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to strip in for
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In this issue ...

Whenever the new millennium begins, the end of 1999 was a time for reflection. This is also a time of looking forward and in this issue the members of the Executive Editorial Board of *Australian Prescriber* speculate on the future of their specialties.

In the past century the management of wounds has dramatically improved. Donald MacLellan updates us on the new approach to chronic wounds. Some wounds require surgery, but there are particular problems if the patient is anticoagulated. Rohini Sridhar and Andrew Grigg provide helpful advice on how to manage patients taking warfarin when they need surgery.

In addition to advances in treatment there have also been developments in diagnostic tests. Michael Pain reviews some of the respiratory function tests which were once research tools, but are now used in everyday practice.

One of the problems of everyday practice is remembering all the effects drugs can have on normal physiological functions. Barry Saker reminds us of some of the commonly prescribed drugs which can affect the kidneys. Patients with renal problems may be interested in the work of the Australian Kidney Foundation which has provided the information on page 20.

The electronic version of *Australian Prescriber* has greatly increased the journal's international readership. Apart from the title, the previous cover had no distinctive features identifying Australia. To correct this anomaly, the Executive Editorial Board has selected a new cover with Aboriginal art as its focus. The painting was created for National Medicines Week in 1998 and tells a story of the quality use of medicines. This story is best told by the artist herself, Jennifer Summerfield (see page 19).

EDITORIALS

A century of progress in cardiovascular medicine

P. J. Fletcher, Professor of Cardiovascular Medicine, and Director, Cardiovascular Department, John Hunter Hospital, Newcastle, N.S.W.

(Aust Prescr 2000;23:2)

Cardiovascular medicine is fortunate to have a wealth of clinical trials providing a solid evidence base from which the clinician can make an informed choice of appropriate, efficacious and cost-effective therapies. This trend will continue because of the growing commitment worldwide to the principles of evidence-based medicine.

The progressive fall in age-adjusted cardiovascular mortality, which has been one of the remarkable success stories of the last 25 years, will continue in this millennium. However, even with this improvement, because of the ageing of the population, the total burden of cardiovascular disease on the health care system and on society will continue to increase.

Nowhere will this be more evident than with cardiac failure. Clinical trials will continue to provide evidence of therapies which reduce mortality and need for hospitalisation. However, producing a clinically meaningful improvement in quality of life in this terrible disease may remain an elusive goal. This is because none of our therapies, other than heart transplantation, has so far managed to influence the fundamental problem of loss of myocardium.

There is the potential for molecular biological techniques to address this issue. Myocardial cells have always been considered as terminally differentiated, from shortly after birth. By unlocking the secrets of the processes which control cell differentiation and division, scientists will soon be able to produce new myocardial cells. This will be the first step in a process which has the potential, in the longer term, to repair the damaged heart.

However, it is in the area of pathogenesis and pathophysiology of disease that these molecular approaches will have their greatest impact. Scientists are just starting to reap the rewards from studying animals with either selective deletions or selective over-expression of specific genes. This allows them to test hypotheses about the role of the gene and its product in the pathogenesis of particular diseases.

Drug therapies for children at the end of this century

Noel Cranswick, Clinical Pharmacologist, Royal Children's Hospital, Melbourne

(Aust Prescr 2000;23:3)

It is only in the 20th century, that we (society) have recognised that children are different to adults. Previous generations would dress children up as adults and often send them out to work at an early age, unable to recognise their social and developmental vulnerability.

Our knowledge of therapeutics in children is languishing, even though many influences on our current use of drugs are based upon mistakes made which affected children (e.g. thalidomide). The end of the 20th century has brought with it a renewed interest in the uniqueness of children and their treatment.

Initial attempts by the American Food and Drug Administration to address the 'vulnerable child' resulted in legislation to ensure that only studies of the highest quality were performed in children. The unfortunate result was that even fewer trials were performed in the young. Children have been identified as therapeutic orphans (only 20% of drugs licensed in Australia have paediatric information). There are now incentives, such as extension of marketing exclusivity, to perform studies in children. I hope that this will result in children having full access to the medicines that they need.

This century will further encourage the safe and efficacious use of medicines in children and adults. The human genome project will have defined many of the differences that currently confound our use of drugs. Drugs and doses will be individualised depending upon individual genotype and phenotype (defined by simple bedside testing). The 'numbers needed to treat' statistic will be a thing of the past. No longer will evidence-based medicine meta-analysis be required for treatment of a population – appropriate therapy will be aimed at individuals based upon their unique characteristics. By the start of the 22nd century, many of the therapeutic approaches in current practice will be considered as antiquated as we now consider the widespread therapeutic use of arsenic.

