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CELEBRATING 30 YEARS

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CONTENTS

Combination inhalers for asthma

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Summary

Patients whose asthma is not well controlled by inhaled corticosteroids may benefit from the addition of a long-acting beta$_2$ agonist. The effects of inhaling a corticosteroid and a long-acting beta$_2$ agonist can reduce symptoms, improve lung function and prevent exacerbations. Once the patient's asthma is controlled it may be appropriate for them to use one of the combination inhalers which contain both types of drug. These combination inhalers may not be more efficacious than inhaling the drugs separately, but they are more convenient.

Key words: budesonide, eformoterol, fluticasone, salmeterol.

(Aust Prescr 2005;28:26–8)

Introduction

Combination inhalers that include both a corticosteroid and a long-acting beta$_2$ agonist are now available for the treatment of asthma. There are currently two combinations in Australia and they have a variety of doses and inhaler devices.

The rationale for the use of combination therapy [1]

Asthma is a chronic inflammatory condition of the airways in which the predominant inflammatory cells are eosinophils.

In this issue…

Drugs for asthma and hypertension always appear in the Top 10 drugs. Although the charts contain several new antihypertensives, Suzanne Hill and Tony Smith remind us that older drugs still have a role. Many patients with hypertension need more than one drug and there is also an increased use of combined therapy in asthma. Christopher Worsnop discusses whether combination inhalers have any advantage over the separate administration of the drugs they contain.

Patients may need a combination of antibiotics if they are at risk of surgical infection. Overuse of antibiotics leads to resistance, so Wendy Munckhof advises on when prophylaxis is indicated.

Surgical patients may need a blood transfusion. As supplies are scarce, James Isbister reviews the factors which need be addressed before blood is ordered.

Inhaled preparations of corticosteroids have become the standard treatment for asthma as these cells are sensitive to their effects.[1,2]

The airway inflammation also produces increased reactivity in bronchial smooth muscle, leading to bronchoconstriction. Stimulation of beta$_2$ adrenergic receptors on smooth muscle cells causes relaxation of bronchial smooth muscle. Beta$_2$ agonists are therefore used for quick relief of bronchospasm. Patients with persistent asthmatic symptoms used to take regular doses of short-acting beta$_2$ agonists, but there was concern that such regular use may worsen asthma and increase asthma deaths. When long-acting beta$_2$ agonists were developed, there were similar concerns. However, it is now clear that they are of benefit, although they should not be used without an inhaled corticosteroid to treat asthma.[1,2]

The interaction between corticosteroids and beta$_2$ agonists

In addition to bronchial smooth muscle, beta$_2$ adrenergic receptors are also present on other cells in the airways including mast cells and vascular endothelium. With chronic use of beta$_2$ agonists, these receptors become down-regulated. However, this can be balanced by the concurrent use of corticosteroids because corticosteroids can interact with the beta$_2$ receptor gene to increase the production of beta$_2$ receptors *in vitro*.[1,2]

Inflammation can desensitise beta$_2$ receptors, and beta$_2$ stimulation can inhibit some aspects of inflammation, such as mast cell mediator release, and plasma exudation from post-capillary venules. Both of these effects can be prevented by corticosteroids. In turn, beta$_2$ agonists can increase the actions of corticosteroids by interacting with glucocorticoid receptors in the nucleus and enhancing their binding to DNA.[1,2]

The appropriate dose of corticosteroids

It has been difficult to demonstrate the dose-response characteristics of inhaled corticosteroids in asthma because the improvement in asthma with steroids takes time and is variable across individuals. However, it is apparent that there is a relatively flat dose-response curve above 1000 microgram per day of beclomethasone or equivalent (1000 microgram per day of budesonide or 500 microgram per day of fluticasone). This means that most control of the airway inflammation is achieved with a low dose of inhaled corticosteroids. Systemic effects can occur at doses at or above 1000 microgram per day of beclomethasone or equivalent. The addition of long-acting beta$_2$

agonists shifts the dose-response curve to the left, so the same benefit is achieved with lower daily doses of the steroid.

Once a patient's asthma is controlled, consideration should be given to reducing the dose of inhaled corticosteroid. Exactly when and how this should be done is not clear as there is insufficient evidence. However, the Global INitiative for Asthma (GINA) guidelines[3] suggest that the patient should be stable for at least three months, and the Australian National Asthma Council guidelines state that dose reduction should be considered after asthma has been stable for 6–12 weeks.[4] Leaving patients on high doses of inhaled corticosteroids can lead to systemic adverse effects, and is not appropriate. Adding a long-acting $beta_2$ agonist may enable a reduction in the dose of corticosteroid.

Clinical data

There have now been many good quality studies showing that the control of moderate or severe asthma can be improved by adding a long-acting $beta_2$ agonist to therapy with inhaled corticosteroids. Adding a long-acting $beta_2$ agonist is superior to doubling the dose of inhaled corticosteroid, or increasing the steroid even further, in gaining control of asthma which is not well controlled. This has been demonstrated across a range of outcomes including asthma symptoms, nocturnal wakenings, use of short-acting $beta_2$ agonist medication, asthma free days, health-related quality of life, asthma exacerbations, spirometry and expiratory peak flows. When attempts are made to reduce the dose of inhaled corticosteroid in patients with stable asthma, the addition of a long-acting $beta_2$ agonist allows a greater reduction in the steroid dose than can be achieved with placebo.

Long-acting $beta_2$ agonists have also been compared with placebo, theophylline and leukotriene receptor antagonists, such as montelukast or zafirlukast, in patients with asthma that is not well controlled with inhaled corticosteroids. They are superior to placebo and theophylline, and have produced similar or better outcomes when compared with adding a leukotriene receptor antagonist to inhaled corticosteroids.

A meta-analysis (called 'MIASMA') of nine parallel group trials compared increasing the dose of inhaled corticosteroids with the addition of salmeterol to inhaled corticosteroids in patients with symptomatic asthma.[5] The daily doses of steroids in patients at the time of randomisation in these trials were 200–1000 microgram of beclomethasone, or 200–500 microgram of fluticasone. Adding salmeterol had benefits which included greater morning peak flows, increased FEV_1*, a higher percentage of days and nights without asthma symptoms, and a higher percentage of days and nights without a need for rescue medication with short-acting $beta_2$ agonists. These benefits were present at three months and six months. There were also fewer exacerbations in patients who added salmeterol. To prevent one exacerbation, 40 patients need to be treated with salmeterol compared with increasing the inhaled corticosteroid dose. The number needed to treat to prevent an asthma exacerbation with inhaled fluticasone varies from 2.1 to 2.9 with daily doses from 1000 microgram to 100 microgram.[6]

With such evidence supporting the combined use of both types of drugs in asthma, it was logical to combine them into one inhaler. Studies comparing single inhalers with inhaling the drugs from separate inhalers have found no disadvantage with the combination products.

The Gaining Optimal Asthma controL (GOAL) study compared a combination of fluticasone/salmeterol with fluticasone alone in 3500 patients with asthma that was not well controlled. A step-up approach was used, with patients starting on a lower dose, and then increasing it after 12 weeks if their asthma was not totally controlled. The fluticasone/salmeterol combination led to a greater proportion of patients having totally or well controlled asthma, with fewer exacerbations, and better health-related quality of life than those receiving fluticasone alone. These benefits were seen in patients who had already been taking inhaled corticosteroids before entering the trial, as well as in those who had not taken steroids before.[7]

Advantages of combination inhalers

It is more convenient for patients who require two asthma drugs to use one, rather than two, inhalers. Another advantage is that it is not possible to stop the steroid if both drugs are given in a single inhaler. This addresses the concern that patients using two inhalers would be tempted to use just the long-acting $beta_2$ agonist, as it produces a symptomatic improvement faster than steroids can. There is a cost advantage in using a combination inhaler instead of two separate inhalers and there is the possibility that indirect costs may also be reduced. The patient's asthma may be better controlled with the combination and, as a lower dose of inhaled corticosteroid may be needed, the adverse effects can be minimised.

Potential limitations of combination inhalers

A possible limitation with any combination preparation is the lack of flexibility in dosing. This is not such an issue with combination inhalers as there are six different strengths of the fluticasone/salmeterol products and two of the budesonide/eformoterol products (Table 1). The eformoterol dose can be increased as the dose in these products is below the maximum that can be used, so patients can vary their dose during exacerbations.

Another limitation is that patients may use the inhaler to relieve bronchospasm and get much higher doses of inhaled steroid than intended, particularly if they have an inhaler that contains a high dose of steroid. To avoid this, judicious prescribing is required with some thought given to the dose of steroid that

* forced expiratory volume in one second

Table 1

Combinations of inhaled corticosteroids and long-acting beta$_2$ agonists available in Australia

Combination	Device	Dose delivered (microgram)
budesonide/eformoterol (dry powder)	Turbuhaler	200/6
		400/12
fluticasone/salmeterol (dry powder)	Accuhaler	100/50
		250/50
		500/50
(aerosol)	Metered dose inhaler	50/25
		125/25
		250/25

each patient needs. Certainly, prescribing the maximum dose for all is not appropriate. If a patient is on a high dose of inhaled corticosteroid, whether in a single drug inhaler or a combination inhaler, the need for the high dose should be reviewed regularly, and the dose reduced if the patient's asthma has been stable for several months at least. Patients also need to be well educated about how to deal with any deterioration in their asthma. In some circumstances, increasing the dose of the combination inhaler would be appropriate, but in others, alternative strategies may be required.

The inhalers are simple and easy to use so there is a temptation to prescribe them to anyone with respiratory problems, including patients with chronic obstructive pulmonary disease. This temptation should be resisted, as the combination inhalers are primarily indicated for asthma. The diagnosis of asthma should not be taken lightly as it usually commits patients to long-term medication. This means that patients must change their attitude to their health as they should monitor their asthma regularly with expiratory peak flow charts, and have plans to enable them to deal with exacerbations.

When to use combination inhalers

The Australian National Asthma Council guidelines suggest adding a long-acting beta$_2$ agonist to inhaled steroids if the patient requires a short-acting beta$_2$ agonist more than once daily in moderate asthma. Combination therapy is recommended for all patients with severe asthma. The GINA guidelines suggest that both moderate and severe persistent asthma should be treated with inhaled corticosteroids and a long-acting beta$_2$ agonist. When starting treatment, the Australian guidelines begin with a higher dose of inhaled steroids. The GINA guidelines suggest starting intensive treatment including combination therapy to get asthma under control quickly and then reducing the dose when the asthma is stable, or starting with lower doses in less severe asthma and increasing treatment if needed. As there is no evidence comparing the different approaches, the options remain open.

