage of new international trade laws in 1995, which stipulated that all countries – even the poorest – were compelled in most instances to purchase brand versions of all new drugs for a minimum of 20 years after they were patented, rather than relying on cheaper generic copies which had long been the mainstay of their health systems. Unfortunately, this success for the industry, effectively handicapping future generic competition, had life-threatening consequences for patients. Patients with AIDS, in particular, found themselves forced to forgo treatment with cheap generic antiretrovirals (then available for as little as $350 per patient per year) despite being unable to afford the equivalent brand name drugs which cost more than $10 000 per patient per year. A public outcry subsequently led to these laws being re-examined.

Of course prices and profits must be sufficiently high to foster a thriving drug industry and to fund research and development of new cures. However, drug company tax returns show that

In this issue...

New drugs, including some of the arthritis treatments mentioned by Anita Lee and Kevin Pile, can be expensive. While developing a new drug can cost a lot of money, Mary Moran asks if profits are sometimes put ahead of people.

Many medicines are developed to treat disorders of lifestyle in wealthy countries. While there are drugs for the treatment of obesity, Louise Baur says they currently have no role in children.

There is always a risk when treating a patient with drugs. Paul Komesaroff discusses some of the ethical issues involved, in the conclusion to our series on perceptions of risk.

Having an intravenous catheter involves a risk of infection. Catheters should therefore not be inserted if they are not needed, but if infection does occur Robert Horvath and Peter Collignon tell us how to treat it.

the bulk of their revenues are not allocated to research. The lion's share goes to marketing and administration, followed closely by returns to shareholders. The US pharmaceutical industry is consistently ranked by Fortune 500 as the most profitable industry in the US, with a staggering 33% return on shareholders' equity (other Top 10 performers deliver returns of between 14% and 26%); and with profits representing a generous 18% of revenues (other Top 10 performers range from 6% to 13%).[3] Compared to these figures, research and development spending comes a poor third.[4] This is not because industry is uninterested in research, indeed, they are anxious to find the next 'blockbuster' drug. The problem is that breakthrough drugs are increasingly rare. The US Food and Drug Administration estimates that only one third of new drugs submitted to it are truly innovative, the remainder being little or no improvement on existing therapies. In the absence of a real breakthrough, the next best thing is to **make** your drug seem like a breakthrough. This explains the huge marketing budgets, the teams of drug representatives visiting general practice surgeries with glossy folders, and the pressure for direct-to-consumer advertising of new drugs (which assumes that consumers are more easily swayed than physicians).

Drug companies, desperate to maintain growth rates and profits, are increasingly turning to standard business remedies. They are cutting out 'deadwood' (low-profit drugs and research targets), focusing on proven winners (blockbuster drugs and key US, Japanese and European markets) and ensuring that governments legislate in their favour, be this regulatory agencies or trade authorities.

Understanding these corporate practices helps us understand what has gone wrong and what needs to change. We are allowing a private sector industry that has other interests at heart to set the agenda on public health. While industry clearly has a central and important role to play, it is up to health professionals and governments to ensure that issues relating to health, not just wealth, are on the table when decisions affecting drug access are made.

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Conflict of interest: none declared

Letters

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

Splitting tablets

Editor, – The recent article (Aust Prescr 2002;25:133–5) 'Splitting tablets' is very useful, but one point needs clarification.

I refer to the statement: 'Tablets that are scored are usually considered by the manufacturer to be suitable for division... ' and to the reference to azathioprine (Imuran) in Table 1.

It is correct that film-coated tablets should not usually be split, but the more important reason not to split Imuran tablets is that it is a cytotoxic drug. Splitting would be likely to release small particles into the air. Strangely though, Imuran tablets are scored. Apparently, the reason for this is that the tablets which are made in just one location are marketed in many countries, and at least one of them (Germany, I think) requires ALL tablets to be scored.

Jeff Lerner
Pharmacist
Southbank, Vic.

Editor, – The article 'Splitting tablets' (Aust Prescr 2002;25:133–5) outlines practical issues on the splitting of tablets. However, it does contain one deficiency. It fails to mention the potential problem associated with the splitting of tablets containing antineoplastic drugs.

Antineoplastic drugs are potentially toxic medicines and it is essential that patients and other healthcare workers adequately understand their correct use. Many antineoplastic drugs have been found to be mutagenic, teratogenic and carcinogenic on the basis of cell DNA and chromosomal studies, animal models and, to a lesser degree, experience in treated patients. The risk associated with occupational low-level exposure has not been determined. Therefore, without evidence to the contrary, risk is assumed to be present.

Tablets and capsules of antineoplastic drugs must be handled in a manner which minimises exposure to healthy individuals. This includes avoiding skin contact and liberation of powdered drug into the air. Based on this premise, antineoplastic drugs in tablet form should not be split or crushed, and capsules should not be opened. Where required, antineoplastic mixtures should be prepared according to accepted standards.

With the increasing number of oral cytotoxic drugs available on the market, prescribers and consumers must be made aware of the potential dangers, albeit small, in splitting these tablets.

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Dr J.L. Marriott and Professor R.L. Nation, the authors of the article, comment:

We thank the correspondents for their useful comments on our article. They are correct in suggesting that tablets containing antineoplastic drugs should not be split. To the best of our knowledge, all but one of the antineoplastic drugs available as tablets are marketed as unscored tablets; the one exception is the 50 mg strength of azathioprine tablet available under three brand names (Azuman, Imuran and Thioprine). In this case, it should not be necessary to even contemplate splitting a tablet as a 25 mg strength tablet is available from one of the manufacturers (Imuran). The 25 mg tablet is unscored and, as with other tablets of this type, should not be split.

Editor, – 'Splitting tablets' (Aust Prescr 2002;25:133–5) was a thought-provoking article on a subject that is not usually given much consideration by either practitioners or patients. I would like to add the following few comments on this topic.

1. In circumstances where the splitting of tablets is permissible, cost benefit improves the patient's compliance. A tablet of double strength may offer a 5–15% cost saving compared to half its strength (although this will vary between countries and products). This not only gives a psychological boost to the cost-conscious patient, but also gives a cumulative benefit for chronic diseases like hypertension and diabetes mellitus because of the increased compliance. Further, a patient when asked to take half of a tablet sometimes feels more secure than with a full tablet.
2. Digoxin has been cited as one of the examples for uneven breaking of a tablet that may lead to clinically significant fluctuations. Any fluctuation in the steady state plasma concentration usually requires nearly five half-lives. Digoxin, despite being a drug with a narrow therapeutic index, is far less likely to fluctuate in a significant manner even if the splitting of the tablet is uneven (even if it happens on a daily basis), because of its long half-life.
3. The article could also have suggested that patients should be warned not to consume split tablets which are altered in colour, consistency and contour because of the risk of adverse effects or ineffectiveness.

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Off-label promotion and prescribing of gabapentin

Editor, – We write to take issue with the article 'Gabapentin documents raise concerns about off-label promotion and prescribing' (Aust Prescr 2003;26:18–9) and the associated editorial comment. Statements in the article are unfounded and are not relevant to the promotion of gabapentin by Pfizer in Australia, which has always been in accordance with the terms of its registration and the Medicines Australia Code of Conduct.

The use of gabapentin for the treatment of neuropathic pain was approved by the Therapeutic Goods Administration (TGA) in 2000. It is therefore not surprising, as the author notes, that there is an 'increasing use' of this drug for this purpose. Use of a simple comparison of sales trends for gabapentin, lamotrigine and vigabatrin to argue that gabapentin is being promoted inappropriately is misleading. Lamotrigine is subject to a boxed safety warning, and concerns about well-documented adverse effects on visual fields may have directed prescribers away from vigabatrin.

The Cochrane Collaboration[1] may have found 'surprisingly few trials' supporting anticonvulsant use in the treatment of chronic pain. However, the two studies involving gabapentin[2,3] were pivotal in nature and provided the basis for the TGA's approval after evaluation. Three subsequent randomised controlled studies[4,5,6] – the last an independent study not sponsored by the manufacturer – have confirmed the effectiveness of gabapentin in the treatment of neuropathic pain in a wide range of diseases. In light of this, it would be more accurate to say that there is scant evidence of anticonvulsants, **other than** gabapentin (i.e. conventional anticonvulsants), being effective in chronic pain.

In summary, gabapentin has now been shown in five well-designed and published studies of 1095 patients to be effective and acceptably safe for the treatment of neuropathic pain.

While not promoting the use of gabapentin in unapproved indications, Pfizer maintains the right to respond in a professional and balanced manner to doctors' questions about unregistered uses of gabapentin or any other product, allowing doctors to observe the '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'.[7] It is then the doctor's prerogative to decide whether gabapentin should be used in such conditions.

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Complementary medicine interactions

Editor, – I refer to the articles 'It's natural so it must be safe' and 'Interactions between complementary medicines and warfarin' (Aust Prescr 2002;25:50–1, 54–6). I would like to draw your attention to the finding that patients may be using complementary medicine while they are in hospital.

A three-week study in a Sydney hospital found that 61 (12%) of the 511 patients, who had their medication history recorded by a clinical pharmacist, were taking a total of 156 complementary medicines (including vitamins). A high proportion (47%) of the complementary medicines had been self prescribed and 25 (41%) patients were taking complementary medicines without the knowledge of their general practitioner. After admission to hospital 22 (36%) patients continued taking 47 different complementary medicines, but only half of these complementary medicines were recorded in the patients' charts.[1]

Eleven (18%) patients were taking drugs which could potentially interact with the complementary medicines they were taking. Six patients were taking more than one potentially interacting complementary medicine. The use of complementary medicines is significant and warrants routine inclusion in the patient medication histories. Information about potential interactions can be obtained from clinical pharmacists, drug information centres and the Therapeutic Advice and Information Service of the National Prescribing Service.