Ageing in the millennium

S. Kanagarajah, Head, Geriatric Medicine, Illawarra Area Health Service, Warrawong, N.S.W.

(Aust Prescr 2000;23:3)

The 20th century has seen a huge change in both longevity as well as social attitudes to ageing. The increase in life expectancy has been due to dramatic improvements in public health, and the application of medical science. The rate of knowledge increase in molecular biology and genetics, in particular, has meant that it is extremely difficult to predict the impact of this on 'healthy ageing'. While cardiovascular disease remains the main cause of mortality and morbidity[1], current treatment options are likely to change dramatically, even within the foreseeable future.

There is much concern that we will survive longer, only to be disabled and therefore dependent on the rest of society. We therefore face very complex questions about how evolving medical advances as well as social changes will impact on the ever-increasing proportion of elderly people. Australia has been a world leader in developing effective and efficient community-based support and rehabilitation for the disabled elderly. However the costs of social support and residential care continue to spiral.

What then will be the role of the doctor and prescriber in this ageing society in the future? While advances will reduce the proportion of disability due to disease, it is likely that there will be a significant (and probably increasing) group of vulnerable elderly people who are dependent, especially on their doctors. These people may not be 'curable', but their lives will be enriched immensely by an empathetic relationship with their doctor which allows them to maintain their autonomy and dignity, have access to wisely applied scientific advances and retain their position as valued members of society.

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Interesting times

John Marley, Professor, Department of General Practice, University of Adelaide, Royal Adelaide Hospital, Adelaide

(Aust Prescr 2000;23:4)

There is an ancient curse, 'may you live in interesting times'. For the latter half of the 20th century it seems that general practice has been its victim. In most countries general practice has gone through multiple re-organisations, profound lows and some major highs. Eventually, governments that have to pay for the delivery of medical care, come round to support for general practice. This is not out of altruism, but a recognition that general practice provides care, which is extremely cost-effective.

The therapeutics revolution following World War II has seen many infectious diseases virtually disappear and conditions which required surgery, such as peptic ulcer disease, as well as others such as hypertension, become almost exclusively treated in general practice.

In prescribing, the uptake of computerised prescription writing is bound to become universal. With it, will come much better decision support systems. These will cope with the uncertainties of general practice in a way that hard line evidence-based medicine currently does not.

General practitioners will work in teams, with other health professionals doing tasks that medical practitioners do not need to do. This already happens in many other countries such as Canada and Holland, and is a liberation rather than a threat. In rural practice, the only viable way to deal with the shortage of rural practitioners is to restructure the way in which medical care is delivered.

In Australia, one of the most highly sought after postgraduate trainings is now general practice. This century is beginning as the last century did, with the bulk of medical care being delivered in general practice.

Whither psychiatry: what might the future hold?

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

(Aust Prescr 2000;23:4)

Mental illness should be a health priority as it is the major cause of community morbidity and untreated illness is a major community cost.

Effective medicines have allowed the community management of patients who previously required prolonged hospitalisation. This process is dependent on developments in psychopharmacology, improved community support and changed attitudes regarding the role of hospitalisation which is now predominantly used for crisis intervention. There has been a major change from the past of shamanism through to alienists and humane therapy with few effective treatments, to a better understanding of the biology of mental illness and its treatment. There is hope for major improvements in treatment with the results of gene studies and the human genome project, better understanding of molecular biology, more effective drug design and improved drug evaluation. However, in the immediate future there is no indication that newer medicines will have greater efficacy than those currently available. Better community awareness and more widespread psychological and social interventions may improve outcomes with available treatments.

Psychiatry is a part of medicine. It can integrate knowledge from psychology and sociology with the new biology. This will lead to a better understanding of the processes of disease and recovery and ultimately improved treatments.

Conquering chemotherapy

J. S. Dowden, Editor

(Aust Prescr 2000;23:5)

Few reading this journal in 2000 will live to see the next century; death for all is inevitable. There should be an increased focus on how we die. As great advances have been made in reducing cardiovascular mortality, the relative importance of cancer will increase.