Prescribing restrictions on combination therapy

Combination inhalers are a restricted benefit if they are prescribed under the Pharmaceutical Benefits Scheme. They are restricted to patients who have previously had frequent episodes of asthma while receiving optimal doses of inhaled corticosteroids, or oral corticosteroids, and who have been stabilised on the relevant inhaled corticosteroid used concomitantly with the relevant long-acting beta$_2$ agonist.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 51)

1. The efficacy of asthma treatment with a long-acting beta$_2$ agonist and a corticosteroid is significantly enhanced if they are combined in a single inhaler.
2. Patients inhaling a corticosteroid for their asthma may be able to reduce the dose if a long-acting beta$_2$ agonist is added to their therapy.

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.

Paracetamol

Editor, – The articles 'The vascular effects of COX-2 selective inhibitors' (Aust Prescr 2004;27:142–5) and 'Perioperative analgesia' (Aust Prescr 2004;27:152–4) advised physicians to opt for paracetamol as a first-line analgesic. Given that the major barrier to more widespread use of paracetamol is the need for at least four doses per day, is there any evidence regarding the benefits or otherwise of extended release paracetamol, and should these drugs be on the Pharmaceutical Benefits Scheme (PBS)?

Nicholas McLernon
Resident Medical Officer, Obstetrics
Osborne Park Hospital
Osborne Park, WA

Professor R.O. Day and Professor G.G. Graham, authors of 'The vascular effects of COX-2 selective inhibitors', comment:

The idea of a sustained release paracetamol is very reasonable. The reduction in the number of daily doses would make long-term therapy with paracetamol more convenient. The problem is that the dose is large and the optimal sustained release tablet, say one that would last for 12 or even 24 hours, would be very large and too difficult to swallow. Cost-effectiveness would also need to be established for it to be subsidised by the PBS.

The dwindling need for selective COX-2 inhibitors

Editor, – Regarding the article 'The vascular effects of COX-2 selective inhibitors' (Aust Prescr 2004;27:142–5), I agree that 'Low-dose aspirin or other anti-thrombotic treatment should be continued in patients receiving selective COX-2 inhibitors who are at risk of thrombosis'. However, one must ask why would we choose selective COX-2 inhibitors instead of conventional non-steroidal anti-inflammatory drugs (NSAIDs) for patients taking anti-platelet therapy?

In the CLASS study, patients who took celecoxib and aspirin (approximately 20% of nearly 8000 patients) had the same annualised incidence of symptomatic ulcers and upper gastrointestinal ulcer complications as patients taking aspirin with an NSAID (either ibuprofen 800 mg tds or diclofenac 75 mg bd).[1] The literature suggests that the principal 'advantage' of upper gastrointestinal safety is lost when a COX-2 inhibitor is co-prescribed with aspirin.

Published reports also show that patients taking COX-2 inhibitors appear to have only slightly fewer upper gastrointestinal symptoms (such as dyspepsia) than patients treated with conventional NSAIDs.[2]

The COX-2 inhibitors have a substantial cost premium, but marginal safety advantages in some selected patients. With reference to your recent editorial 'Expensive new drugs – do we really need them?' (Aust Prescr 2004;27:136–7), the data would suggest that the COX-2 inhibitors are another example of expensive new drugs with an unclear cost-benefit value for the Pharmaceutical Benefits Scheme.

Paul Kubler
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Professor R.O. Day and Professor G.G. Graham, authors of the article, comment:

Dr Kubler is correct in stating that, in the CLASS study, patients treated with celecoxib and aspirin had the same incidence of upper gastrointestinal complications as patients receiving the non-selective non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac or ibuprofen. A similar result was found in the TARGET study of the COX-2 selective drug, lumiracoxib, versus naproxen or ibuprofen.[1] It has, however, been suggested that a selective COX-2 inhibitor and low-dose aspirin should be used with a gastroprotective drug, such as a proton pump inhibitor or misoprostol, in patients at high risk of gastrointestinal damage, although the value of such combinations is presently unknown.[2]

The comparative effects of the COX-2 selective drugs and the non-selective NSAIDs on dyspepsia is a more difficult question because many patients in clinical trials note that they have dyspepsia even when they are taking placebo. Consequently, the occurrence of dyspepsia during treatment with the COX-2 selective inhibitors can only be evaluated from controlled clinical trials when placebo was administered.

It is therefore of note that the incidence of dyspepsia and related effects during treatment with celecoxib was very similar to that recorded during dosage with placebo, but markedly lower than during treatment with naproxen.[3]

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Rofecoxib withdrawal

Editor, –The article 'The vascular effects of COX-2 selective inhibitors' (Aust Prescr 2004;27:142–5) is now out of date. The COX-2 selective inhibitors including rofecoxib, celecoxib, meloxicam and diclofenac (diclofenac is about as selective as celecoxib) have never been shown to have an overall advantage over less selective anti-inflammatory drugs for any patient group.[1] There has never been a good justification for prescribing any of these drugs outside of a trial. The huge ongoing death toll could have been avoided in 1999–2001 but regulators, companies, patients' groups and educators have all done too little too late and many have pulled in the wrong direction. Our organisation, Healthy Skepticism, is one of the few who did warn against COX-2 selective inhibitors but we did not have the resources to get our message across.[2,3]

The root cause of this disaster is a vicious cycle of misleading drug promotion and inappropriate prescribing. We call for a Royal Commission to investigate major reforms that could avoid similar disasters in the future and dramatically improve medical research and health care.[4] The first step forward is to understand and accept that a major easily avoidable disaster has occurred. We urge *Australian Prescriber* to become part of the solution by publishing an article accurately summarising all the relevant evidence about COX-2 selective inhibitors.

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Quality use of generic medicines

Editor, –The excellent editorial, 'Quality use of generic medicines' (Aust Prescr 2004;27:80–1) states 'confusion could be greatly reduced if generic names of the drugs were required to be **more prominent** [my emphasis] on the label than the 'brand' names'.

Recently, I was called to an elderly lady who had collapsed and was unable to get up from the floor. She was severely hypotensive because she had taken a double dose of enalapril, one that I had prescribed for her and one with a different brand name, prescribed by a locum doctor.

This is such an obvious danger that it needs to be confronted before more severe accidents and deaths occur.

How can the labelling requirement suggested in the *Australian Prescriber* editorial be brought about?

Peter Gould-Hurst
General practitioner
Campbelltown, SA

Dr Leonie Hunt, Director, Drug Safety and Evaluation Branch, Therapeutic Goods Administration, comments:

The issue of safe labelling of prescription medicines is under review in several areas. The Australian Pharmaceutical Advisory Committee (APAC) has a working party that is reviewing the issue of brand substitution generally. Looking at labelling specifically, the legal requirements for labelling of medicines are contained within both Australian government and state/territory legislation. The Therapeutic Goods Administration (TGA), through its Labelling Orders, regulates matters such as the minimum font size of lettering that may be used and essential information that must be included on labels for prescription medicines. The Labelling Order is currently under review.

The TGA has also been working with stakeholders from the health professions, industry and consumer groups to develop a Best Practice Labelling Guideline for Prescription Medicines.

The draft version of this document recommends equal prominence be given to the active ingredient or generic name and the brand name and makes recommendations on other aspects of label design to try to ensure that all relevant information is clearly presented to health professionals and consumers. This includes advice that both medicine names need to be displayed on at least three sides of the container for standard packaging.

Signing the script

Editor, – I would like to commend Dr Nisselle and *Australian Prescriber* for the editorial 'Signing the script' (Aust Prescr 2004;27:108–9), which raised awareness of the responsibilities that medical practitioners assume when they prescribe on the Pharmaceutical Benefits Scheme (PBS). Unfortunately, the 1973 legislation Dr Nisselle quoted relates to Medicare rather than pharmaceutical benefits.

The relevant legislation is found in regulation 19B of the *National Health (Pharmaceutical Benefits) Regulations 1960.* This states that it is an offence to write a prescription bearing the letters 'PBS' when it is not a PBS prescription.

A prescriber who prescribes a medication under the PBS for a condition which falls outside the PBS indications may be committing a criminal offence under the *National Health Act 1953.* The relevant legislation is found in Paragraph 103(5)(g) of the *National Health Act 1953* and states that a person shall not:

> by means of impersonation, a false or misleading statement or a fraudulent device, obtain, or by any of those means aid or abet another person to obtain, a pharmaceutical benefit or a payment in respect of the supply of a pharmaceutical benefit;

A prescriber acting in this manner may also be referred to a Professional Services Review Committee to determine whether or not they have engaged in inappropriate practice.

J. Trabinger
Manager
PBS Compliance Branch
Health Insurance Commission
Canberra

Editor, – Dr Nisselle reminds us that a judge can imprison us, under current legislation, for making therapeutically effective and cost-effective treatment decisions.[1] There are instances with 'SPs' where deeming that as '... criminal fraud' is both irrational and unacceptable.

Experienced professionals tend not to respond to threatening behaviour, even when it originates from official bodies that accord themselves the status of 'authorities'. Some categories of rules, and laws, can only ever aspire to be guidelines. The proportions that are neither enforced, nor monitored, attest to that historical reality. The legislation has never been systematically enforced for many SPs during its 30-year existence. Draconian threats of imprisonment and fines are counter-productive and one suspects they have diminished respect for, and co-operation with, those 'authorities'. Few doctors in our town would be available for consultations if the regulations were enforced.

Education may change doctors' behaviour. Unfortunately the situation has evolved where an undue portion of doctors' knowledge about drugs emanates from drug companies. Authorities have lessened their funding and leadership roles; it might be preferable to balance the drug company billions spent on advertising with more non-partisan funding and leadership, rather than the threats in the legislation. Drug representatives take doctors to dinner, not to prison; they have (sadly) achieved greater influence over the profession.

Ken Gillman
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Dr P. Nisselle, author of the article, comments:

Though Dr Gillman may see the statutory sanctions as empty 'threats' (as, at least for 'SP' prescribing, they are rarely enforced), they are still law, and law made to place some discipline on the use of taxpayer funds. The PBS is the most rapidly growing component of the Commonwealth's funding of health care. While doctors hate the gate-keeper role that is thrust on them, for example, by restricted benefits, we also hate it when new medications are refused a PBS listing at all.

Those sections of the Act are to remind us of our responsibilities. We are not responsible for the Government's decision as to what drugs are, or are not, available under the PBS. Our responsibility is not to break the law. We give patients advice. If that advice is, that they take a medication which is not available to them as a PBS benefit, then we need to advise them of that fact and tell them of the cost. It is then a matter for them, whether they wish to pay that cost, or ask you to prescribe a cheaper alternative, or possibly be referred to an agency which will provide the medicine at no direct cost. It is not for us to make a social judgment that it is unfair for a particular patient to have to pay a full private fee for a particular medication and then, accordingly, ignore the law. If you feel strongly enough about it, lobby your local member, etc., to have the drug's classification changed. In the interim, don't 'bend' the law.