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Compliance in urban Aboriginal children

Editor, – Australian Aboriginal children experience the highest rates of bacterial respiratory diseases reported in the literature and often have poor treatment outcomes.[1]

Many tribal Aborigines are now sending their children to schools in capital cities. The children are set up in accommodation, often without adult supervision. Volunteers assist in everyday activities including attempting to oversee nutritional and medication needs.

These children are at risk of being unable to take their medications. In their home environment, they are used to having any medications given to them directly by bush health professionals.

In the urban situation, a child from a tribal environment who is prescribed an antibiotic to be taken three times daily for a number of days is just not going to do it. It has been the experience of volunteers who visit these children that unless they are there to give the medication, it is not going to be taken. Taking medicines themselves is just not part of the children's culture.

My plea would be to all prescribers to attempt to think of **once-daily** alternatives to multiple daily doses. Additionally, pharmacists dispensing for these children should be aware of limitations under which the volunteers operate and a discreet telephone call to the prescriber might be in order.

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Recommendations for warfarin in Victorian public hospitals

Editor, – There are currently two brands of warfarin available in Australia (Marevan and Coumadin), both manufactured by the Boots Company. These brands have not been demonstrated to be bioequivalent.[1] There is no clinical justification for both products, and availability contributes to potential medication errors and confusion for patients and carers.[2,3,4]

The problem has been considered by the Melbourne Teaching Hospitals' Drug Usage Group (MTHDUG). This consists of 11 member hospitals and 19 associate member hospitals and is an affiliate of the Victorian Drug Usage Advisory Committee.

MTHDUG approached the manufacturer in early 2001 suggesting that consideration be given to phasing out one of the brands, however it has been reluctant to do so. Consequently, MTHDUG after communication and feedback from key stakeholders with an interest in the monitoring and prescribing of warfarin has made the following recommendations:

1. that Coumadin, the more widely used brand, be the primary brand of warfarin to be stocked and prescribed in Victorian hospitals;
2. that Marevan will be supplied only if specifically requested for a particular patient.

The impact of this strategy will be limited initially to patients commencing warfarin therapy in public hospitals. It is hoped that other institutions and individual doctors who also start warfarin therapy will also consider only prescribing Coumadin. Substitution of Coumadin in patients whose INR is stable on Marevan will require close monitoring.

MTHDUG is notifying community pharmacists and general practitioners about the recommendations through a range of professional forums and publications. Assessment of the impact of these recommendations will be ongoing.

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Treatment of childhood obesity

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SYNOPSIS

Obesity in childhood and adolescence is common and is associated with significant psychological and medical morbidity. Effective management of obesity in this age group has a family-focused approach, especially with pre-adolescent patients. It helps families and young people make healthier food choices and provides ongoing support. Small achievable goals are set for behaviour change, such as reducing sedentary behaviour. The success of treatment is defined in a variety of non-weight-related and weight-related ways. There is little information available to guide the use of drugs in managing paediatric obesity, although clinical trials are currently underway.

Index words: overweight, physical activity, diet.

(Aust Prescr 2003;26:30–2)

Introduction

The early 21st century has seen the development of a global epidemic of obesity in many countries, including Australia.[1] Children and adolescents are increasingly affected. In 1995, 19–23% of Australian children and adolescents were overweight or obese. Between 1985 and 1995 the prevalence of being overweight in this age group had almost doubled and that of obesity had more than tripled.[2] The dramatic increase in obesity in the community is related to major environmental changes that have occurred over the past two decades, with people living more sedentary lifestyles and having access to energy-dense foods.

Children and young people with obesity often have significant disease-related psychological and medical morbidity, as well as an increased risk of premature death from cardiovascular disease. Once obese, the likelihood of remaining so into adulthood is very high, especially for the obese adolescent. Family doctors are well placed to intervene early and provide management of this significant problem.[3]

Raising the issue

The issue of obesity and its management needs to be raised sensitively. Obese children or adolescents are usually very concerned about their problem but may not specifically ask for help. This is often confounded by the fact that most obese children have obese parents. Some people will welcome the opportunity for immediate intervention, whereas in others you may simply be laying the foundation for later acceptance of therapy.

Clinical assessment of the obese child or adolescent

All obese children and adolescents should have a full history and physical examination performed.[4] Their height and weight should be measured and body mass index (BMI; weight/height^2) calculated. As BMI varies normally throughout childhood, it should be plotted on BMI-for-age charts such as those available from the US Centers for Disease Control web site.[5] Waist circumference can be used as a proxy for abdominal obesity. Complications that should be sought on physical examination include hypertension, acanthosis nigricans (thickened pigmented skin indicative of insulin resistance), striae, intertrigo, hepatomegaly (fatty liver) and an abnormal gait due to joint problems. Warning signs of other, rare, causes for the obesity include short stature and developmental delay. Drugs such as corticosteroids can also be a cause for obesity. In patients with severe obesity, especially if there is a family history of diseases associated with insulin resistance, test for dyslipidaemia, insulin resistance, glucose intolerance and liver abnormalities. A history of sleep apnoea should be sought, but this can be difficult to identify by questioning.

Therapeutic goals

Treatment 'success' will involve non-weight-related outcomes, as well as weight-related outcomes. These include:

- an improvement in self-esteem
- an increase in healthy lifestyle behaviours for the whole family
- an improvement in the comorbidities of obesity
- parental or patient realisation that long-term behaviour change is required
- weight maintenance or weight loss, or, in the still-growing child, a decrease in the rate of weight gain
- a decrease in waist circumference.

Weight loss targets are generally not set when managing overweight and obesity in childhood. For example, the younger child may be able to 'grow into' an appropriate weight adjusted for height. The primary goal should be behavioural change.

Family-focused approach

Families influence food and activity habits and thus effective therapy of obesity must be family focused. Several studies have shown that long-term maintenance of weight loss can be

achieved when the intervention is family based.[6,7] Altered lifestyle patterns within the whole family, as well as parental modelling and support of the child, are all important factors in a successful outcome. Often several family members or other carers may need to be engaged in the therapy, either directly or indirectly.

Pre-adolescent versus adolescent patients

A developmentally appropriate approach to management needs to be used. For example, there is increasing evidence that treatment of pre-adolescent obesity with the parents as the exclusive agents of change is superior to an approach principally centred on the child. Indeed, focusing on the child in the treatment program may result in an increase in anxiety and withdrawal from therapy.[7] When dealing with the obese pre-adolescent child, sessions involving the parent or parents alone, without the child being present, are the most effective. However, a different approach is clearly needed for the adolescent patient. The few studies of the management of adolescent obesity suggest that it may be most effectively managed when the adolescent patients and their parents have the opportunity to attend at least some support sessions separately.

Physical activity

An increase in physical activity during treatment is a long-term predictor of maintained 'non-obesity'. The type of activity (i.e. 'lifestyle' exercise versus 'programmed' exercise) also appears to be important for sustained weight loss. While both forms of exercise help promote initial weight loss, the child or adolescent is more likely to continue long-term with the 'lifestyle' form of activity. This includes activities that can be incorporated readily into the child's or adolescent's lifestyle, for example walking, cycling, swimming, dancing to music, informal ball games and playing outside. Obese children, or their families, should be encouraged to incorporate some opportunities for incidental activity into their everyday lifestyle:

- is it possible to walk part or all of the way to or from school?
- are there safe parks or cycleways nearby where children can play?
- think of activity as fun, rather than as 'doctor-prescribed exercise'
- keep a ball or a frisbee or a skipping rope in the car
- parents should not fetch and carry for their children – small chores provide an opportunity for incidental activity
- star charts can be used for simple self-monitoring
- adolescents may appreciate having a companion for activities.

Reducing sedentary behaviour

Interestingly, encouraging a decrease in sedentary behaviour may be more effective than aiming for an increase in physical activity. If families and young people are encouraged to be aware of situations when they are being sedentary, then they may more readily choose to be active. The following should be considered:

- how many hours per day are television, videos, video games or computers used and can this be decreased (e.g. to a maximum of two hours per day)?
- is the family car used to take children to and from school or other short journeys?

Changing food choices and eating behaviour

Involvement of the entire family in making a change to a sustainable and healthy food intake is usually vital. This is because changes in shopping and cooking practices, and altered attitudes to snacking and mealtimes, may all be required. Essentially, the focus should be on behaviour change rather than a prescribed diet. Vulnerable eating behaviours in the family may include skipping breakfast or lunch, having regular high fat snacks, drinking large volumes of soft drinks or fruit juice, snacking frequently in the after-school period and regularly having take-away meals or eating out. A healthier food intake may include the following:

- using low-fat dairy products
- increasing amounts of fruit and vegetables
- stocking a range of low-fat snacks that the child enjoys
- making time to eat breakfast
- eating meals together as a family
- drinking water with meals
- planning non-food rewards e.g. toys, CDs, outings to the park
- taking lunch from home to school.

Indications for referral

The vast majority of children and adolescents who are overweight or obese can be managed in the community by their family doctors or other health professionals. However, those with significant metabolic complications of obesity, or with growth failure or other signs suggestive of endocrine or genetic disease, will need referral to a paediatrician or specialist clinic. In a very small proportion of obese children and their families significant psychosocial disturbance may be present – this warrants referral to a specialist child and adolescent psychiatric service.