Chemotherapy can cure certain cancers. Unfortunately, in advanced cancers chemotherapy often merely delays the inevitable, sometimes only for a few weeks. In that short time the patient may have to endure unpleasant adverse effects. Chemotherapy aims to destroy all dividing cells, in the hope that normal cells will recover faster than cancer cells.

Patients are poisoned to the edge of their existence and products such as G-CSF allow us to push them even closer to the precipice. Some patients will fall because of their treatment rather than the disease.

The ability to destroy abnormal cells while sparing normal tissues has a strong appeal. Although it is still in its infancy, immunotherapy could be the way forward. There have been attempts to put the theory into practice, but there is a need to find antigens which are more specific for tumour cells.

I hope that by the end of the next century, we will be able to use the body's own immune system to fight cancer. This would allow us to consign aggressive chemotherapy to the list of twentieth century treatments, which already seem medieval.

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.

St. John's wort

Editor, – I enjoyed reading Professor Mitchell's article on *Hypericum perforatum*, 'St. John's wort – quack medicine or novel antidepressant treatment?' (Aust Prescr 1999;23: 112–3). It is nice to see some openness about herbal medicine in the medical profession. I would like to comment on hyperforin, one of the active ingredients in hypericum. It is true that studies have confirmed the antidepressant activity of hyperforin, however, this compound is very unstable, especially during the drying process of the herb, hence it is unlikely that the extracts which have been shown to be effective in many different clinical trials contained any hyperforin. Yet they worked. The hypericums may not have antidepressant activity in their isolated form, however one study has shown that oligomeric procyanidins (OPCs) are necessary for the bioavailability of hypericum. Hypericum extracts are now being marketed which are standardised to both hypericum and hyperforin, however these are only marker compounds for quality control. When the whole herb extract is used, St. John's wort is a safe and effective medicine for depression, anxiety and tension.

Michael Thomsen

Medical Herbalist

South Hobart, Tas.

Antidepressants

Editor, – I refer to the articles on the new antidepressants (Aust Prescr 1999;22:106–8, 108–11). I have read elsewhere that antidepressants have not been shown to work better than an active placebo such as benztropine mesylate. Active means a placebo that makes you feel as though you are taking something by producing adverse effects such as a dry mouth. Could one of the authors of your recent antidepressant articles comment?

Kevin O'Dempsey

General Practitioner

Kallangur, Qld.

Associate Professor T.R. Norman, the author of 'The new antidepressants – mechanisms of action', comments:

'Active placebos' have been employed occasionally in controlled evaluations of antidepressant drugs. Most often these have been used in tricyclic antidepressant trials to maintain the 'blind' as these drugs are well known for their anticholinergic effects and can often be distinguished from placebo on this basis. Over the course of evaluation of new antidepressants some trials will show no significant difference from placebo, but the weight of clinical evidence is that the new antidepressants are clearly more effective than placebo. Several reasons for the failure to distinguish a psychotropic medication from placebo can be recognised, such as inclusion of incorrect diagnostic groups, mild forms of depressive illness, failure to include a placebo washout period prior to commencing trial medication, and non-compliance with the study drug. Non-specific factors in treatment are also important and the psychotherapeutic aspect of a patient regularly consulting with someone willing to listen to their problems cannot be ignored. Furthermore, it should be recognised that the natural history of depression is for recovery to eventually take place, without treatment. (Medications can considerably shorten the period to recovery.) Clearly, if patients are at the point of recovery then any treatment, active drug or placebo, will apparently be 'successful'.

Chronic wound management

D. G. MacLellan, Professor of Surgery, Canberra Hospital, Canberra

SYNOPSIS

The cause of a chronic wound must be identified before treatment can begin. This assessment includes an evaluation of the patient's general health, nutrition and medication. The cause of the wound dictates the management including the choice of dressing. Moist wound dressings are now preferred. As ulcers may take months to heal prevention is important. Patients with diabetes particularly need instruction on how to take care of their feet. A multidisciplinary approach is recommended.

Index words: diabetes, dressings, ulcers, infection.

(Aust Prescr 2000;23:6–9)

Introduction

Wound healing is an absolute prerequisite for survival. Without the ability to heal wounds, the body will succumb to haemorrhage or infection. It is no surprise that wound healing practices have been recorded from the time of the Smith Papyrus in 1700 BC.