The use of Latin

Editor, – Dr Nisselle's remarks on the legal significance of prescription writing are very much to the point (Aust Prescr 2004;27:108–9). I would like to take him up on the statement that 'prn' is an antiquated Latin abbreviation, when in the next column he uses an equally antiquated Latin term, 'mens rea', no less than three times. This term is one of a whole library of Latin terms used by the legal fraternity to befuddle the rest of the population. Why choose 'prn' when there are 'bd', 'tid', 'bid', 'ac', 'pc' and many other Latin abbreviations, some of which get more use than 'prn'. Used properly these abbreviations are very helpful in saving time and space.

In the 1950s there was an arrangement between Yugoslavia and the UK for reciprocal medical treatment of visitors. Inevitably, some British tourists fell sick and returned home with summaries of their treatment. These were written in Latin so I was able to translate the diagnosis and treatment. I would not have been capable of doing this if the summaries had been in one of the local languages.

I might add that I was not a Latin scholar, having as much trouble with 'ut' and the subjunctive as anyone. However, I think medicinal Latin was a very useful attribute and I do regret its loss.

L.A. Lees
General practitioner
Dapto, NSW

Dr P. Nisselle, the author of the article, comments:

Like Dr Lees, I have both nostalgic and practical reasons for personally wanting to retain Latin abbreviations in medicine. Nostalgic, because it reminds us of the history and traditions of medicine. Practical, because using shorthand saves a lot of time. But is it still safe? Dr Lees talks about being in practice in the 1950s. Many younger doctors and pharmacists have no knowledge of the abbreviations that were in common usage at that time. The lawyers have preserved Latin better than doctors. Phrases like 'mens rea' and 'res ipsa loquitur' are still in common use because they are still taught in law school. Latin remains alive in medicine, for example, in anatomy but even there, plain English is encroaching. Materia Medica is no longer taught. I doubt if any medical faculty in Australia still teaches Latin prescribing instructions in their pharmacology course.

In day-to-day office general practice, many general practitioners now use prescription writing software which is fast, efficient, safe and can be programmed to provide plain English, unambiguous instructions for taking each medication prescribed. Safety overcomes my nostalgia. If you know for certain to which pharmacist the patient will take your script, and if you know for certain that the particular pharmacist understands all the abbreviations you use, and if you know that every doctor who subsequently will use the record you generate of that consultation understands Latin abbreviations, then you might choose to save time and use Latin-based shorthand like 'prn'. For me, there are too many 'ifs' in that statement. Safe prescribing requires clear, unambiguous instructions.

Editor, – I am saddened by the misuse of the Latin abbreviations 'tds' and 'tid' which today are almost universally used for 'three times daily'. In Latin (and in common usage through my career) 'tds' (*ter die sumendus*) translates as 'to be taken three times a day' (*sumendus* = to take). Hence 'tds' should be used for oral medications. 'tid' (*ter in die*) translates as 'three times daily' and should be used for external medications.

Unfortunately, the distinction has been blurred over the years and both abbreviations are now treated as equivalents. If we are to continue to use Latin abbreviations in the directions, we should use the correct terminology. Perhaps this shift in meaning has occurred because Latin is a subject that has been dropped from most schools and, I presume, the curriculum for medical and pharmacy students.

Peter Castellaro
Pharmacist
Clayfield, Qld

John Youngman, Chair, Australian Council for Safety and Quality Working Party, Standard Medication Chart, comments:

Medication errors are a significant cause of harm to patients. Standardisation of processes and their constituent components has been demonstrated to reduce medication errors. In April 2004 Australian health ministers agreed to support the introduction of the National Inpatient Medication Chart into public health facilities by mid-2006. The Australian Council for Safety and Quality in Health Care formed a working party to develop the chart which will be pilot tested in 30 public and private facilities. This national chart will build on the content and implementation of a standard chart used in Queensland public hospitals.

The National Inpatient Medication Chart is underpinned by a core set of principles and an agreed set of abbreviations, particularly focusing on the prescribing and administration of medicines in hospitals. Medication administration guidelines adopt 'mane' for morning, 'nocte' for night, 'bd' for twice a day, 'tds' for three times a day, 'qid' for four times a day, and for the administration of antibiotics '6 hrly' and '8 hrly'. Such standardisation will enable medical and nursing staff moving across facilities to use the same abbreviations and so reduce the likelihood of a misunderstanding or a mistake in the prescribing, dispensing and administration of medications to patients.

Tramadol

Editor, – I read with interest the addition of tramadol to the already long list of medications that cause the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Aust Prescr 2004;27:97). The temporal relationship between serum sodium level and tramadol use appears to have secured the diagnosis.

While not so relevant to the elderly population, SIADH is essentially a diagnosis of exclusion where, in the presence of normovolaemia, other sinister (if not treatable) causes have been excluded.[1] It is important that readers should not get the impression that the diagnosis is based on solitary serum sodium and osmolality measurements. It is critical that, together with other osmotically active analytes, urinary sodium and urinary osmolality are measured in parallel in the overall assessment of hyponatraemia. This will assist in further understanding the pathophysiology which remains, as stated, hypothetical at this stage.

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Drugs and breastfeeding

Editor, – After reading the book review of 'Drugs and breastfeeding' (Aust Prescr 2004;27:154), I looked up the US product information for metronidazole in the 2000 Physicians' Desk Reference.

The information under Carcinogenicity states that pulmonary tumours were found in all six studies done in mice including one with dosing only every fourth week; there were also malignant tumours in the liver and malignant lymphomas. In rats, there were liver and mammary tumours. And finally, the drug is genotoxic – it damages the DNA directly.

Under the heading Nursing Mothers, it says, 'because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug'. It further states that, 'metronidazole is secreted in human milk in concentrations similar to those found in plasma'.

Based on this information, I take issue with the reviewer who says that, based on this book, she is reassured that metronidazole 'will do the baby no harm'. On the contrary, there is tremendous potential for harm and the US product information actually says not to nurse when using metronidazole. So much for the usefulness of this book!

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Molika In, Pharmacy Department, The Royal Women's Hospital, Melbourne, comments:

Prescribing for breastfeeding women is a potentially complex decision. Clinicians are often faced with a dilemma when reading product information, as these documents tend to recommend ceasing breastfeeding whenever medications are required. Weaning a baby may, however, not be practical and immediate treatment may be required. Various resources are available and should be used by clinicians in order to make informed decisions and weigh up the risks and benefits with breastfeeding women requiring treatment.

The product information for metronidazole clearly states a potential mutagenicity and carcinogenicity association in animals but not in humans. Several studies showed this association with short treatment courses of metronidazole as not statistically significant.[1] Also, the cytogenic effects occur only when there is a metabolic reduction of metronidazole, as in hypoxic tumour cells. Metronidazole has been used therapeutically for more than 40 years and its use in breastfeeding has been reviewed over two decades.[2]

Metronidazole is excreted in the breast milk, but very few cases of adverse effects have been reported and even then the correlation is questionable. Recent reports show no obvious adverse effects associated with mothers taking metronidazole while breastfeeding. Even more reassuring is the fact that the dose of metronidazole received by a breastfeeding infant is far lower than the dose used for treating neonates, infants or children.

Current literature and The Royal Women's Hospital Drugs and breastfeeding guide suggest the benefits of continuing breastfeeding outweigh the theoretical potential cancer risk posed by metronidazole.[3,4]

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A fuller list of references can be found with this article on the *Australian Prescriber* website www.australianprescriber.com

First-line medicines in the treatment of hypertension

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Summary

The goal of therapy in uncomplicated hypertension is to reduce cardiovascular risk by lowering the patient's blood pressure. If non-drug treatment is ineffective, the choice of drug treatment is determined by its safety and efficacy. When safety and efficacy are equal the lowest cost drug should be prescribed. For most patients the first choice drug is a low-dose thiazide diuretic.

Keywords: antihypertensives, therapeutic guidelines.

(Aust Prescr 2005;28:34–7)

Introduction

Hypertension requiring treatment exists when a patient's blood pressure, measured on at least three separate occasions, exceeds the threshold pressures which predict an increased cardiovascular risk, in the absence of complicating features such as diabetes mellitus and overt cardiovascular disease. These patients commonly have a family history of hypertension, but clinical assessment and selective investigation reveal no primary underlying cause of the hypertension.

While there is no absolute cut-off between normal and elevated blood pressure, current guidelines advise treatment for patients whose systolic pressure is 160 mmHg or greater, or whose diastolic pressure is 95–100 mmHg or greater. If other risk factors for cardiovascular disease are present, such as hyperlipidaemia, smoking, obesity or a family history, treatment should be started at 140/90–95 mmHg.[1] The patient's predicted cardiovascular risk, which can be calculated from available tables[2], should determine the time for intervention. The higher the risk, the sooner treatment should start.

Once a decision has been taken to intervene, and provided that urgent reduction of the blood pressure is not needed, a period of non-drug treatment is recommended. Reducing excess weight, salt and alcohol intake coupled with increased exercise all reduce blood pressure. However, few studies have shown prolonged effectiveness of these interventions and study design has often been poor.[3] In a majority of patients medication will also be needed to reach their target blood pressure.

Can we rely on trials to guide the choice of antihypertensive drug?

Controlled clinical trials are often criticised for their lack of representativeness. This may undermine the doctor's confidence in applying the results to individual patients, however, we have no better evidence than these trials. The differences which occur between trials are often exploited in drug promotion, so how do we account for these discrepancies?

The differences may reflect the design of the trials. Results from non-randomised studies are more likely to be favourable to the drug of interest than those of randomised trials. Within randomised trials, less weight should be given to the results if allocation to treatment or control arms was not concealed. The populations included in the trials may not be comparable (for example, the ALLHAT and the ANBP2 studies[4]). Patient outcomes may be expressed in different ways (incidence of stroke, of coronary disease, 'all-cause' cardiovascular morbidity or mortality) that render comparison difficult or impossible. Undeclared conflict of interest may impinge, if not on the results of a study, then at least on its interpretation. Finally, all studies work with samples of the total patient population and the simple play of chance influences the result of any one trial. This is why greater reliance should be placed on the results of trials with larger patient numbers or on systematic reviews or meta-analyses of several studies.

Choice of first-line drugs

Although the results of clinical trials vary, it is important to select a drug that works well and is safe and affordable for the individual patient.