Follow-up

Several frequent visits in the initial period (e.g. once every week or fortnight) may be required in order to discuss progress in making small lifestyle changes and also to set new, achievable goals. Subsequent less frequent follow-up visits over the long term appear to be useful in supporting the parent or young person in making sustainable lifestyle changes. Referral to an accredited dietitian for additional support in making lifestyle changes may be of help.

Other therapies

The current clinical management of paediatric obesity involves behavioural therapy. There is little information to guide the use of other treatment approaches (for example, very low calorie diets, obesity surgery, drug therapy or hospitalisation), although there may be a role for their use in morbidly obese patients. Experience from adult studies suggests that they need to be used in the context of a behavioural management program. No drugs are currently approved for the treatment of paediatric obesity, although therapeutic trials are underway with drugs such as orlistat and sibutramine. Such therapy, if used at all, should only be given in a specialist setting.

Conclusion

Obesity is increasingly prevalent in childhood and adolescence. Family doctors are well placed to manage this problem. Effective management of obesity in this age group will include:

- having a family-focused approach, especially with pre-adolescent patients
- setting small, achievable goals for behaviour change
- targeting sedentary behaviour
- helping families and young people to make healthier food choices
- providing ongoing support as families and young people make sustainable lifestyle changes.

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Conflict of interest: none declared

Self-test questions

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

1. The management of childhood obesity should involve the whole family.
2. An obese child with short stature requires further investigation.

Your questions to the PBAC

Availability of bulking and osmotic laxative agents as pharmaceutical benefits

During my research for a presentation on managing constipation and the use of laxatives in the aged-care setting for our local nursing home, I consulted published guidelines and other references for information. My search also included the Schedule of Pharmaceutical Benefits. It was then that I became aware just how difficult it is for prescribers to follow guidelines in this area. Stimulant laxatives (such as bisacodyl) are covered quite comprehensively, despite being considered as third- or fourth-line agents by the guidelines. Bulking agents and osmotic agents are poorly covered in the Schedule, but are listed as first- or second-line treatments in most of the references I consulted. This anomaly has resulted in the common use of stimulant laxatives at our facility (and, I suspect many others) when non-pharmacological interventions have failed. Can the PBAC consider widening the restrictions on these agents, particularly lactulose, to include residents of aged-care facilities? Ease of use makes lactulose especially attractive. A laxative-free nursing home may be a dream, but a stimulant-free one may be achievable!

Alison Hilet
Pharmacist
Moama, NSW

PBAC response:

The Pharmaceutical Benefits Advisory Committee (PBAC) is legally required, in evaluating applications for Pharmaceutical Benefits Scheme (PBS) subsidy, to take into account the clinical effectiveness, safety and cost-effectiveness (value for money) of the medication concerned compared to other available therapies.

Importantly, a medicine cannot be subsidised via the PBS unless the PBAC makes a positive recommendation. In other words, a decision by the Committee not to recommend a medicine be subsidised is binding on the Government.

The PBAC has considered the listing of lactulose for the treatment of patients in domiciliary or nursing home care in the past. However, the PBAC was of the opinion that lactulose is an expensive synthetic disaccharide which is no more effective than other cheaper osmotic laxative preparations, and it is associated with abdominal discomfort in a number of patients. The Committee felt that further widening the indication would encourage unnecessary and definitely non-cost-effective use.

The PBAC is reluctant to recommend laxative products for listing on the PBS and considers that other measures such as modification of diet can be used in the treatment of constipation in most patients.

Anticholinergic bronchodilators

J. Paul Seale, Professor of Clinical Pharmacology, University of Sydney, and Consultant Physician, Department of Respiratory Medicine, Royal Prince Alfred Hospital, Sydney

SYNOPSIS

Inhaled atropine causes bronchodilatation, but systemic absorption via the lung results in unwanted adverse effects. Ipratropium bromide and tiotropium bromide are structural analogues of atropine which have minimal systemic absorption following inhalation because of their quaternary ammonium structure. These anticholinergic drugs are useful bronchodilators in chronic obstructive pulmonary disease. They are rarely indicated in asthma. Bronchodilators provide symptomatic relief and improve health-related quality of life in patients with chronic obstructive pulmonary disease, but they do not influence the decline in lung function. The only measure currently known to halt this decline is stopping cigarette smoking.

Index words: chronic obstructive pulmonary disease, ipratropium bromide, tiotropium bromide.

(Aust Prescr 2003;26:33–5)

Introduction

The pharmacological properties of anticholinergic drugs have been recognised for over 100 years. Stramonium, a member of the Datura genus of plants, is a commonly mentioned source of anticholinergic bronchodilator therapy in 19th century medical literature. Burning the roots, stems and seeds of these plants created an aerosol of potent alkaloids, particularly atropine, which is the prototype of the currently used anticholinergic drugs. In the 1950s asthma cigarettes, made from stramonium, were widely used. With the subsequent availability of preparations of pure atropine sulfate for nebulisation, there was no further use of stramonium.

The popularity of these treatments declined with the advent of inhaled beta adrenoceptor agonists and because of the systemic anticholinergic adverse effects of nebulised atropine. More recently, structural analogues of atropine, such as ipratropium and tiotropium (which are not readily absorbed via the lung), have been developed as inhaled bronchodilators.

Vagal innervation of the lung

Cholinergic nerve fibres arise in the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve in the brainstem. They travel down the vagus nerve to parasympathetic ganglia within the walls of the airways. From these ganglia, short postganglionic fibres innervate airway smooth muscle and the submucosal glands in the lung. Activation of motor vagal nerve fibres releases acetylcholine at the neuro-effector junctions, where it binds to postsynaptic receptors, resulting in bronchoconstriction. Stimulation of the vagal nerve fibres innervating submucosal glands leads to an increase in mucus secretion.

Animal studies show that cholinergic innervation is greatest in larger airways and diminishes peripherally. Studies in humans have shown that cholinergic bronchoconstriction occurs mainly in larger airways whereas bronchodilatation induced by beta adrenergic drugs occurs in both large and small airways. The resting bronchomotor tone in normal airways has a cholinergic component, because giving an anticholinergic drug such as atropine causes bronchodilatation while the inhalation of edrophonium, an acetylcholinesterase inhibitor, results in bronchoconstriction.

Muscarinic receptors

The effects of vagal stimulation in the lung are mediated via muscarinic receptors. These receptors mediate the mucus secretory response to vagal nerve activation. Cholinergic agonists will stimulate mucus secretion from both submucosal glands and from goblet cells within the epithelium. These goblet cells are a major source of mucus in peripheral airways.

There are several different subtypes of muscarinic receptor. The muscarinic receptors on airway smooth muscle belong to the M_3 subtype and the presynaptic muscarinic receptors on vagal motor nerve fibres belong to the M_2 subtype. These M_2 receptors are called autoreceptors because their activation by acetylcholine inhibits further release of acetylcholine from the nerve terminals.

Anticholinergic bronchodilators

Atropine

Giving atropine, either systemically or as a nebulised solution, results in bronchodilatation. Inhaled doses of 2.5 mg atropine are associated with adverse effects such as dryness of the mouth, tachycardia, palpitations and blurred vision. With higher inhaled doses, systemic absorption can result in urinary retention (particularly in the elderly), headache and changes in mental status. Atropine is therefore no longer given as a nebulised solution.

Ipratropium bromide

Ipratropium bromide is a structural analogue of atropine, with a quaternary nitrogen structure. This structure reduces the ability of the molecule to cross cell membranes. There is, therefore, less systemic absorption with nebulised ipratropium than with nebulised atropine. Ipratropium blocks methacholine-induced bronchoconstriction, and induces bronchodilatation

in patients with asthma and patients with chronic obstructive pulmonary disease (COPD). There are no measurable effects on sputum volume, sputum viscosity or mucociliary clearance with clinically recommended doses of ipratropium.

The maximal bronchodilatation with ipratropium, inhaled from a metered-dose inhaler, occurs with a dose of 40–80 microgram. Although some bronchodilatation is evident soon after inhalation the maximal response occurs 1.5–2.0 hours afterwards. The duration of significant bronchodilatation after a standard dose of ipratropium is 4–6 hours.

Ipratropium cannot be detected in the blood after an inhalation. In experimental studies, where it has been given parenterally, its half-life has been estimated to be three hours. Long-term studies have shown no evidence of diminished responsiveness (tachyphylaxis) with regular therapy.

The main adverse effects of ipratropium relate to its anticholinergic activity. Up to 15% of patients will report transient dryness of the mouth and 'scratchiness' in the throat. In some studies up to 30% of patients have reported a bitter taste. These adverse effects rarely lead to patients discontinuing the drug if they perceive that it is helping them. Cardiovascular effects (tachycardia and increased cardiac output), which are typical of beta agonists (if taken in sufficient doses to result in systemic absorption) are not seen with the usual doses of ipratropium.

The main clinical indication for ipratropium bromide is the symptomatic relief of breathlessness in patients with COPD. It is rarely required for the treatment of patients with asthma because proper treatment of asthmatic patients with inhaled corticosteroids and long-acting beta agonists provides good control for the majority of patients. The extent of bronchodilatation with ipratropium in patients with COPD is similar to that achieved with inhaled beta agonists. The choice between ipratropium and beta agonists for a patient with COPD is determined by the patient's tolerance of the drug, rather than its efficacy. If troublesome adverse effects are encountered with either ipratropium or with beta agonists, the patient may well tolerate the other drug because the adverse effect profile for each drug is quite different.