In the last two to three decades there has been a revolution in wound management. Since the discovery of the first growth factor in 1962 – epidermal growth factor – the science of wound repair and regeneration has advanced enormously. Other research has prompted the change from the outdated 'dry dressing technique' to the moist wound concept of healing.[1] These two major advances have led to a rethinking of the management of wound repair and to an exponential growth in the development of new wound dressings.

Unfortunately, the management of both acute and chronic wounds is inconsistent and thus wounds consume an inordinate amount of the Australian health budget.[2] Wound care practices can and must be optimised. However, progressive wound management is not inextricably determined by the use of modern wound dressings. To increase wound healing, the clinician must understand the process of wound repair and adhere to the basic principles of wound management.

Principles of wound healing

Before treating a wound, it is essential to find the underlying cause and consider other patient factors which may delay wound healing. After deciding which wound dressing is most appropriate, it is important to plan how to maintain healing and prevent recurrences. The major deficiency in the management of chronic wounds is the failure of clinicians to adhere to these basic principles of wound healing (Table 1).

Define the aetiology

It is remarkable how infrequently objective efforts are made to find the cause of wounds, particularly chronic wounds such as leg ulcers. As a consequence, optimal wound healing rates are not achieved and the ulcer either will not heal or recurs all too quickly. The major causes of wounds are well known (Table 2) and they should be looked for in each patient.

Table 1

Principles of wound healing

1. Define the aetiology
2. Control the factors affecting healing
3. Select an appropriate moist wound dressing
4. Plan for maintenance of the healed wound

Table 2

Major causes of wounds

Acute	*Chronic*
Trauma	Ulcers
Burns	Pressure
Crushing injuries	Traumatic wounds
Lacerations	Surgical wounds
	Neoplastic wounds
	Leg ulcers
	Arterial
	Venous
	Vasculitic
	Neoplastic
	Neuropathic

A systematic and rational approach to defining wound aetiology requires a careful history, a complete physical examination and appropriate investigations. Many protocols exist to ensure that the proper diagnosis is made. One such example is the protocol for the investigation of leg ulcers (Fig. 1).[3]

Control factors affecting wound healing

Both intrinsic and extrinsic factors will affect wound healing rates (Table 3). Optimal control of these factors ensures that the patient's overall health is improved which in turn benefits wound healing.