Comparative efficacy

The criteria by which we select one class of drug as first-line treatment are usually dominated by comparative efficacy. In hypertension all the five major drug classes (low-dose thiazides, beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists) are efficacious in reducing blood pressure and cardiovascular events.

Recent results from very large studies and (many) meta-analyses show that it is the reduction in blood pressure itself that leads to lower cardiovascular morbidity and mortality. It is the reduction in blood pressure that counts and not the drug class used to reduce it.

While the conclusion of the National Heart Foundation guidelines (2004)[5] that 'Drugs from any of the five major classes are suitable for initiation and maintenance of antihypertensive therapy' is correct, this is true only if efficacy is considered

alone. Other considerations also have a place in the choice of first-line drugs. The World Health Organization program, the 'Guide to good prescribing', emphasises comparative safety, convenience and cost as well as efficacy as important discriminators in making choices.[6]

Comparative safety

Compared with drugs used for other chronic disorders, antihypertensives are among the safest. They cause very little specific organ toxicity and many of them have been in use for many years so their adverse effects are well known. Periodically there are alarms about particular classes – for example, the precipitation of vascular occlusion with short-acting calcium channel blocking drugs or cardiovascular collapse with hypotension when starting an ACE inhibitor. However, most of these problems can be avoided with appropriate prescribing and monitoring of treatment.

A different insight is obtained from studies in which patients have had to stop their treatment because of adverse effects. In a meta-analysis of 190 monotherapy trials in patients with essential hypertension, discontinuations due to adverse events were commoner with calcium channel blocking drugs (6.7%) than with diuretics or angiotensin receptor blockers (3.1% for each). This suggests that calcium channel blocking drugs have a lower priority as first-line therapy.[7] Although 'discontinuation due to adverse event' may be a relatively crude way of quantifying differences between drugs and may not capture the full details of differences in adverse outcomes, it does provide some objective information about comparative tolerability.

For a patient who experiences an adverse event from a beta blocker or a calcium channel blocker, depending on the nature of the adverse event, there are sufficient differences within these pharmacological classes to warrant trying an alternative within the class in some circumstances. This is not the case for thiazides, ACE inhibitors or angiotensin receptor blockers.

Diabetes

Patients with hypertension are often overweight and have an increased likelihood of developing diabetes, independent of treatment. The small extra risk of type 2 diabetes with the long-term use of thiazide diuretics was reported in the 1960s when relatively high doses were used. It is re-emerging as a concern based on recent trials suggesting that a greater proportion of patients have developed diabetes on thiazides than on other antihypertensives.

A systematic review of this evidence points out that every estimate of new diabetes in these trials has been derived as a secondary end point, that is, the studies were not designed to focus on incident diabetes as a primary end point, and that a final conclusion cannot be reached at present.[8] The highest quality trials suggest that diabetes incidence is unchanged or increased by thiazides and beta blockers, and unchanged or decreased by ACE inhibitors, calcium channel blockers and angiotensin receptor blockers. However, there are no data on long-term outcomes using the very low doses of diuretic now recommended (daily doses of hydrochlorothiazide, chlorthalidone and indapamide not exceeding 12.5 mg, 12.5 mg and 1.5 mg respectively) although it would be expected that the metabolic effects would be less.

A prudent approach is to measure serum potassium, uric acid and fasting glucose before prescribing and not use diuretics (or beta blockers) if the fasting blood glucose is at, or above, 6.1 mmol/L. Fasting glucose should be monitored periodically in patients on continuing diuretic treatment.

Comparative convenience

Ensuring long-term adherence to medication is one of the major problems in managing hypertension. Anything that will make the task easier will give a competitive edge to drugs in that class. While evidence for better adherence to a regimen with once-daily oral dosing is limited, most patients prefer to take medication once a day. The five main classes of antihypertensive all include drugs, or specific formulations, for once-daily dosing.

Comparative cost

In the absence of major differences in efficacy, safety and convenience, comparative cost may become the final discriminator. In a Pharmaceutical Benefits Scheme (PBS) which is continually under threat, small differences in cost (to the taxpayer) in treating a condition which affects 10–15% of the population can add up to substantial sums, particularly as treatment is usually lifelong.

The comparative cost to the PBS of representative drugs from the five classes of antihypertensive drugs is shown in Table 1. The table includes the dose ranges used in the major studies which showed the efficacy of the drugs in reducing cardiovascular events.

Conclusion

If we combine the evidence from each of the selection criteria, it is difficult to escape the conclusion that treatment of patients with uncomplicated hypertension should be started with low-dose thiazide-type diuretics. Failure to respond adequately will probably require the addition of another drug, while the emergence of unacceptable adverse effects is a reason for changing to an alternative class of drug.

There will always be the need to tailor treatment to the individual patient, and it will nearly always be inappropriate, for example, to give a patient with gout a diuretic or a patient with asthma a beta blocker. However, for most patients with uncomplicated hypertension low-dose thiazide-type diuretics should be first-line therapy.

Table 1

Costs of monotherapy for essential hypertension

Drug	Recommended daily dose	Dispensed price*	1 month's treatment
Thiazide chlorthalidone†	12.5–25 mg	$10.92 (100 x 25 mg)	$1.63–$3.28
Beta blocker atenolol††	50–100 mg	$9.77 (30 x 50 mg)	$9.77–$19.54
ACE inhibitor lisinopril†	10–40 mg	$22.12 (30 x 10 mg) $26.63 (30 x 20 mg)	$22.12–$53.26
Calcium channel blocker amlodipine†	2.5–10 mg	$39.12 (30 x 10 mg)	$9.78–$39.12
Angiotensin receptor antagonist candesartan§	8–16 mg	$22.94 (30 x 8 mg) $27.69 (30 x 16 mg)	$22.94–$27.69

* dispensed price of maximum quantity listed in the Schedule of Pharmaceutical Benefits (April 2005)

† based on: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981-97.

†† based on: Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003.

§ based on: Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 2003;21:875-86.

The choice of add-on therapy, which may be required later in up to two-thirds of patients, is not as clearly defined. Beta blocking drugs and ACE inhibitors are effective when used with a diuretic. Beta blockers may also be used with dihydropyridine calcium channel blocking drugs (but should not be used in combination with verapamil or diltiazem).

How do these recommendations match those of expert bodies in Australia and overseas? They are consistent with the recommendations of Therapeutic Guidelines: Cardiovascular, 2003 and go further than those of the National Heart Foundation, 2004 which provide no specific recommendation as to first-line choice. The 2003 World Health Organization (WHO)/International Society of Hypertension statement on management of hypertension advises: 'for the majority of patients without a compelling indication for another class of drug, a low dose of a diuretic should be considered as the first choice of therapy on the basis of the comparative trial data, availability, and cost.'[9] Other guideline groups, such as the National Institute for Clinical Excellence in the UK, have adopted a similar position to that of WHO, again based on an independent, comprehensive review of the clinical evidence.[10]

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Dr Hill was a member of the World Health Organization/ International Society of Hypertension group which constructed the 'Statement on management of hypertension'. Professor Smith was Chair of the Writing Group which assembled Therapeutic Guidelines: Cardiovascular, 2003. Neither has an affiliation with any pharmaceutical company.

Self-test questions

The following statements are either true or false (answers on page 51)

3. Patients with essential hypertension taking calcium channel blockers stop their medication because of adverse effects more frequently than those patients taking diuretics.
4. Thiazide diuretics are no longer first-line treatment for uncomplicated hypertension.

Top 10 drugs

These tables show the top 10 subsidised drugs in 2003–04. The tables do not include private prescriptions.

Table 1

Top 10 drugs supplied by DDD/1000 pop/day *

Drug	PBS/RPBS †
1. atorvastatin	80.697
2. simvastatin	51.468
3. diltiazem hydrochloride	35.470
4. ramipril	31.725
5. omeprazole	21.631
6. irbesartan with hydrochlorothiazide	20.889
7. irbesartan	19.931
8. salbutamol	19.919
9. frusemide	19.403
10. sertraline	17.108

Table 2

Top 10 drugs by prescription counts

Drug	PBS/RPBS †
1. atorvastatin	7,097,744
2. simvastatin	6,008,468
3. paracetamol	4,714,533
4. omeprazole	4,537,098
5. irbesartan	3,371,882
6. celecoxib	3,240,047
7. salbutamol	3,220,045
8. atenolol	3,136,071
9. rofecoxib	3,028,529
10. ramipril	2,871,065

Table 3

Top 10 drugs by cost to Government

Drug	Cost to Government ($A)	DDD/1000/day PBS/RPBS †	Prescriptions PBS/RPBS †
1. atorvastatin	397,430,210	80.697	7,097,744
2. simvastatin	363,667,949	51.468	6,008,468
3. omeprazole	197,471,882	21.631	4,537,098
4. salmeterol and fluticasone	163,196,875	– ‡	2,666,465
5. olanzapine	150,962,947	2.941	717,460
6. clopidogrel	128,213,796	6.446	1,617,367
7. pravastatin	125,298,133	14.150	2,131,080
8. esomeprazole	111,540,717	9.694	2,265,197
9. alendronic acid	99,266,727	7.942	1,921,121
10. rofecoxib	95,196,777	10.912	3,028,529

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

† PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

‡ Combination drugs do not have a DDD allocated

Source: Drug Utilisation Sub-Committee (DUSC): Drug Utilisation Database

Antibiotics for surgical prophylaxis

Wendy Munckhof, Infectious Diseases Physician and Clinical Microbiologist, Princess Alexandra Hospital, and Senior Lecturer in Medicine, University of Queensland, Brisbane

Summary

Surgical antibiotic prophylaxis is defined as the use of antibiotics to prevent infections at the surgical site. Prophylaxis has become the standard of care for contaminated and clean-contaminated surgery and for surgery involving insertion of artificial devices. The antibiotic selected should only cover the likely pathogens. It should be given at the correct time. For most parenteral antibiotics this is usually on induction of anaesthesia. A single dose of antibiotic is usually sufficient if the duration of surgery is four hours or less. Inappropriate use of antibiotics for surgical prophylaxis increases both cost and the selective pressure favouring the emergence of resistant bacteria.

Key words: surgery, drug utilisation.

(Aust Prescr 2005;28:38–40)

Introduction

Wound infections are the commonest hospital-acquired infections in surgical patients.[1] They result in increased antibiotic usage, increased costs and prolonged hospitalisation.[2] Appropriate antibiotic prophylaxis can reduce the risk of postoperative wound infections, but additional antibiotic use also increases the selective pressure favouring the emergence of antimicrobial resistance. Judicious use of antibiotics in the hospital environment is therefore essential.

Surgical antibiotic prophylaxis is defined as the use of antibiotics to prevent infections at the surgical site. It must be clearly distinguished from pre-emptive use of antibiotics to treat early infection, for example perforated appendix, even though infection may not be clinically apparent.