Tiotropium bromide

Tiotropium bromide is a structural analogue of ipratropium. *In vitro* studies have shown that tiotropium has a half-life on the M_3 receptor of approximately 36 hours, whereas the receptor binding half-life of ipratropium is three hours. The duration of this binding to M_3 receptors may explain why a single inhaled dose of tiotropium results in bronchodilatation which lasts for approximately 24 hours. Large-scale clinical trials have shown that tiotropium inhaled once daily increases the forced expiratory volume (FEV_1) and quality of life in patients with COPD.

In comparative studies patients took tiotropium once daily, or ipratropium four times daily, for one year. Both drugs improved quality of life, but tiotropium resulted in a higher FEV_1 at the end of the dose interval.[1] Tiotropium also lengthened the time to first exacerbation and the time to first hospital admission due to an exacerbation of COPD. The number of patients who need to be treated with tiotropium for one year to prevent one exacerbation is nine, and 23 need to be treated to prevent one admission due to COPD.

Inhaled tiotropium is an effective once-daily anticholinergic bronchodilator in patients with COPD. There are no long-term studies of tiotropium in asthma so it is not indicated for patients with asthma.

Combination therapy

Anticholinergic drugs and beta adrenoceptor agonists produce bronchodilatation via separate mechanisms so there are theoretical reasons why they may be used in combination. Several studies have shown that the combination of ipratropium with a beta adrenoceptor agonist (either fenoterol or salbutamol) produces greater bronchodilatation than either drug alone.[2] None of these studies has investigated whether a higher dose of the single drug (either ipratropium or beta agonist) would have achieved the same result as the combination. However, a higher dose of either drug would carry with it the greater risk of unwanted adverse effects. Both beta agonists and ipratropium are therefore frequently used in combination to treat inpatients with acute exacerbations of COPD. There is also a place for the combination of beta agonists and ipratropium in maintenance therapy for COPD, primarily to minimise the risk of adverse effects with higher doses of either ipratropium or the beta agonist.

Delivery devices

Anticholinergic drugs are available as metered-dose inhalers or as solutions for nebulisation. Provided that patients use metered-dose aerosols properly, they are just as effective as nebulisers. Clinical studies in asthma in which bronchodilator administration by metered-dose inhalers (plus large volume spacer devices) has been compared with administration via nebulisers, show that the resultant bronchodilatation is comparable. Similar small studies in patients with COPD have shown that good inhaler techniques with metered-dose aerosols should be as effective as nebulised solutions in regular long-term therapy.[3] Large volume spacers and metered-dose aerosols are therefore the preferred method of drug delivery because they are cheaper than nebulisers and just as effective. The costs involved with nebulisers include both the purchase of the machine and the cost of the unit dose vials. This more expensive method of drug delivery should be reserved for patients who are unable to use a metered-dose aerosol and a large volume spacer.

Long-term outcomes

Although bronchodilators offer symptomatic relief in patients with COPD, no bronchodilators have been found to affect the annual decline in FEV_1. Smoking cessation is the only measure which is known to reduce the decline of FEV_1. Hence, the most important step that can be taken with patients with COPD is to stop smoking.

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Conflict of interest: Professor Seale has served on the advisory groups of several pharmaceutical companies which produce respiratory drugs, including GlaxoSmithKline and Boehringer Ingelheim.

Self-test questions

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

3. Anticholinergic bronchodilators are more effective than beta agonists.
4. Anticholinergic bronchodilators do not prevent the decline of lung function in patients with chronic obstructive pulmonary disease.

Medicinal mishap

Topical drug with systemic risk

Prepared by Lloyd Morgan, General Practitioner (retired), Lorne, Vic.

Case

A 75-year-old woman with hypertension and diabetes was prescribed warfarin for atrial fibrillation. During three and a half years of treatment her INR was 2.3–2.5.

When her INR rose to 14.1 on 27 February I thought it was a laboratory error (she displayed no bleeding) but told her to stop the warfarin. On 2 March the INR was 12.0, but she had developed huge bruises on all limbs and carpal tunnel pain. By 6 March the INR was 6.2, but the woman had bigger thigh and cheek haematomas. On 10 March the ecchymoses were subsiding and warfarin was resumed when the INR fell to 1.7.

Comment

The cause of this patient's problems was probably an interaction with an antifungal drug. Her dentist had prescribed amphotericin lozenges and miconazole oral gel on 9 February. She asked me on 13 February if these products might affect her warfarin, but as they were topical preparations I ignorantly reassured her.

Her dentist was also unaware of the potential interaction when the patient asked him about her warfarin. He may have been alerted had she been a surgical case rather than someone having her dentures fixed. The hospital pharmacy computer was not linked to her community pharmacist so there was no warning of the interaction between warfarin and miconazole.

Warfarin interacts with several antifungals including itraconazole, fluconazole and ketoconazole. The interaction may be mediated through the cytochrome P450 system.[1] Miconazole can inhibit the metabolism of drugs by cytochrome P450 3A and 2C9 and this is probably how it increases the effect of warfarin.

Although miconazole oral gel has a low bioavailability some is absorbed into the systemic circulation. This may be sufficient to cause a significant interaction with warfarin. Several reported cases involved bleeding.[2,3] As the consequences of bleeding can be catastrophic, high INR may require more intense treatment than this patient received.[4]

The interaction can also occur with other formulations of miconazole but may not be mentioned in the product information. There have been reports with topical cream[5] and vaginal pessaries.[6]

Conclusion

Topical medications can have systemic effects including drug interactions. As miconazole oral gel is available without a prescription, the public as well as health professionals need to be warned about the potential interaction with warfarin.

The case also serves as a reminder not to dismiss patients' concerns too quickly. A check of the product information would have alerted me to the interaction between miconazole oral gel and warfarin.

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Disease modifying drugs in adult rheumatoid arthritis

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SYNOPSIS

Effective treatment of rheumatoid arthritis now involves starting disease-modifying antirheumatic drugs at the time of diagnosis. This aims to slow development of the irreversible joint damage that leads to long-term disability. Many patients are treated with methotrexate. This is effective, but like other disease modifying drugs it has serious adverse effects. Monitoring patients is important particularly if they are taking a combination of drugs for their arthritis.

Index words: sulfasalazine, methotrexate, leflunomide.

(Aust Prescr 2003;26:36–40)

Introduction

Rheumatoid arthritis affects 1% of the Australian population. It is characterised by symmetrical polyarthritis involving the small joints of the hands and feet. Despite treatment, rheumatoid arthritis patients may still have progressive joint destruction, deformity and disability and a reduced life expectancy.

Rheumatoid arthritis should be suspected when there are three or more swollen joints, half an hour or more of morning stiffness and metacarpophalangeal or metatarsophalangeal joint involvement.[1] Early referral to a rheumatologist is recommended for a shared care approach. This allows accurate early diagnosis, and determination of baseline damage and disease activity with clinical, laboratory and radiographic markers. Markers of a poor prognosis include early bone erosions, a positive rheumatoid factor, genetic markers (HLA-DR4 subgroups), functional status and inflammatory markers.

General approach to drug therapy

Drug therapy is just one component in the treatment of rheumatoid arthritis, which also includes non-pharmacological treatments such as physiotherapy and exercises. All patients should be instructed in the self-adjustment of simple analgesics and anti-inflammatory drugs as these complement therapy with slow-acting disease-modifying antirheumatic drugs (DMARDs). The DMARDs are no longer withheld until radiographic joint erosions develop. They are now introduced at the diagnosis of rheumatoid arthritis, aiming at quick eradication of inflammation. It is important as their efficacy is greatest early in the course of the disease. Response to therapy with a single DMARD is often suboptimal and trials have found that combination therapy with methotrexate, sulfasalazine and hydroxychloroquine can be more effective.[2]

In Australia the first choices for rheumatoid arthritis treatment are methotrexate, sulfasalazine and leflunomide (see Fig. 1). They are usually begun as individual drugs or in combination with hydroxychloroquine. Their efficacy is similar so the choice of drug often relates to cost and restrictions under the Pharmaceutical Benefits Scheme (PBS), or to avoidance of adverse events secondary to alcohol consumption, sulfa allergies, or lack of contraception.

Short-term pulses of oral or depot intramuscular corticosteroids may be used to suppress flares of active rheumatoid arthritis at any stage of disease management. Similarly, intra-articular corticosteroids can be used by experienced clinicians to treat individual joints. Starting maintenance or prolonged therapy with oral corticosteroids should only be considered after treatment failures and consideration of the comorbidity they may induce.

A patient's response to therapy is optimally monitored using semi-objective criteria such as the duration of early morning stiffness, a self-reported scale for joint pain and level of functioning for household tasks, and counting of tender or swollen joints. These criteria are then combined with objective markers of inflammation (C-reactive protein and ESR) to evaluate disease activity.

Methotrexate

Although it has been in use since 1951, methotrexate is the current 'gold standard' of rheumatoid arthritis treatment. It has the highest rate of continued long-term treatment, maintaining efficacy without excessive toxicity and can be used alone or in combination. Methotrexate is proven to slow radiographic progression of disease, but it takes 6–8 weeks for the onset of benefit.