Table 3

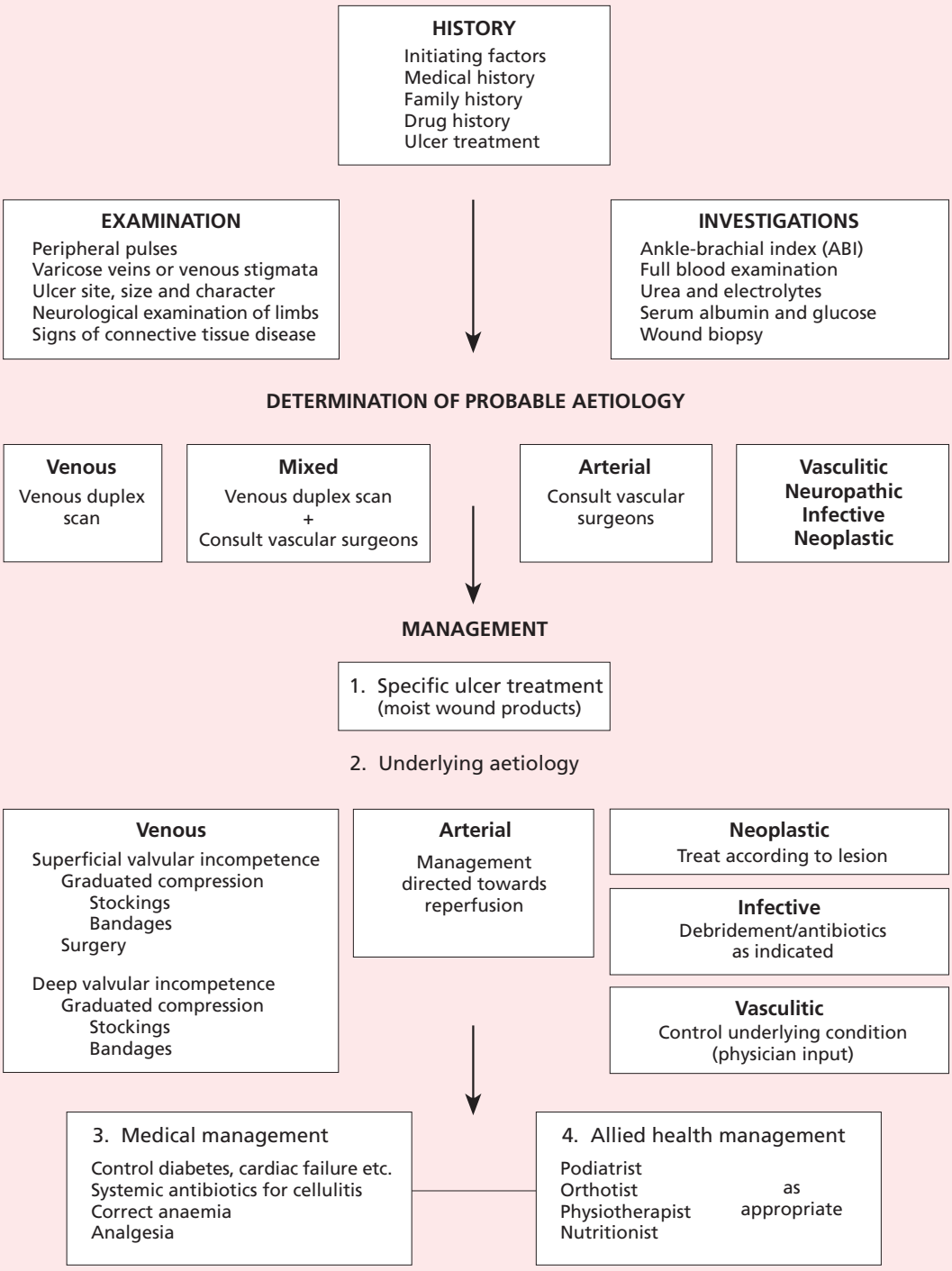
Factors affecting wound healing

Intrinsic factors	*Extrinsic factors*
Health status	Mechanical stress
Diabetes	Debris
Circulation	Temperature
Anaemia	Desiccation
Immune status	Infection
Age	Chemical stress
Nutritional status	Medication

Fig. 1

The protocol for the investigation of leg ulcers

(Based on the chart devised by D.G. MacLellan for the Wound Foundation of Australia)



Intrinsic factors

The patient's general health has important implications for wound healing. Many medical conditions adversely affect wound healing rates and some cause specific wound healing problems. For example, wounds in patients with diabetes have a poor inflammatory response and a higher rate of infection. Optimising diabetic control improves wound healing.

The nutritional status of the patient can often be overlooked in the clinical assessment. An adequate intake of calories is required for the energy demands of the normal reparative process. Certain vitamins and trace elements (vitamins C, A, K and B, zinc and copper) are also essential for wound healing. These are mostly available in a well balanced diet with plenty of fresh fruit and vegetables.

Painful wounds also can result in vasoconstriction and decreased tissue oxygen. The patient's pain must be treated or it will delay wound healing.[4]

Extrinsic factors

Mechanical stress

Unrelieved pressure on a pressure ulcer will contribute to ongoing tissue destruction. Any patient who is immobile, in bed or in a chair is particularly vulnerable to the development of pressure ulceration.

Debris

Wounds containing necrotic tissue will not heal. Debris and necrotic tissue must be removed. Surgical and autolytic debridement are essential components of wound healing.

Temperature

As cells and enzymes function optimally at body temperature, a temperature fall of 2ºC is sufficient to affect biological processes. A simple dressing replacement can drop the wound temperature for up to four hours before it slowly returns to normal. The wound should therefore be insulated and not left exposed for longer than necessary.

Desiccation

Cells, enzymes and growth factors cannot function in a dry environment. Wounds should not be 'dried out' by exposure to the air or the sun, chemical means or dry bandages. Drying kills the surface cells and increases the reparative requirements. Granulation tissue is fragile and is easily damaged. In particular, the removal of dry dressings can disrupt the wound healing process and return it to an earlier (inflammatory) phase of healing. A moist wound significantly enhances the healing process.

Clinical infection

The features of infection include increasing pain and pus at the wound site, lymphangitis, lymphadenopathy and systemic features, such as fever or rigors. Clinically significant infections must be treated with appropriate antibiotics.

There is considerable overuse of wound swabs for microbiological assessment of chronic wounds. Too often this leads to the inappropriate prescribing of antibiotics. As wound swabs generally remove the surface bacteria, they frequently only identify the non-pathogenic colonising organisms on the wound surface. Wound swabs should be confined to ulcers showing clinical evidence of infection which have slough or tissue that can be gathered by the swab. If there is infection, the pathogenic bacteria are in the tissue and a biopsy may be needed to find them.