The original surgical antibiotic prophylaxis experiments were performed 40 years ago in pigs. The results concluded that 'the most effective period for prophylaxis begins the moment bacteria gain access to the tissues and is over in three hours'.[3] Since then there have been many studies in animal models and in humans undergoing surgery. This has resulted in the principles of antibiotic prophylaxis (see box) becoming an accepted part of surgical practice.[4]

Approximately 30–50% of antibiotic use in hospital practice is now for surgical prophylaxis. However, between 30% and 90% of this prophylaxis is inappropriate. Most commonly, the antibiotic is either given at the wrong time or continued for too long.[5] Controversy remains as to duration of prophylaxis and also as to which specific surgical procedures should receive prophylaxis.[4]

Indications for surgical antibiotic prophylaxis

A classification system which ranks procedures according to their potential risk for infectious complications has greatly facilitated the study of surgical antibiotic prophylaxis. This system ranks procedures as:

- clean
- clean-contaminated
- contaminated.

This has become a widely accepted standard (Table 1).[6]

Widely accepted indications for antibiotic prophylaxis are contaminated and clean-contaminated surgery and operations involving the insertion of an artificial device or prosthetic material. Less well-accepted indications for prophylaxis include clean operations in patients with impaired host defences or patients in whom the consequences of infection may be catastrophic, for example neurosurgery, open heart surgery and ophthalmic surgery.

Principles of surgical antibiotic prophylaxis

- Decide if prophylaxis is appropriate
- Determine the bacterial flora most likely to cause postoperative infection (not every species needs to be covered)
- Choose an antibiotic, based on the steps above, with the narrowest antibacterial spectrum required
- Choose the less expensive drug if two drugs are otherwise of equal antibacterial spectrum, efficacy, toxicity, and ease of administration
- Administer dose at the right time
- Administer antibiotics for a short period (one dose if surgery of four hours duration or less)
- Avoid antibiotics likely to be of use in the treatment of serious sepsis
- Do not use antibiotic prophylaxis to overcome poor surgical technique
- Review antibiotic prophylaxis protocols regularly as both cost and hospital antibiotic resistance patterns may change

Table 1

Classification of surgical procedures according to infection risk [6]

Type of surgery	Definition	Examples	Indication for surgical antibiotic prophylaxis
Clean surgery	Healthy skin incised Mucosa of respiratory, alimentary, genitourinary tract and oropharyngeal cavity not traversed	Herniorrhaphy, mastectomy, cosmetic surgery	Not recommended
	Insertion of prosthesis or artificial device	Hip replacement, heart valve	Recommended
Clean-contaminated	Respiratory, alimentary or genitourinary tract is penetrated under controlled conditions without unusual contamination	Laryngectomy, uncomplicated appendicectomy, cholecystectomy, transurethral resection of prostate gland	Recommended
Contaminated	Macroscopic soiling of operative field	Large bowel resection, biliary or genitourinary tract surgery with infected bile or urine	Strongly recommended

Table 2

Commonest postoperative infective pathogen by type of surgery

Type of surgery	Commonest postoperative pathogens	Suitable antibiotic choice
Insertion of prosthetic heart valves Insertion of prosthetic joints	Staphylococci	Intravenous cephalothin **or** intravenous cephazolin
Instrumentation of the lower urinary tract	Enteric Gram-negative bacteria, enterococci	Intravenous gentamicin
Colorectal surgery	Enteric Gram-negative bacteria, enterococci anaerobes	Intravenous metronidazole **plus either** intravenous cephalothin **or** intravenous cephazolin **or** intravenous gentamicin
Upper respiratory tract surgery	Aerobic and microaerophilic streptococci, anaerobes	Intravenous cephalothin **or** intravenous cephazolin

Choice of antibiotic

The choice of the antibiotic for prophylaxis is based on several factors. Always ask the patient about a prior history of antibiotic allergy, as beta-lactams are the commonest type of antibiotics used in prophylaxis. A history of severe penicillin allergy (anaphylaxis, angioedema) means that cephalosporins are also contraindicated, as there is a small but significant risk of cross-reaction.

Most importantly, the antibiotic should be active against the bacteria most likely to cause an infection (Table 2). Most postoperative infections are due to the patient's own bacterial flora. Prophylaxis does not need to cover all bacterial species found in the patient's flora, as some species are either not particularly pathogenic or are low in numbers or both.

It is important to select an antibiotic with the narrowest antibacterial spectrum required, to reduce the emergence of multi-resistant pathogens and also because broad spectrum antibiotics may be required later if the patient develops serious sepsis. The use of 'third generation' cephalosporins such as ceftriaxone and cefotaxime should therefore be avoided in surgical prophylaxis. Often several antibiotics are equal in terms of antibacterial spectrum, efficacy, toxicity, and ease of administration. If so, the least expensive drug should be chosen, as antibiotics for surgical prophylaxis comprise a large portion of hospital pharmacy budgets.

Commonly used surgical prophylactic antibiotics include:

- intravenous 'first generation' cephalosporins – cephazolin or cephalothin
- intravenous gentamicin
- intravenous or rectal metronidazole (if anaerobic infection is likely)

- oral tinidazole (if anaerobic infection is likely)
- intravenous flucloxacillin (if methicillin-susceptible staphylococcal infection is likely)
- intravenous vancomycin (if methicillin-resistant staphylococcal infection is likely).[7]

Parenteral 'second generation' cephalosporins such as cefotetan have improved anaerobic and aerobic Gram-negative cover compared to first generation cephalosporins. They are sometimes used as a more convenient, but more expensive, alternative to the combination of metronidazole plus either first generation cephalosporin or gentamicin for abdominal surgical prophylaxis.

The bacterial flora in some hospitalised patients may include multi-resistant bacteria such as methicillin-resistant staphylococci. An assessment then needs to be made for each surgical procedure about whether or not prophylaxis with parenteral vancomycin is indicated. Unnecessary use of vancomycin selects for vancomycin-resistant enterococci (VRE), vancomycin-intermediate *Staphylococcus aureus* (VISA), and vancomycin-resistant *Staphylococcus aureus* (VRSA), the first two of which already occur in Australian hospitals.

Route and timing of antibiotic administration

It is critical to ask the patient about beta-lactam allergy prior to anaesthesia to minimise the risk of anaphylaxis under anaesthesia. A test dose of antibiotic is not necessary before surgery if the patient denies antibiotic allergy.

Prophylactic antibiotics are usually given intravenously as a bolus on induction of anaesthesia to ensure adequate tissue concentrations at the time of surgical incision. This timing of dosing is particularly important for most beta-lactams which have relatively short half-lives. Vancomycin has to be infused over one hour so it must be started earlier so the infusion finishes just before induction.

Intramuscular antibiotics are less commonly used than intravenous antibiotics. They are typically given at the time of pre-medication so that peak tissue levels are attained at the most critical time, the time of surgical incision.

Oral or rectal antibiotics need to be given earlier to ensure adequate tissue concentrations during surgery. Metronidazole suppositories are commonly used in bowel surgery and must be given 2–4 hours before it begins. Topical antibiotics are not recommended, with the exceptions of ophthalmic or burns surgery.

Duration of antibiotic administration

Persistence of tissue concentrations past the period of surgery and recovery of normal physiology following anaesthesia does not improve efficacy and increases toxicity and cost. If the operation lasts four hours or less, one antibiotic dose is usually sufficient.[8] In prolonged surgery of greater than four hours, further antibiotic doses may be required to maintain the concentration, particularly if the antibiotic has a short half-life. Continuing antibiotic prophylaxis until surgical drains have been removed is illogical and also of unproven benefit.

Conclusion

Surgical antibiotic prophylaxis is an effective management strategy for reducing postoperative infections, provided that appropriate antibiotics are given at the correct time for appropriate durations and for appropriate surgical procedures. In most cases, surgical antibiotic prophylaxis is given as a single intravenous dose as soon as the patient is stabilised under anaesthetic, prior to skin incision. It is important to use a narrow spectrum antibiotic appropriate to the site of surgery. Hospital surgical antibiotic prophylaxis protocols should be regularly reviewed, as both the cost of individual antibiotics and the endemicity of multi-resistant bacteria in certain units or hospitals are subject to frequent change.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 51)

5. Narrow spectrum antibiotics are not appropriate for use in surgical prophylaxis.
6. Surgical antibiotic prophylaxis should continue until any surgical drains are removed.

Dental notes

Prepared by Associate Professor R.G. Woods of the Australian Dental Association

Antibiotics for surgical prophylaxis (page 38)

The principles set out in the article can readily be applied to oral surgery. Most oral surgery is approached intra-orally although some, for instance open reduction of certain mandibular fractures, is approached externally. In general dental practice, the most common oral surgical procedure requiring an incision would be the removal of unerupted mandibular or maxillary third molars. Removal of these molars often requires removal of bone.

Many unerupted or partly erupted third molars develop a communication with the mouth, and the adjacent tissues are susceptible to infection, often with an anaerobic organism. Anaerobic streptococci and bacteroides are commonly associated with these infections.

Even if the infection associated with erupting or partly erupting third molars has been treated with an antibiotic it is likely that, even in the absence of major symptoms of infection, bacterial contamination will persist. In these circumstances the surgical procedure of third molar removal may be classified 'contaminated' using the criteria of Table 1 of the article.

Appropriate antibiotics for dental surgical prophylaxis include oral or intravenous amoxycillin or intravenous ampicillin or, if there is a history of penicillin allergy, oral cephalexin (if penicillin allergy is mild), oral or intravenous clindamycin or intravenous lincomycin. If oral antibiotics are used, they must be given at least one hour before the procedure to ensure adequate tissue concentrations at the time of the procedure. Intravenous prophylaxis is effective as soon as antibiotic administration is complete. Intravenous administration of some antibiotics, such as lincomycin or clindamycin, should be by slow infusion.[1] Whether the antibiotic should be continued following third molar surgery where there has been a history of infection, is a matter of clinical judgement.

Although less frequent, surgery for removal of chronic granulomatous infections in maxillary or mandibular bone is also common. These infections which usually involve bone loss and sometimes development of a cyst are usually associated with infected or non-vital pulp tissue. The surgical procedure would be classified 'contaminated'. The organisms associated with an infection of this sort are not likely to be anaerobic unless they are associated with necrotic tissue, for instance a non-vital dental pulp. The antibiotics recommended for infected third molar surgery would be appropriate where an anaerobic infection is suspected. When there has been no necrotic tissue associated with the development of infection, amoxycillin, or in the penicillin-allergic patient, cephalexin (if penicillin allergy is mild), or clindamycin would be appropriate antibiotics.[1]

Reference

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Book review

Australian Medicines Handbook Drug Choice Companion: Emergency and primary care

Adelaide: Australian Medicines Handbook Pty Ltd; 2004.