Mechanism of action

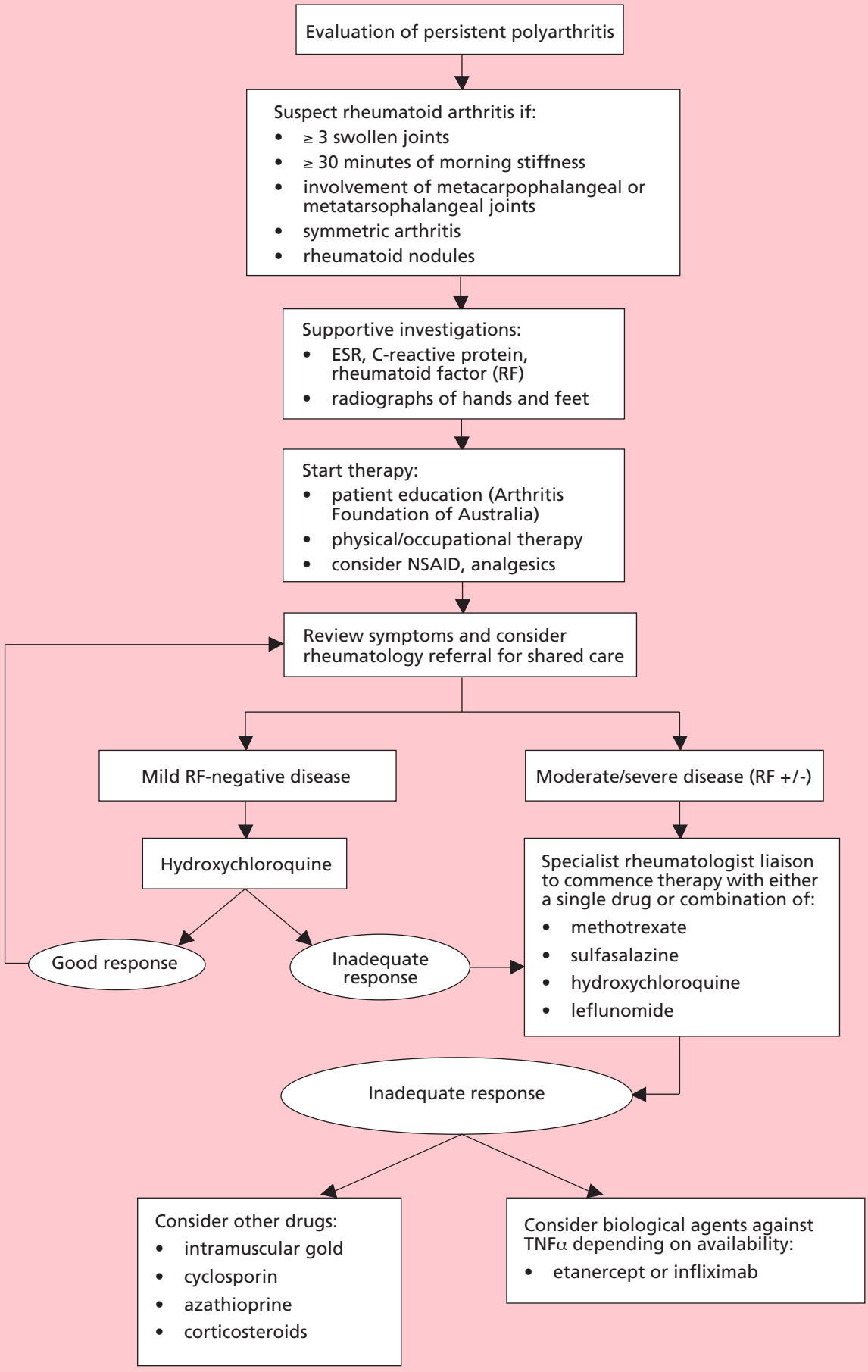
Methotrexate is a folic acid antagonist cytotoxic drug. By binding to dihydrofolate reductase, methotrexate interferes with DNA synthesis and cell replication.

Maintenance dose

For maintenance, patients ordinarily take a SINGLE WEEKLY dose of 7.5–20 mg (orally, or by intramuscular or subcutaneous injection). Intramuscular or subcutaneous weekly administration of the same methotrexate dose may reduce any nausea experienced with the oral route. It is very important that patients know that they should only take methotrexate once a week. Naming the day they should take their tablet can

Fig. 1

Management of rheumatoid arthritis



help them remember.[3,4] For example, methotrexate can be prescribed as 'Methotrexate 10 mg, take one tablet on Tuesdays ONLY'.

Co-prescription of both 2.5 mg and 10 mg tablets is not recommended, as the tablets may be confused especially by those with impaired eyesight.

Adverse effects

About 60% of patients may have mild toxicity, but less than 30% cease the drug in the first year because of adverse effects. Common adverse effects include nausea the day after the dose is taken, mouth ulcers, reversible alopecia, rash, and increased rheumatoid nodule formation. Rarer adverse effects include bone marrow suppression, hepatic fibrosis/cirrhosis (increased with alcohol consumption) and pulmonary infiltrates/allergic pneumonitis (possibly increased in smokers). Folic acid (0.5–1 mg/day) reduces gastrointestinal and mucosal adverse effects and is recommended as a concomitant prescription.

Monitoring

Patients should have a fortnightly full blood count, creatinine, and liver function tests for the first three months, monthly for three months, then six weekly thereafter once the dose is stable. Watch for changes in blood cells and monitor for 2–3 fold elevation (above the upper limit of the normal range) in liver enzymes (AST and ALT), or reduction in albumin. If, despite dosage adjustment or cessation of methotrexate, the AST or albumin are abnormal in at least five of the routine 6-weekly blood tests performed over one year, then a liver biopsy should be considered.

Contraindications

Methotrexate should not be used in patients with pre-existing bone marrow aplasia or cytopenias, immunodeficiency, severe hepatic disorders, or active infectious disease. Concomitant alcohol intake or hepatotoxic drugs are also contraindicated. Patients frequently ask about a safe level of alcohol consumption, but this has not been studied.

Drug interactions

Trimethoprim or trimethoprim-sulfamethoxazole can increase bone marrow suppression, probably by an additive antifolate effect. Non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates can inhibit the renal excretion of methotrexate. This is important for chemotherapeutic doses, but NSAIDs have no effect on the low doses of methotrexate used for rheumatoid arthritis and they can be cautiously co-prescribed. Patients and general practitioners must be aware of the pharmacy and prescribing software alerts that do not distinguish between low and high doses. Hepatotoxicity is potentially increased with the co-administration of azathioprine, sulfasalazine or leflunomide as part of combination therapy.

Advice in pregnancy/breastfeeding

Methotrexate was originally used as an abortifacient and is associated with congenital abnormalities. Breastfeeding is contraindicated because of neonatal immunosuppression, neutropenia and growth retardation.

Sulfasalazine

This drug contains an anti-inflammatory and antibiotic (acetylsalicylic acid and sulfapyridine), and slows the radiographic progression of rheumatoid arthritis. Used alone or in combination with methotrexate and/or hydroxychloroquine, it takes 6–12 weeks for the onset of its benefits.

Mechanism of action

Sulfasalazine is cleaved in the colon by bacterial enzymes to release acetylsalicylic acid and sulfapyridine. The method of action of sulfapyridine is unclear but may involve inhibition of the transcription factors which are increased in inflammation.

Maintenance dose

Patients take 1–1.5 g twice a day, starting at 500 mg/day and increasing by 500 mg a week. Some rheumatologists escalate the dose more slowly than this.

Adverse effects

Up to 30% of patients experience mild gastrointestinal disturbances (nausea, vomiting, loss of appetite, diarrhoea), skin rash and pruritus. Neurological symptoms of headache, dizziness or depression also occur. In males there is oligospermia with impaired motility. This does not act as a contraceptive and reverses three months after stopping treatment. Rarer adverse effects include leucopenia, bone marrow depression, haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency, abnormal liver function tests, hepatitis and abdominal pain. As sulfasalazine inhibits absorption of folate it can cause folate deficiency.

Monitoring recommended

Full blood count and liver function are tested every two weeks for three months, then three monthly thereafter.

Contraindications

Sulfasalazine should not be prescribed for patients who are hypersensitive to salicylates or sulfonamide derivatives. It is also contraindicated in patients with haematological, renal or hepatic dysfunction.

Advice in pregnancy/breastfeeding

Sulfasalazine can be used in pregnancy. Very small amounts of drug are found in breast milk, so it can be used cautiously by breastfeeding mothers.

Leflunomide

Leflunomide is the newest of the commonly used DMARDs. It has comparable clinical and radiographic efficacy to methotrexate and sulfasalazine. Due to its cost leflunomide is only subsidised by the PBS for patients in whom methotrexate is ineffective or inappropriate. While leflunomide is predominantly taken alone it is sometimes given with methotrexate, but this increases the risk of toxicity.

Mechanism of action

Leflunomide primarily inhibits replication of activated lymphocytes by blocking the *de novo* synthesis of pyrimidines and hence DNA. It also has a weak anti-inflammatory action.

Maintenance dose

A loading dose of 100 mg/day is given for three days. This is followed by 20 mg/day unless adverse effects necessitate 10 mg/day. A loading dose results in a faster time of onset of benefit compared to methotrexate. However, loading doses are increasingly not being used because of gastrointestinal adverse effects.

Adverse effects

The commonest adverse effects are nausea and diarrhoea which are experienced by 20–30% of patients, but they may settle with continued treatment. Skin rash and reversible alopecia occur in 5–10%. Elevations of liver enzymes (AST and ALT) occur with sole use of leflunomide, and affect up to 60% of patients if it is combined with methotrexate. Rarer adverse effects include severe bone marrow suppression, infections and persistent abnormal liver function tests despite dose reduction.

Monitoring recommended

Full blood count, creatinine, and liver function are tested monthly for the first six months, and 1–2 monthly thereafter. If combined with methotrexate, monthly testing is recommended.

Contraindications

Leflunomide should not be given to patients with severe immunodeficiency, impaired bone marrow function, or severe uncontrolled infections. As liver impairment is also a complication, excessive alcohol consumption should be avoided.

Drug interactions

Methotrexate increases the risk of hepatotoxicity in patients taking leflunomide. As leflunomide inhibits cytochrome P450 2C9, it can interfere with drugs such as phenytoin, warfarin and tolbutamide.

Advice in pregnancy/breastfeeding

Leflunomide is teratogenic and is contraindicated in both pregnancy and breastfeeding. Due to a prolonged enterohepatic recirculation, women should not conceive for one year after stopping treatment, unless they have a 'washout' procedure with cholestyramine (8 g three times a day for 11 days). Men wishing to father a child should consider discontinuing leflunomide and undergoing a cholestyramine washout.

Hydroxychloroquine

Primarily used in combination with other drugs, hydroxychloroquine may be used as the sole drug in patients with mild rheumatoid arthritis and the absence of adverse prognostic factors. It has a slow onset (2–6 months) and has been shown to improve long-term functional outcome, although no studies have been undertaken to document retardation of radiographic damage.[5]

Mechanism of action

Hydroxychloroquine interferes with antigen presentation and the activation of the immune response by increasing the pH within macrophage phagolysosomes.

Maintenance dose

Treatment begins with 200–400 mg daily for 1–3 months. Once a response is achieved, the dose can be reduced to 200 mg daily.

Adverse effects

Gastrointestinal symptoms predominate (epigastric burning, nausea, bloating, diarrhoea). Skin rashes and alopecia are common and hydroxychloroquine may exacerbate psoriasis. Patients may develop hyperpigmentation in sun-exposed areas. Retinal toxicity with macular damage is rare, but patients should wear sunglasses in strong sunlight. Corneal deposits (reversible if the drug is ceased) are seen in less than 0.1% of patients but the risk increases if the dose exceeds 6 mg/kg/day.

Monitoring recommended

Ophthalmological monitoring is a controversial area because it was originally developed for chloroquine with its greater ocular toxicity. Patients taking hydroxychloroquine should have a baseline ophthalmologic review (colour vision, visual fields, fundoscopy), especially if they have pre-existing eye disease or diabetes, and then six-monthly thereafter. No specific laboratory monitoring is required.

Contraindications

Patients with pre-existing maculopathy should not take hydroxychloroquine.

Advice in pregnancy/breastfeeding

Hydroxychloroquine should be avoided in pregnancy. Low concentrations are found in breast milk, therefore caution is recommended if the patient is breastfeeding.

Gold injections

Gold has been used in the treatment of rheumatoid arthritis since 1927. It was one of the first drugs to demonstrate retardation of radiographic damage, but in the last 20 years, injectable gold has moved from being first-line treatment to at least fourth. A genuinely slow-acting drug, gold often requires therapeutic trials of up to six months.

Mechanism of action

Gold affects lysosomal membranes and inactivates lysosomal enzymes within the synoviocyte.

Maintenance dose

After test doses for allergy, patients start with 50 mg intramuscularly every week for about six months (or until 1 g total). They then continue on 25–50 mg every 2–4 weeks.

Adverse effects

There is a high attrition rate. Most of the 30% of patients who develop symptoms within the first year cease treatment. Skin rashes (pruritus, erythema, eczema), mouth ulcers and diarrhoea are common. Less common are bone marrow suppression (thrombocytopenia, aplastic anaemia, agranulocytosis) or membranous glomerulonephritis with proteinuria. The reaction of flushing, hypotension and sweating that occurs shortly after

an intramuscular injection of aurothiomalate is uncommon but frightening. Rare effects include gold deposits in the lens or cornea (reversible with cessation of therapy), peripheral neuropathy, Guillain-Barré syndrome and encephalopathy.

Monitoring recommended

The urine should be tested for protein at the time of each injection. A weekly full blood count to check for neutropenia and eosinophilic reaction is recommended for the first three months and 2–4 weekly thereafter.

Contraindications

Gold is contraindicated in patients with gross renal or liver disease, diabetes, or blood dyscrasias. Other contraindications include exfoliative dermatitis or a history of hypersensitivity to gold.

Advice in pregnancy/breastfeeding

Gold crosses the placenta and is not recommended during pregnancy, although there is no evidence of increased neonatal malformations. It is also not recommended during lactation as gold is excreted in breast milk and absorbed by the infant.

Future directions

A major advance in the treatment of rheumatoid arthritis has been the development of biological therapies, in particular drugs directed against the pro-inflammatory cytokine TNF-α.[6] Etanercept, a recombinant soluble TNF-Fc fusion protein, and infliximab, a chimeric anti-TNF monoclonal antibody, are approved for the treatment of refractory rheumatoid arthritis. Patients improve rapidly (within weeks) with these drugs and have less radiographic progression compared with methotrexate alone. However, disadvantages are the need for parenteral administration (subcutaneous or intravenous routes), the high cost and the absence of long-term safety data when used in the broader community. The annual costs of these new drugs have to be weighed against the personal and societal expense of joint replacements, hospitalisations and disability. They are likely to be restricted to patients with active ongoing joint inflammation despite oral corticosteroid therapy and treatment with the standard therapies.

Conclusion

The goals of rheumatoid arthritis treatment are to slow disease progression and achieve remission. Early liaison with a rheumatologist will enable earlier assessment and commencement of DMARD treatment to improve the long-term outcome of rheumatoid arthritis.

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Conflict of interest: none declared

Self-test questions

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

5. Patients with rheumatoid arthritis who are going to respond to hydroxychloroquine usually show evidence of benefit within one month of starting treatment.
6. Patients taking methotrexate for rheumatoid arthritis should take their dose on the same day each week.

Patient support organisation

Arthritis Foundation of Australia

See page 45

Controlling intravascular catheter infections

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SYNOPSIS

Sepsis related to intravenous catheters is the commonest cause of bloodstream infections in Australia. The risk of infection is highest with percutaneous central venous catheters, somewhat lower with tunnelled or subcutaneous catheters, and lowest with peripheral intravenous catheters. The best prevention is removal of intravenous lines when they are no longer necessary. Optimal insertion techniques and line maintenance are also important. Once infection occurs, the line should generally be removed. Antibiotic therapy is directed against suspected micro-organisms (usually staphylococci) and modified with the results of cultures. If septic shock occurs general supportive measures including intravenous fluids, inotropic drugs and observation in an intensive care unit will also be necessary.

Index words: sepsis, bacteraemia, bloodstream.

(Aust Prescr 2003;26:41–3)

Introduction

Intravenous catheters are indispensable in modern medicine and are no longer restricted to hospital inpatients. There is a growing number of patients on 'home' intravenous therapy, predominantly for total parenteral nutrition or cancer chemotherapy. However, these devices are increasingly associated with sepsis and are now the commonest cause of all bloodstream infections. These infections cause significant morbidity and mortality.

Rates of intravascular catheter-associated bloodstream infections

In Australia, there are at least 3500 cases of intravenous catheter-associated bloodstream infections annually. These are associated with a case fatality rate of 24%, and the mortality rate directly attributable to intravenous catheter sepsis is 12%. This equates to 1.5 bloodstream infections per 1000 admissions.[1]

Percutaneous central venous catheters are associated with 23 bloodstream infections per 1000 catheters. In contrast, catheters in peripheral veins are associated with only 0.36 bloodstream infections per 1000 catheters.[2] Peripheral vein catheters remain *in situ* an average of 1.5 days, while central venous catheters remain *in situ* about four times longer (an average of 5.5 days). The daily infection risk with central venous catheters is about 20 times that of peripheral catheters. Tunnelled or surgically implanted catheters (Hickmans, Portacath) and peripherally inserted central venous catheters appear to have a quarter the daily risk of percutaneous central venous catheters, but they still pose a much higher risk than peripheral catheters.

Why there is such a disproportionate infection rate of central venous catheters is unclear. It may reflect the poorer health of patients requiring this type of therapy as well as the longer duration of intravenous access in this group. The infusion of total parenteral nutrition, the use of triple lumen (versus single lumen) catheters, and some catheter insertion sites (jugular and femoral sites in particular) are independent risk factors. However, all these factors only partially account for the marked differences in daily infection risk rates.

Of concern, is the observation that a large number of intravenous catheters (including central venous catheters) in hospitalised patients are not in active use for prolonged periods of time but remain *in situ* 'just in case'. Also, some catheters are being used for interventions that are not necessary (for example, total parenteral nutrition when nasogastric feeding is possible).

Pathogenesis

There are several modes of colonisation with pathogens.[3] At the skin entry site, the outer surface of the catheter can become colonised with organisms originating from the skin. These bacteria can then migrate proximally along the catheter's surface to reach the bloodstream. Alternatively, the catheter's inner surface may become colonised by introduction of organisms through the catheter hub (e.g. from the hands of hospital staff). Rarely, micro-organisms may be introduced by contaminated infusate (especially total parenteral nutrition). The point at which colonisation changes to invasive infection is unclear, but it is thought to be related to the number of organisms present on the catheter, and is time dependent (infection is rare within the first 48 hours of catheter placement).