181 pages. Price $50, students $45, including GST

Robyn Wilkinson, Emergency Medicine Registrar, Tamworth Base Hospital, Tamworth, NSW

This handy little book consists of protocols which can be applied to a range of problems commonly encountered in acute care medicine. For each condition, the format features explicit instructions regarding drug choices and doses and their indications and contraindications. Where relevant, it also contains advice about non-pharmacological and supportive treatments. Most conditions also include brief but sensible practice points and for many conditions there is an evidence-based rationale for the protocol. There are, in addition, appendices regarding choice of endotracheal tube size, interpretation of arterial blood gases and respiratory function tests and prescribing paediatric fluids.

The information contained in the handbook is practical, concise, up-to-date and accurate. However, different sections vary in their clinical utility. Perhaps the most interesting and useful section of the handbook is the section regarding treatment of poisoning. In contrast, I wonder at the inclusion of the section on infectious diseases, and suspect that this handbook is not about to replace Antibiotic Guidelines in this area.

My major criticism of the book is that it is, at least at first, a little difficult to navigate. There are no clear divisions between sub-sections of the book and I imagine this might make it difficult to find what you want in an emergency. However, once this has been overcome, the instructions are succinct and easy to read. Overall, it is an interesting and informative read, but most of the handbook consists of information which is already the regular practice of doctors in emergency departments. I therefore suspect it will be of most use to medical practitioners who do not frequently encounter the conditions discussed. As such, I would highly recommend it for use by practitioners working in rural and remote areas.

The role of chemotherapy in the treatment of pancreatic carcinoma

David Goldstein, Senior Staff Specialist, Institute of Oncology, Prince Henry and Prince of Wales Hospitals, and Conjoint Associate Professor, University of New South Wales, Sydney

Summary

Patients with unresectable and metastatic pancreatic cancer are incurable and optimal palliation is the goal of therapy. If these patients have symptoms of biliary or duodenal obstruction they may benefit from palliative bypass procedures. Pain associated with local tumour infiltration may be palliated with radiation, with or without chemotherapy, or by coeliac nerve blocks or local neurosurgical procedures. Chemotherapy with gemcitabine has modest objective response rates, but can improve symptoms.

Key words: gemcitabine, palliative care.

(Aust Prescr 2005;28:42–4)

Introduction

Pancreatic cancer remains one of the most feared gastrointestinal tract malignancies. There are 1800 new cases annually and the overall median survival is 3–5 months with a 12-month survival of 10% and a five-year survival of 3%.[1,2] Pancreatic cancer is usually diagnosed late, curative surgery is rare and requires specialised expertise found in few centres.[3] It is characterised by early metastasis and resistance to all cancer treatment modalities.

The aetiology is not well understood, but risk factors thought to be associated with pancreatic cancer include smoking which increases risk twofold and chronic pancreatitis which increases the risk 5–15 fold. Hereditary cancer accounts for about 5%, but overall up to 60% of cases remain unexplained.[4]

Management of locally advanced disease (see box)

An important minority of patients present with truly localised but inoperable disease. Local control remains an important issue in this group of patients in terms of symptomatic palliation of pain, and prevention of bleeding and obstruction. These patients may benefit from palliative bypass of biliary obstruction by endoscopic, radiologic or surgical techniques. Duodenal obstruction may require a surgical bypass.

Local radiation may palliate pain associated with unresectable cancer, but it has no impact on survival. An alternative approach is the use of coeliac plexus blocks. These are associated both with improved pain control in otherwise opioid-resistant patients and in one study with increased survival.

The role of combined local radiation and chemotherapy emerged some 30 years ago. The Gastrointestinal Tumor Study Group showed a doubling in median survival with chemo-irradiation compared to radiation alone.[5] There have been several conflicting studies, but there is promise that the therapeutic ratio will improve with modern radiotherapy techniques and three-dimensional planning systems. Patients should be invited to enrol in trials of these techniques to identify optimal strategies. Ultimately it remains to be proven whether chemotherapy alone or combined therapy can give this group of patients the greatest promise of tumour control, symptom palliation and survival with less toxicity.

Management of metastatic disease

There have been major changes in the management of patients with metastases. The improvements in supportive care used to manage the symptoms of locally advanced disease have dramatically altered quality of life. The use of anabolic drugs such as megestrol acetate, dexamethasone and pancreatic supplements may also improve quality of life.

Until 1995 there was little evidence that chemotherapy provided any benefit, as the drugs were toxic and did not significantly improve survival. In randomised trials no combination regimen was superior to 5-fluorouracil (5-FU) alone, however perceptions have changed after two small randomised studies showed improved survival over best supportive care.[6,7]

Treatment options in locally advanced pancreatic cancer

- palliative surgical bypass, endoscopic or percutaneous radiologic biliary stent placement
- for pain palliation: radiation therapy with or without chemotherapy or coeliac nerve blocks/chemical splanchnicectomy/local neurosurgical procedures
- chemotherapy alone
- radiation therapy and chemotherapy with 5-fluorouracil

Investigational: radiation therapy and chemotherapy with other drugs such as gemcitabine

Gemcitabine

Gemcitabine is a deoxycytidine analogue, which is converted by deoxycytidine kinase into an active triphosphate metabolite and induces its own activation intracellularly. It has substantial anticancer activity in non-small cell lung cancer, pancreatic cancer, ovarian cancer and non-Hodgkin's lymphoma. The first study in patients with pancreatic cancer refractory to 5-FU showed a response rate of 9.5%, a six-month survival of 31%, and a median survival of 3.9 months. A subsequent initial therapy study which randomised patients to receive gemcitabine or 5-FU showed a significant increase in one-year survival (18% versus 5%) and improved quality of life specifically focusing on the issues important in pancreatic cancer, namely pain, weight loss and performance status.[8] Subsequent confirmation in a large phase IV report on over 3000 patients has reinforced this finding.[9] Gemcitabine has subsequently been studied in a large number of randomised phase III studies. These studies, involving comparisons including both 5-FU and novel therapies, have confirmed the initial data.

An overview of all the large reported phase III studies shows that after a median 3–4 cycles of chemotherapy, the response rate is 15–25%, with a median survival of 5–6.7 months and one-year survival of 18%.[10] Gemcitabine has consistently been superior to other single drugs. Attempts to improve upon this by combination with other drugs that are either synergistic in laboratory studies or other tumours have had mixed results. Neither cisplatin, nor a variety of permutations of 5-FU, nor any of a number of novel chemotherapy drugs have improved survival. As a result single drug gemcitabine remains the drug of choice for patients with metastatic pancreatic cancer who have a reasonable performance status and opt for chemotherapy.

The principal adverse effects of gemcitabine are nausea, vomiting and neutropenia. In an overview of 3000 patients only 4% discontinued because of drug-related adverse events.

New drugs

Novel targeted drugs have received extensive attention in view of the relative insensitivity of pancreatic cancer to conventional therapy. Metalloproteinase inhibitors to inhibit metastatic spread and an attempt to inhibit components of the tumour-activating pathway, such as ras, using a farnesyl transferase inhibitor have been ineffective. 5-FU in optimised schedules such as infusional 5-FU or in combination with leucovorin, or capecitabine, or new drugs such as irinotecan, does not increase survival over gemcitabine alone. Most recently, adding oxaliplatin has improved progressive-free survival, but not overall survival.[11]

Other studies have been directed at inhibition of epidermal growth factor receptor. There has also been substantial interest in the role of angiogenesis inhibitors following reports of enhanced activity in colon cancer for 5-FU and irinotecan when combined with bevacizumab – a vascular endothelial growth factor ligand inhibitor. Other receptor inhibitors are also likely to be studied given the high expression of vascular endothelial growth factor receptor on pancreatic cancer cells. Some of these are in the early stages of clinical investigation.

Although the increased activity of combination therapy has not translated into improved overall survival, response rates are reaching 30% so further studies of combinations of newer drugs are likely. Outside of clinical trials, however, single drug gemcitabine remains the chemotherapy of choice for metastatic disease.

Adjuvant therapy

Perhaps most promising are recent data suggesting an improved outlook for those patients who undergo potentially curative surgery, all of whom remain at very high risk of relapse. The European Study Group for Pancreatic Cancer (ESPAC) 1 trial is the largest adjuvant therapy study ever performed. It was built in part upon the Gastrointestinal Tumor Study Group results and also a small Scandinavian study which randomised 47 patients to combination chemotherapy and found an increased median survival of 23 months compared with 11 months for observation.

The ESPAC was a 'pragmatic' study that randomised 541 patients from 11 European countries. It had four arms with a 2 x 2 factorial design that compared the effects of adjuvant chemoradiation, chemotherapy, chemoradiation followed by maintenance chemotherapy, and observation. Just over half of the patients were randomised to the 2 x 2 factorial design, the rest were recruited to a non-factorial arm. These complexities make accurate analysis of the findings quite difficult. When all the results were pooled, adjuvant chemotherapy was superior to no chemotherapy with a median survival of 19.7 months versus 14 months ($p = 0.0005$). The 2 x 2 factorial result is also significant; the five-year survival rate was 20% in those receiving chemotherapy and 8% in those not[12], strengthening the conclusions. The study used 5-FU chemotherapy given for five days per month as a bolus injection, and this should now be regarded as the standard against which all new adjuvant studies should be performed.

Conclusion

Pancreatic cancer remains a formidable problem, but recent advances have at least resulted in a small but meaningful proportion of patients living longer. Similarly, a much larger group is now being offered a better quality of life through improved palliation. Promising new avenues of therapy are a reason for cautious optimism.

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Associate Professor Goldstein has acted as an advisor on several occasions for Eli Lilly and for other oncologic pharmaceutical companies, including Pharmacia/Pfizer, Roche, Merck AG and Novartis. He is on the board of the Australasian gastrointestinal clinical trials group and the executive of the Clinical Oncology Society of Australia. He is principal investigator on a number of current and recent trials in pancreatic cancer.

Self-test questions

The following statements are either true or false
(answers on page 51)

7. The pain of pancreatic cancer may be resistant to opioids.
8. Adjuvant therapy does not improve survival after surgical resection of pancreatic cancer.

Book review

Therapeutic Guidelines: Dermatology. Version 2.

Melbourne: Therapeutic Guidelines Limited; 2004.

410 pages. Price: $33, students $25.30, plus postage

Paul Buckley, General practitioner, Canberra

I had not read the first version of these guidelines previously, although I am familiar with other titles in the series. Having now reviewed these dermatology guidelines in detail, they will become an essential part of my therapeutic armamentarium.

The guidelines provide a thorough review of dermatological conditions, including an overview of basics, like morphology, types and distribution of lesions, and practical procedures like biopsies, intralesional steroid injections, dressings and patch testing. They include many useful tables, which provide an aide memoire for a variety of conditions and their management.

This volume is a comprehensive and up-to-date review, with detailed sections on cosmetic dermatology, drug reactions and particularly good contributions on nail disorders, eczema, vasculitis, leg ulcers and wound healing. Recently approved drugs like imiquimod for actinic keratoses and superficial basal cell cancers, and pimecrolimus for eczema are included, so the guidelines are contemporaneous.

Criticisms include the alphabetic format, the inclusion of a chapter on burns, a relatively superficial review on melanoma and the frequent recommendations for referral to a dermatologist for conditions which could be managed by a general practitioner with an interest and a little training in dermatology.

Notwithstanding, the guidelines are a very thorough, up-to-date review of most things dermatological. The index is comprehensive and the tables and boxes provide a valuable resource. The fundamentals of diagnosis and treatment, including the often overlooked basics like emollient therapy, are included.

The Dermatology Guidelines provide a valuable tool for general practitioners and students, and for those experienced in dermatology.

The decision to transfuse a patient

James P. Isbister, Consultant in Haematology and Transfusion Medicine, Royal North Shore Hospital and Pacific Laboratory Medicine Services, and Clinical Professor of Medicine, University of Sydney, Sydney

Summary

Advances in surgical techniques have reduced the need for blood transfusion and most anaemias can now be managed without transfusions. While the haemoglobin concentration assists the decision to transfuse a patient, there is no single threshold for transfusion. The need to give a blood component is also difficult to assess, but guidelines are available. Although Australian blood supplies have a high degree of safety, attention to details such as patient identification and compatibility will help to reduce adverse outcomes when a transfusion is indicated.

Key words: anaemia, blood, surgery.

(Aust Prescr 2005;28:45–7)

Introduction

The transfusion of blood or its components (plasma, platelets, cryoprecipitate) has an important role in modern medicine and surgery. However, in recent years this role has been reassessed, especially in anaemia and in the perioperative setting. The majority of anaemias can now be treated without the transfusion of homologous blood, and careful risk assessment and the use of blood conservation techniques have made 'bloodless' surgery possible for most elective procedures.

Indications for blood transfusion

Blood transfusion is indicated to control the effects of a haematological deficiency, or to prevent problems, until the injury or disease process can be corrected or resolves. The focus should be on the patient's specific clinical problem, with transfusion viewed as an option only when alternatives have been considered and optimally used when possible.

Assessing acute blood loss and when to start transfusion remains controversial. However, it is reasonable to say that volume resuscitation does not need blood in the first instance. The decision to use blood should be made in the context of the patient's cardiocirculatory and respiratory status and haemoglobin level after resuscitation with clear fluid. If blood loss is accurately assessed a better prediction as to when red cell transfusion may be needed can be made.

Homologous blood transfusion should not necessarily be regarded as the first line of therapy for patients with haemopoietic defects, and in patients having elective surgery it is often possible to minimise or eliminate the need for transfusion. Clearly, if homologous blood can be avoided its potential hazards need not be considered. Making a decision to use blood components can be difficult and much debate continues in relation to the indications for their use.

Before giving patients blood or a blood component it is useful to ask a series of questions.

- What is the haematological defect?
- What is the most appropriate therapy for the patient?
- Are there alternatives to homologous transfusion?
- Is a blood component indicated and where should it be obtained from?
- What are the potential hazards of transfusion/component therapy?
- Can the risk of adverse effects be avoided or minimised?
- How should the treatment be administered and monitored?
- What is the time frame of the decision-making process?
- What is the cost of the haemotherapy?
- Is the patient fully informed of the medical decisions?

The clinician in the perioperative setting is confronted with the following decisions.

- Is this patient a potential 'bleeder', what is the haemostatic defect and what therapy is available to minimise bleeding?
- In patients without a pre-existing haemostatic defect, to what point can I haemodilute the patient before requiring transfusion of specific blood components?
- Are there autologous techniques appropriate for this patient (what, when and how)?
- Do I need to give homologous red cells?
- At what point does attention to haemostasis as well as oxygen transport become a consideration?

Evidence-based transfusion medicine and clinical guidelines

As with all modern medical therapy, transfusion and blood component therapy presupposes an understanding of the natural history of untreated and treated disease. In many disorders the clinical problem is well understood and there is good evidence for the benefits of transfusion or non-transfusion. Transfusion medicine, especially in the perioperative setting, therefore lends itself to the appropriate use of clinical guidelines

Table 1

Summary of National Health and Medical Research Council guidelines for the transfusion of fresh blood products [1]

Red cell concentrates	Use of red blood cells is likely to be inappropriate when Hb>100 g/L unless there are specific indications. If red blood cells are given at this concentration, reasons should be well documented. Use of red blood cells may be appropriate when Hb is 70–100 g/L. In such cases, the decision to transfuse should be supported by the need to relieve clinical signs and symptoms and prevent significant morbidity and mortality. Use of red blood cells is likely to be appropriate when Hb<70 g/L. In some patients who are asymptomatic and/or where specific therapy is available, lower threshold levels may be acceptable. In the context of acute bleeding and hypovolaemia, the haemoglobin is only one consideration in determining the need for red blood cells. Additional factors to consider include the patient's cardiopulmonary reserve, total volume of blood loss, oxygen consumption and arterial disease.	
Platelet concentrates	Prophylaxis	Bone marrow failure when the platelet count is <10 x 10^9/L without risk factors or <20 x 10^9/L in the presence of additional risk factors (e.g. fever, antibiotics, evidence of systemic haemostatic failure). Maintaining the platelet count at >50 x 10^9/L in patients undergoing surgery or invasive procedures. Inherited or acquired qualitative platelet function disorders, depending on clinical features and setting. In these situations the platelet count is not a reliable indicator for transfusion.
	Haemorrhage	Use of platelets is likely to be appropriate in any patient who is bleeding when thrombocytopenia is considered a major contributory factor and when the platelet count is <50 x 10^9/L in the context of massive haemorrhage/transfusion and <100 x 10^9/L in the presence of diffuse microvascular bleeding.
Fresh frozen plasma	Replacement of single factor deficiencies where a specific or combined factor concentrate is not available. Immediate reversal of warfarin effect in the presence of potentially life-threatening bleeding when used in addition to vitamin K and possibly prothrombin complex concentrate (prothrombinex-HT). Treatment of the multiple coagulation deficiencies associated with acute disseminated intravascular coagulation. Treatment of inherited deficiencies of coagulation inhibitors in patients undergoing high-risk procedures where a specific factor concentrate is unavailable. In the presence of bleeding and abnormal coagulation parameters following massive transfusion or cardiac bypass surgery or in patients with liver disease.	
Cryoprecipitate	Use of cryoprecipitate may be considered appropriate in patients with fibrinogen deficiency where there is clinical bleeding, an invasive procedure, trauma or disseminated intravascular coagulation. The use of cryoprecipitate is not generally considered appropriate in the treatment of haemophilia, von Willebrand's disease, or deficiencies of factor XIII or fibronectin, unless alternative therapies are unavailable.	

Hb haemoglobin concentration

Table 2

Multimodality approach to perioperative blood management

	Tolerance of anaemia	Optimising red cell mass	Minimising blood loss
Preoperative	Transfusion guidelines	Haematological assessment	Haemostatic assessment and pre-emptive haemostasis planning
Intraoperative	Tolerating haemodilution and 'acceptance' of lower red cell mass ? Potential role for haemoglobin substitutes Minimising O_2 demand	Strict transfusion criteria	Anaesthetic techniques Surgical techniques Normovolaemic haemodilution Autologous haemostatic techniques Local haemostatic agents Red cell salvage
Postoperative	Minimising O_2 demand Education	Haematinics strategy – erythropoietin, iron, folate, vitamin B_{12}	Close clinical monitoring

(see Tables 1 and 2). If there is a reasonable probability of a patient requiring a red cell transfusion a sample of blood should be sent to the laboratory for 'type and screen'. Units of blood will only be released upon specific request by the clinician.

The clinician's responsibilities

The clinician requires a core knowledge of transfusion medicine focusing on the following:

1. Has the clinical problem (e.g. anaemia) been correctly diagnosed and can it be corrected in the short or long term by specific therapy?
2. Is there evidence that blood component therapy should improve the short- and long-term outcome for the patient?
3. What alternatives are available?
4. Have the specific clinical or laboratory criteria for transfusions been satisfied?
5. Have the risks been assessed and balanced against the predicted benefits of blood component therapy?
6. Has an appropriate blood component been selected?
7. Who will administer and monitor the blood component?
8. What end points will be measured to assess benefit?
9. Is the patient appropriately informed about the risks and benefits of transfusion or no transfusion?
10. Is the transfusion process being correctly documented and audited, from the decision to transfuse through to end points and complications?

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Professor Isbister is Chair of the Australian Red Cross Blood Service Advisory Council and a member of the Board.

Correction

Bowel preparation (Aust Prescr 2005;28:16)

In the box of examples of some of the products available for bowel preparation, Picoprep appeared to be listed as a magnesium preparation. Although it does contain magnesium oxide, it also contains sodium picosulfate and is therefore similar to Picolax which was listed as a diphenylmethane preparation.

Your questions to the PBAC

Glucosamine

As a pharmacist doing home medicines reviews, I frequently come across patients suffering from osteoarthritis who are taking (selective or non-selective) non-steroidal anti-inflammatory drugs (NSAIDs) for relief. As these patients often also suffer from conditions such as hypertension or heart failure, my recommendations include comments about NSAIDs interfering with blood pressure control, or aggravating heart failure. Many patients are on ACE inhibitors, diuretics and the NSAID, which constitutes the 'triple whammy' that puts them at increased risk of acute renal failure. Problems arise when I wish to suggest alternatives. Regular maximum dose paracetamol is fine if it works. There is evidence that glucosamine is effective, and may slow the progression of the disease. However, many patients will not take glucosamine because of the cost, compared to their NSAID which is subsidised by the Pharmaceutical Benefits Scheme. Considering the amount spent on COX-2 inhibitors and the cost of dealing with patients hospitalised by adverse effects (gastrointestinal complications, aggravated heart failure, acute renal failure), I am surprised that glucosamine is not subsidised.