The role of biofilms (collections of bacteria adherent to the catheter surface and organised within an extensive glycocalyx) is important. Although micro-organisms in biofilms are visible on microscopy, they are often unculturable, and are protected from the effects of antibiotics. If biofilms are present, cure is usually only possible by removing the catheter.

Table 1

Major pathogens with approximate frequencies[2]

Pathogens	*Frequency*
Coagulase-negative staphylococci	35%
Staphylococcus aureus	25%
Yeasts (especially candida species)	10%
Enterococci and streptococci	10%
Pseudomonas species	5%
Enteric Gram negative bacilli (e.g. Klebsiella)	15%
Other	5%

Microbiology

Skin-associated micro-organisms are the predominant isolated pathogens (see Table 1). Coagulase-negative staphylococci (e.g. *Staphylococcus epidermidis*) are the commonest, possibly because they appear to have the best adherence to inert surfaces. *Staphylococcus aureus* infections are second in frequency, with the infection risk being highest in patients with neutrophil defects or venous thrombophlebitis. Enteric mucosal micro-organisms such as enterococci, *Enterobacteriaceae*, pseudomonas, and candida species may colonise the catheter either by colonising the skin, by colonising the infusate (especially total parenteral nutrition) or by haematogenous seeding from mucosal breaches.

Diagnosis

In the majority of bloodstream infections associated with central venous catheters, there will be little or no evidence of sepsis at the insertion site (in contrast to infections associated with peripheral vein catheters).

The diagnosis of catheter-associated bloodstream infection requires a positive culture of blood from a peripheral vein and clear evidence implicating the catheter as the source. The culture of 15 or more colonies of a pathogen from a catheter tip is diagnostic of catheter-associated bloodstream infections. Unfortunately, this method only has a positive predictive value of 16–31% because most catheter tip cultures are negative.[4]

Another approach to diagnosis (which conserves the catheter) is simultaneous culture of blood drawn peripherally and blood drawn from the catheter. As the density of organisms is greatest in the catheter specimen (if it is the source of sepsis), the catheter blood culture will usually become positive at least two hours earlier than the peripheral blood culture (using the Bactec system). This technique has been reported to have a sensitivity and specificity of greater than 90% and a positive predictive value of approximately 80%.

Treatment

Catheter removal is usually essential in all cases of catheter-associated bloodstream infections, with the exception being some cases associated with Hickmans or Portacath catheters. Even with these, catheter removal is still essential if *Staphylococcus aureus* or candidal septicaemia occurs and strongly recommended if Gram negative bacilli (due to likelihood of treatment failure) are isolated from blood cultures.

If low virulence organisms such as coagulase-negative staphylococci are isolated, removal of the line itself may be sufficient to resolve the infection, but usually the patient is also treated with one week of intravenous antibiotics. If a Hickmans or Portacath is involved and is not removed, the patient is treated with two weeks of intravenous antibiotics. This may control the infection in 80% of cases, however, if the bacteraemia or fever persist despite appropriate antimicrobial therapy, the central venous catheter must be removed.

If bloodstream infection is suspected and the catheter is replaced, the new central venous catheter should not be passed over a guide-wire at the same venepuncture site. If it is, the new catheter will almost certainly be contaminated with the same organism (see Table 2 for further prevention issues).

While awaiting blood culture results, empiric therapy to cover staphylococci and Gram negative bacilli (i.e. vancomycin, or flucloxacillin in combination with an aminoglycoside) is the best initial treatment. The regimen may be modified once the pathogen is identified.

If *Staphylococcus aureus* is isolated, treat with antibiotics (e.g. flucloxacillin if sensitive) for a minimum of 14 days after catheter removal (4–6 weeks therapy if persistent fevers or a suspected distant focus of infection). If candida is isolated,

Table 2

Prevention of catheter-related infection

General measures

- Do not insert an intravenous catheter unless essential (would oral therapy suffice?)
- Adequate skin preparation and aseptic technique
- Full aseptic technique for central venous catheters (gowns, gloves and drapes)
- Cover site with sterile, semi-permeable dressing
- Disinfect access sites before use
- Scrupulous hand hygiene by staff
- Remove catheter when no longer clinically necessary

Type and site of catheter

- Use peripheral catheter rather than central catheter if possible
- Routinely replace peripheral catheters within 48–72 hours (no evidence for routine replacement of central venous catheters)
- Peripherally inserted venous catheter instead of subclavian/jugular/femoral central venous catheter if possible
- If central venous catheter used, the subclavian site has the lowest infection risk, whilst the jugular vein and femoral vein sites have the highest infection risks
- Use a peripherally inserted venous catheter or tunnelled central venous catheter or totally implantable device if more than 14 days access predicted
- Use central venous catheters with as few lumens as possible
- Catheters with surface irregularities, polyvinyl chloride or polyethylene are associated with higher infection risks
- Antibiotic or antiseptic impregnated catheters can reduce sepsis rates with central venous catheters especially if a unit has a high rate of catheter-associated sepsis

treatment is generally with a triazole (e.g. fluconazole) for at least 14 days after the last positive blood culture. The fungal isolate should be fully identified, as species other than *Candida albicans* are often resistant to triazoles.

If the patient remains febrile after removal of the device, three sets of blood cultures should be obtained. Endocarditis or septic thrombophlebitis should be suspected if blood cultures remain positive for more than 48 hours after the device has been removed.

Conclusion

Catheter-related sepsis is a common complication of modern medical therapy. Reduction of this complication may be achieved by minimising intravenous access. If there is no absolute need for intravenous access, remove the intravenous line. Use peripheral access rather than central venous catheters wherever possible. When central venous catheter access is necessary, use peripherally inserted venous catheters or tunnelled/implanted lines if possible. If bloodstream infections occur, removal of the intravenous line is essential, with only a few exceptions (Hickmans- or Portacath-associated bloodstream infections with low virulence organisms such as coagulase-negative staphylococci).

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Self-test questions

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

7. Removal of the catheter is necessary in patients with catheter-related bloodstream infections caused by *Staphylococcus aureus*.
8. Central venous catheters inserted at the subclavian site have a higher risk of infection than those inserted into the femoral vein.

Book review

Paediatric Pharmacopoeia

Melbourne: Women's and Children's Health, Royal Children's Hospital; 2002.

The book is available in three formats. (Prices include GST but not postage.)

- Paediatric Pharmacopoeia, 13th ed. $49.50
- Paediatric Pharmacopoeia – Pocket Prescriber, 1st ed. $9.90
- Paediatric Pharmacopoeia e-book. $99
- 3-set package, one copy of each. $143

Peter D. Jones, Associate Professor of Health, The University of Newcastle, Director, University Department of Rural Health, Northern NSW, Tamworth, and Chair of the Specialist Advisory Committee for General Paediatrics, Royal Australasian College of Physicians

The three versions of Paediatric Pharmacopoeia make up an excellent resource to help with the prescribing of drugs to children. They are published by the Pharmacy Department of the Royal Children's Hospital, Melbourne. In their current format they are very useful references for doctors treating children in hospital or emergency department settings.

The Pocket Prescriber appears to be a new publication. It offers an alternative to Frank Shann's Drug Doses[1], which is the current booklet used in hospitals throughout the country to help calculate doses in children. The Pocket Prescriber is a larger, heavier and more expensive booklet than Drug Doses (86 mm wide versus 72 mm wide, 100 g versus 50 g, $9.90 versus $6.50), but still fits into the top pocket of my standard business shirt. It is filled with excellent information and it is good to see the antibiotic guidelines in the booklet. It is well presented with a much sturdier red cover than Drug Doses and I think its slight increase in size and weight means that it will be less easy to lose on the wards. This booklet should be an essential piece of equipment for all doctors working with children in a hospital setting. Hospitals should ensure that staff who prescribe and administer drugs to children have a copy of this book and refer to it frequently because I am certain that it could lead to fewer prescribing errors in hospital care.

The Paediatric Pharmacopoeia, 13th edition, is another very useful little book that contains some extra information and specific warnings about each drug. The e-book is easy to navigate and has the most potential to be a useful resource for general practitioners and paediatricians who are prescribing for children in the community. It is easy to find the immunisation schedule, and with time the guidelines may start to have more relevance to community-based rather than hospital-based care. The e-book does contain information about the presentation options of particular drugs (i.e. tablet and mixture strength) and the different trade names available in Australia. I believe the e-book could be improved by including information regarding Pharmaceutical Benefits Scheme prescriptions to make this package of resources more applicable to doctors working outside the hospital setting.

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Ethical perspectives on the communication of risk

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SYNOPSIS

Ethical clinical practice requires good communication about the risks of treatment causing harm. As health professionals and patients often have different perceptions of risk, it is important to discuss risk in terms the patient can understand. Even if a patient is willing to take the risks, health professionals have an ethical obligation not to recommend inappropriately risky treatments. Giving patients time to reflect on what a particular decision means for them is an important part of communicating information about risks.

Index words: consumers.

(Aust Prescr 2003;26:44–5)

Whenever a doctor recommends a course of therapy it is essential that the reasoning underlying this advice is discussed with the patient, together with an outline of potential risks, benefits and maybe alternatives. This is not merely because free choice is important but also because it is a part of the doctor's role within the clinical encounter to help patients learn about the nature, consequences and courses of their illnesses and to facilitate reflection about the personal meanings attached to them.