I would like to know whether a cost-effectiveness formula has been applied to glucosamine, and what the chances are of it being subsidised. Has it been considered at all? Is there no multinational drug company out there lobbying for it, so it doesn't even find its way to the Pharmaceutical Benefits Advisory Committee (PBAC). Does the PBAC only consider drugs that are presented by the drug companies, or do you ever go searching (through the clinical trials) for other (cost-effective) drugs?

Julie Brennan
Pharmacist
Moruya, NSW

PBAC response:

The Pharmaceutical Benefits Advisory Committee (PBAC) bases its recommendations on the evidence submitted to it. An application for listing requires appropriate data and evidence supporting the submission so manufacturers are usually in the best position to provide such information. The PBAC cannot compel a manufacturer to make an application for a particular drug or condition. To date, no application meeting the criteria for listing on the Pharmaceutical Benefits Scheme (PBS) has been submitted. Consequently, the PBAC cannot recommend that glucosamine be listed on the PBS.

Medicinal mishap

Severe hyponatraemia associated with omeprazole

Prepared by Adam Morton, Physician, Mater Misericordiae Hospital, South Brisbane, and John Mackintosh, Oncologist, Mater Private Hospital, South Brisbane

Case

A 43-year-old woman presented with epigastric pain and tenderness nine days after completing her second cycle of chemotherapy for a temporoparietal lymphoma. She was prescribed omeprazole 20 mg twice a day.

Two days later, after three doses of omeprazole, the patient complained of nausea, weakness and feeling twitchy. Physical examination was unremarkable, but her serum sodium concentration had fallen from its pre-treatment value of 138 to 117 mmol/L. Her serum urate was 0.12 mmol/L, urine sodium was 35 mmol/L and urine osmolality 615 mmol/L. Plasma glucose and tests of thyroid, adrenal and renal function were normal. This is consistent with the syndrome of inappropriate antidiuretic hormone secretion.

The patient was given one litre of hypertonic saline over 24 hours and was placed on fluid restrictions. The omeprazole was ceased. Within three days her sodium concentration had returned to normal and has remained so over the ensuing eight months without fluid restrictions.

Comment

In 2003–04, omeprazole was the fourth most commonly prescribed drug on the Pharmaceutical Benefits Scheme.[1] Seven previous cases of hyponatraemia have been associated with proton pump inhibitors. With the exception of one case ascribed to lansoprazole, all these cases followed exposure to omeprazole.[2,3,4,5,6,7,8] Consistent features were the:

- rapid onset of hyponatraemia with the majority of cases presenting within 11 days of starting treatment
- severity of hyponatraemia
- rapid recovery after cessation of the drug.

The Adverse Drug Reactions Advisory Committee has received 18 reports of hyponatraemia associated with omeprazole, including six where it, or esomeprazole, was the sole suspected drug.

Hyponatraemia has a variety of causes including renal salt wasting and inappropriate antidiuretic hormone secretion.[9] Our patient probably had drug-induced inappropriate secretion of antidiuretic hormone.

Although we used hypertonic saline, it is important to remember not to correct the patient's sodium concentration too quickly. Rapid replacement of sodium can induce the osmotic demyelination syndrome which is potentially fatal.

Conclusion

This is a rare adverse drug reaction, but it is included in the product information of omeprazole. As our patient developed hyponatraemia after three doses, this adverse reaction needs to be considered whenever there is clinical deterioration even after brief exposure to a proton pump inhibitor.

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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 Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Emtricitabine

Emtriva (Gilead)

200 mg capsules

Approved indication: HIV infection

Australian Medicines Handbook section 5.4.1

The current treatment of HIV infection involves giving antiviral drugs from different classes. This may require the patient to take medications several times a day.[1] Most of the regimens include nucleoside reverse transcriptase inhibitors to prevent viral replication. This class is now expanded by the addition of emtricitabine, an analogue of cytosine.

Emtricitabine is taken once a day. It is rapidly absorbed and then phosphorylated within cells to its active form. While the elimination half-life of emtricitabine is 10 hours the intracellular half-life of emtricitabine-triphosphate is 39 hours. Most of the drug is excreted in the urine so the dose requires adjustment in patients with renal impairment.

A multinational double-blind trial studied emtricitabine in 571 patients who had not previously been treated with antiretroviral drugs. These patients were randomised to take emtricitabine or stavudine, in addition to didanosine and efavirenz. After 48 weeks 78% of the emtricitabine group and 59% of the stavudine group had fewer than 50 copies of viral RNA/mL.[2]

Another trial studied 440 patients who were already taking combinations of antiviral drugs including lamivudine. The patients were randomised to either continue lamivudine or to switch to emtricitabine. After 48 weeks 72% of the patients taking lamivudine and 67% of those taking emtricitabine had fewer than 50 copies of viral RNA/mL.

Common adverse effects are diarrhoea, nausea, abdominal pain and nightmares, but these may occur less frequently than with stavudine. Skin discolouration was observed in 3% of the previously untreated patients given emtricitabine.[2] Liver function, blood cell counts and triglyceride concentrations may be affected by emtricitabine.

Resistance can develop during treatment. In previously untreated patients, viral mutations occurred in 4% of those taking emtricitabine and 11% of those taking stavudine.[2] As emtricitabine is structurally similar to lamivudine, a virus which is resistant to lamivudine will probably be resistant to emtricitabine.

While a once-daily treatment may improve compliance, it will require further study to see if emtricitabine has a clinically significant advantage. At present, its efficacy has only been proven with surrogate end points.

References *†

1. Palmer C. HIV treatments and highly active antiretroviral therapy. Aust Prescr 2003;26:59-61.
2. FTC-301A Study Team. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients. JAMA 2004;292:180-90.

Iron sucrose

Venofer (Baxter Healthcare)

5 mL vials containing 20 mg/mL

Approved indication: iron deficiency anaemia associated with haemodialysis

Australian Medicines Handbook section 7.6

Patients who are having regular haemodialysis can develop anaemia. The patients' demand for iron will increase when they are given erythropoietin. If oral supplements of iron are unable to meet this increased demand, parenteral iron should be considered.

Iron sucrose solution is given by intravenous infusion. The molecule then dissociates with the elemental iron being taken up by iron stores and the sucrose being eliminated in the urine. When administered with erythropoietin, iron sucrose will increase the haemoglobin in reticulocytes.

A clinical trial of iron sucrose solution involved 77 patients who had dialysis-associated anaemia and had been taking erythropoietin for at least four months. The patients were given a slow injection three times a week. Seventy completed a course of 10 doses (1000 mg iron). Within five weeks of completing the course, 60 patients had a haemoglobin greater than 11 g/dL, from a baseline mean of 10.3 g/dL, on at least one occasion. There were also increases in serum ferritin and transferrin saturation. Although erythropoietin doses were reduced the change was not significant.[1]

Some patients can have an allergic reaction to iron products. In the pivotal trial there were no cases of anaphylaxis.[1] The common adverse events reported in trials of iron sucrose include hypotension, cramps, nausea, vomiting and headache.

A trial in the USA has tested iron sucrose in 23 patients who were hypersensitive to iron dextran. Most of the patients completed the course of injections and none of them withdrew because of adverse effects.[2]

While iron sucrose may have an advantage over iron dextran its safety and efficacy needs to be compared with other parenteral iron formulations such as iron polymaltose.

References *

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2. Van Wyck DB, Cavallo G, Spinowitz BS, Adhikarla R, Gagnon S, Charytan C, et al. Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American Clinical Trial. Am J Kidney Dis 2000;36:88-97.

Tolterodine tartrate

Detrusitol (Pfizer)

1 mg and 2 mg tablets

Approved indication: overactive bladder

Australian Medicines Handbook section 13.1.1

Incontinence is a common problem, but many cases can be helped by behavioural modification programs.[1] Some cases are caused by detrusor instability. The symptoms of urinary frequency and urgency may improve with drug treatment. Tolterodine adds to the choice of anticholinergic drugs for this problem.

Tolterodine is a competitive antagonist at muscarinic receptors. This action reduces bladder contraction. Improvements in urodynamic function can be detected after two weeks of treatment.

Patients take tolterodine twice a day. It is well absorbed but is then extensively metabolised by the liver. The active metabolite also has an antimuscarinic action. This metabolism involves cytochrome P450 2D6, an enzyme of which some people have little. Clearance is reduced in these 'poor metabolisers', but, because of the way tolterodine and its active metabolite are bound to protein, the overall effect of the drug is unchanged. The dose should be reduced in patients with liver disease. Less than 1% of the drug is excreted unchanged in the urine, but a lower dose is recommended in patients with impaired renal function.

Although tolterodine increases the volume excreted per micturition, it has not significantly reduced the frequency in all of the placebo-controlled studies. One 12-week study of 293 patients compared tolterodine, oxybutynin and placebo. At the end of the study, frequency had respectively decreased by 21%, 20% and 11%. The corresponding increases in the volume excreted per micturition were 27%, 31% and 7%. In patients with urge incontinence, tolterodine reduced the number of incontinent episodes by 47% compared to 19% in the placebo group, however there was a 71% reduction in the oxybutynin group.[2] The need for treatment should be reviewed after six months, but some studies suggest that the effect of tolterodine continues for up to a year of treatment.

The majority of patients will experience adverse effects during treatment with tolterodine. Some of these adverse effects are predictable because of the drug's action, for example dry mouth, constipation and blurred vision. Patients with narrow angle glaucoma should not take tolterodine. Other adverse effects of tolterodine include headache, dyspepsia and dry eyes. In the comparative study, oxybutynin caused more adverse effects and patient withdrawals than tolterodine.[2] This should be

interpreted with caution as the starting dose of oxybutynin in the study was higher than usual.

Tolterodine may interact with other drugs that have anticholinergic effects. There is also a potential for adverse interactions with drugs which have cholinergic effects, such as the cholinesterase inhibitors used in the treatment of dementia.

When considering drug treatment for patients with incontinence, prescribers will need to ask if the patient would prefer a drug which may be less efficacious, but might have fewer adverse effects. While tolterodine does appear to help some people with incontinence, its use for overactive bladder is more controversial.

A report from New Zealand suggests that tolterodine has been promoted for use by patients without incontinence as a strategy to expand the market for the drug.[3] While there has been a campaign to raise awareness of overactive bladder in New Zealand, a systematic review concluded that anticholinergic drugs are of questionable clinical significance for the condition. Over 48 hours, patients will have one less micturition than patients taking a placebo, but they will be more than twice as likely to complain of a dry mouth.[4]

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

† At the time the comment was prepared, a scientific discussion about this drug was available on the web site of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int).

Correction

Articaine hydrochloride with adrenaline (Aust Prescr 2005;28:19)

Although the sponsor has registered both 1.7 and 2.2 mL cartridges, only the 2.2 mL cartridges have been marketed in Australia.

Answers to self-test questions

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

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