Clinical communication is complex, generally finely balanced, with both style and content requiring constant adjustment in relation to contextual and personal variables. The concept of 'risk', and the way it is used in the clinic, is complex, with the word having several possible meanings and many connotations. Significant discrepancies often exist between patients' and clinicians' use of the word risk. While for doctors, a risk may be defined in precise, mathematical terms – for example, as the probability of the occurrence of a particular adverse event – how such a definition is interpreted by a patient in the clinical setting can be highly variable.[1,2]

A complication in discussions of risk is that people make decisions for reasons that are not always entirely rational. They accept risks as a routine part of work, recreational and sporting activities. Many people are prepared to take complementary medicines in the absence of evidence of safety or efficacy, and the limited success of public health campaigns against alcohol and tobacco use emphasises that avoiding risk is not the sole criterion guiding people's decisions about their health. Even when risks are clearly recognised the implications are not straightforward. For example, the female sex partners of injecting drug users with good knowledge about HIV risk often continue to engage in risky behaviour.[3]

Extensive research has provided useful information that can assist in the development of effective communication about risk. For example, common perceptions of risk are based on both objective considerations and subjective judgements.[1] While objective considerations are important for the analysis of probabilities and consequences, subjective judgements determine the interpretations individuals place on these calculations in their own personal lives.

Good communication always requires an appreciation of the values of each participant in the discussion. Social science research has repeatedly emphasised that individual perceptions of risk may be affected by personal factors, which may be linked to values.[4,5] These include:

- demographic factors such as age and gender
- education and early experiences
- the nature of the risk, its consequences and alternatives
- portrayal of risk in the media and popular culture
- the availability of information
- the degree of personal trust in the regulatory authorities.[6,7]

For example, women are more likely to perceive greater risk than men in the use of alcohol and other drugs[8], and education may lead either to increased or decreased concern with risk. Demographic factors and difficulties in understanding information may influence a patient's decision to participate in medical research.[9] Personality and psychological characteristics are also of great importance.[10]

An 'optimistic bias' is often expressed with respect to health risks.[11,12] The risks are often underestimated by those who take them, both in specific areas, such as HIV and drug taking[13], and more generally.[14] Accordingly, the responsibility of a doctor does not cease with the approval or acquiescence of the patient. Rather, regardless of the patient's views, the clinician has an obligation not to embark on or recommend reckless or inappropriately hazardous treatments. This means that recommendations must be able to be supported by evidence, or at least strong arguments.

The quality and quantity of available evidence can vary, clinical contexts themselves are extremely diverse, and evidence from large-scale clinical trials may have limited applicability to specific conditions. It has become commonplace to refer to the notion of a 'risk:benefit ratio', which weighs beneficial outcomes against potential harms. This concept[15] for the most part has little rigorous content or validity, since perceptions of risk vary according to context, and the perception of benefits also varies.

There are no algorithms to guarantee adequate communication. Factual information is important, but is not in itself sufficient. Formalised definitions of risk, such as those of the International

Commission on Radiological Protection[16] (which defined risk as the probability of a harmful outcome such as lethal cancer) and the tendency to insist on stereotyped formulations to explain the meanings of probabilities by drawing comparisons with common experiences (like driving a certain distance in a motor car) do not necessarily enhance communication. Nor do they help individuals to make sense of risk in their own particular contexts. Similarly, rigid policies or strategies about communication of risk aimed at achieving predetermined outcomes are likely to be ineffective. Neither purely factual campaigns nor those based on fear can reliably change people's behaviour.[9,10]

Clinicians should assist patients to reflect upon the possible personal consequences of a proposed course of action and to make sense of the information provided in relation to their own personal value systems. Communication of risk must be tailored to the needs and levels of understanding of individual patients. Both the circumstances and the content of communication are important. Privacy and an unhurried, secure setting may be critical. The use of words is important, with ordinary use of language being preferred over technical jargon wherever possible. Different patients will have different requirements regarding standards of proof of risk, safety and benefit and will arrive at different conclusions. Part of the everyday responsibility of the doctor is to respond with openness and flexibility to such differences.

In summary, communication about risk in medicine is a multifaceted process. Objective criteria, factual data, and ongoing research are essential, but need to be supplemented with an awareness of the broader, ethical context within which the clinical process is framed.

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Conflict of interest: none declared

This article is the final one in a three-part series on risk. See also

- 'Perceptions of risk – a legal perspective' by J. McPhee in Vol. 25 No. 5, October 2002
- 'Variation in perceptions of risk between doctors and patients: risks look different when they are close to home' by H. Bastian in Vol. 26 No. 1, February 2003.

Patient support organisation

Arthritis Foundation of Australia

(See Disease modifying drugs in adult rheumatoid arthritis, page 36)

The Arthritis Foundation of Australia, which began as the Australian Rheumatism Council, is an advocacy, research and fundraising body. It aims to improve the quality of life of people who have arthritis or a related condition, those who care for them, and people at risk of developing arthritis, by reducing and preventing the effects of musculoskeletal disorders.

Arthritis Foundations in every State and Territory provide group meetings, a range of activities and talks, and self-management programs for both arthritis and osteoporosis. In these programs people learn about medications and develop strategies to manage their condition such as balancing exercise and rest, managing stress, and undertaking physical treatments such as hydrotherapy and physiotherapy.

The Arthritis Foundation produces fact sheets on forms of arthritis and treatments, endorsed where appropriate by the Australian Rheumatology Association. The Foundation seeks cures, preventions and better treatments by supporting scientific and medical research into arthritis.

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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.

Fibrin sealant

Tisseel Duo 500 (Baxter)

1.0 mL, 2.0 mL and 5.0 mL kits, each containing a syringe of sealer protein solution and a syringe of thrombin solution

Approved indication: surgical haemostasis

Australian Medicines Handbook section 7.4

This product is a sealant which can be used as an adjunct to surgical techniques for controlling blood loss. It can also be used as an adjunct in the closure of colostomies.

In addition to fibrinogen, the kits contain vials of thrombin, calcium chloride and a fibrinolysis inhibitor. The fibrinogen is reconstituted with the fibrinolysis inhibitor solution and the thrombin is mixed with the calcium chloride solution. Syringes containing the two mixtures are then loaded into a device which delivers equal volumes of each mixture to the wound. The thrombin converts the fibrinogen to fibrin which seals the wound. It takes two hours for the sealant to reach its full strength, but it reaches 70% strength in 10 minutes. The fibrinolysis inhibitor then stops the fibrin being broken down too quickly. As the preparation can take up to 40 minutes the product is unsuitable for unexpected brisk bleeding.

Topical applications of sealants have been used successfully to reduce bleeding in facial surgery, knee arthroplasty, skin grafting, vascular reconstruction and cardiac surgery. Other studies, for example of tonsillectomy, show no advantage.

There is limited published information on this particular sealant preparation. Its fibrinogen and thrombin components are derived from blood donations so there is a potential for transmitting infection. The fibrinolysis inhibitor has a bovine origin so some patients may have hypersensitivity reactions to cow protein.

A laboratory study compared a range of fibrin tissue adhesives. It found that this product took longer to prepare than a cryoprecipitate from a single donor, but had a greater binding power.[1] Although this fibrin sealant could be made up in advance of a procedure, it has to be discarded after four hours. It is also much more expensive than autologous preparations.[1]

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Tadalafil

Cialis (Eli Lilly)

10 mg and 20 mg tablets

Approved indication: erectile dysfunction

Australian Medicines Handbook section 13.3

The treatment of impotence changed when sildenafil was launched in 1998. Over 17 million men have been prescribed

sildenafil and in 2001 it generated sales of US$1.5 billion. There is therefore a large potential market for oral treatments of erectile dysfunction.

Although it has a different structure, tadalafil acts in the same way as sildenafil. It inhibits the phosphodiesterase type 5 enzyme to reduce the inactivation of cyclic guanosine monophosphate (cGMP). This inhibition helps to maintain the smooth muscle relaxation, in the corpus cavernosum of the penis, which produces an erection. As the production of cGMP requires the release of nitric oxide in response to sexual arousal, tadalafil will have no effect in the absence of sexual stimulation.

Tadalafil is more slowly absorbed than sildenafil. The median time to the maximum concentration is two hours compared to one hour. In addition, tadalafil has a much longer half-life than sildenafil (17.5 hours versus 4 hours). It can still be effective 36 hours after a dose. Tadalafil is mainly eliminated by metabolism. This metabolism involves cytochrome P450 3A4 so there is a potential for interactions with drugs which inhibit or induce this enzyme.

Few of the clinical trials of tadalafil have been published in full. Overall the efficacy of tadalafil 20 mg for successful sexual intercourse is 75% compared with a placebo response of 32%. The efficacy is likely to be less in patients with diabetes.

Only 1.7% of patients in clinical trials stopped treatment because of adverse events, but 26% had at least one adverse effect. Headache and dyspepsia are the commonest adverse effects. As tadalafil causes vasodilatation it can provoke flushing and falls in blood pressure. It may therefore potentiate the effect of antihypertensive drugs. Tadalafil is contraindicated in patients taking nitrates. As the clinical trials excluded men with unstable cardiovascular disease, tadalafil should not be prescribed for these patients. These contraindications include men with a recent history of stroke, heart failure or myocardial infarction and those with unstable angina or uncontrolled hypertension or arrhythmia.

Although tadalafil is a more potent inhibitor of phosphodiesterase type 5 than sildenafil is, the clinical relevance is uncertain. There appear to be no published trials which compare the two drugs or investigate if patients who do not respond to one drug will respond to the other. As tadalafil causes fewer ocular adverse effects it may have a role in patients who have developed abnormal vision while taking sildenafil, however there are no reports of this usage.

Answers to self-test questions

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

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