Chemical stressors

All antiseptics are cytotoxic! They damage cellular elements and the microcirculation of the wound. Although antiseptics may have a role in the topical management of heavily contaminated acute traumatic ulcers, they are often inappropriately used for long periods of time on chronic ulcers. The need to sterilise a chronic ulcer to achieve healing is unproven and there is thus little evidence to support the ongoing use of antiseptics in chronic wound management.

Drugs

Many medications have adverse effects, which interfere with, or delay wound healing. Steroids and anti-inflammatory drugs are immunosuppressive and reduce the inflammatory phase of wound healing. Although many of these drugs are essential for the patient's continuing health, it is important to realise they can have a deleterious effect on wound healing. Many older patients are on multiple drugs, some of which may affect wound healing, so wound management is an opportunity for a medication review.

Select an appropriate wound dressing

Many types of wound dressings are available (see 'Current concepts in wound dressings' Aust Prescr 1996;19:11–3). The choice of dressing is influenced by the type of wound.

Plan for maintenance of healing

Consideration must be given to the maintenance of healing in order to prevent recurrences. For example, in chronic venous insufficiency due to deep valvular incompetence, maintenance includes the long-term use of measured and fitted graduated compression hosiery. In addition, good skin care, regular exercise, a balanced diet and careful control of other medical conditions will further benefit the patient and assist in the prevention of recurrences.

Chronic leg ulcers

One of the commonest chronic wounds encountered in general practice is leg ulceration. Not only is the prevalence of leg ulcers relatively high but many patients suffer their leg ulcers for many years without healing. Recurrence rates are also depressingly high.

It cannot be over-emphasised that the key to successful healing begins with the accurate determination of the aetiology (Fig. 1). The cause directs the management plan.

Arterial ulcers

Assessing the arterial perfusion in patients with leg ulceration is essential. The clinical history will give some indication about the degree of lower limb ischaemia. Palpation of the peripheral pulses and auscultation for bruits will add objective evidence. A hand-held Doppler can be used to assess the presence and characteristics of the arterial flow. With the additional use of a blood pressure cuff and sphygmomanometer, the ankle-brachial index (ABI) may be estimated:

$$\text{ABI} = \frac{\text{ankle systolic pressure}}{\text{brachial systolic pressure}}$$

An ABI of 0.9–1.1 is considered normal, but below 0.8 is an indication of arterial insufficiency. Caution is advised if any compression therapy is being considered in the management of leg ulcers with ABI ratios of less than 0.8.

Venous ulcers

The diagnosis of venous aetiology relies on an appropriate history of venous disease, clinical evidence and objective assessment by venous duplex scanning. A further requirement is the exclusion of significant arterial insufficiency. The optimum method of treating the venous ulcer is with graduated compression therapy using either a high or low

Table 4

Foot care

Do:	*Do not:*
Wash feet daily – mild soap	Use corn cures
Inspect feet daily	Use hot water bottles
Treat problems urgently (early)	Walk barefoot
Visit the podiatrist regularly	Cut corns/callosities
Wear sensible shoes	Self-treat foot problems

stretch bandage. These bandages are applied from the toes to the knee and require an underfelt of orthopaedic wool or equivalent to protect the skin particularly over pressure points. Compression therapy, particularly multilayer, is highly effective in healing venous ulcers and is thus the mainstay of treatment. Crepe bandages do not deliver or sustain the compression needed to heal venous ulcers.

Once appropriate compression therapy begins patients should be encouraged to walk and exercise. In particular, the calf muscle pump should be active. When not walking or exercising, it is advisable that the feet are elevated. However, elevation of the legs is not an acceptable alternative to walking and exercise.

Diabetic foot ulcers

Foot ulcers in diabetics are preventable! Prevention requires a multidisciplinary approach as does successful management of foot ulcers should they occur. The patient should be educated in foot care and instructed to examine their feet daily (Table 4). Careful and regular examination of the patient's feet by the clinician should also assist in uncovering problems in time to prevent ulcer development (Table 5). A foot ulcer in a diabetic patient can have dire consequences as it can lead to amputation and increased mortality. Three main factors determine the aetiology of the diabetic foot ulcer either individually or in concert: neuropathy, ischaemia and infection.

Treatment is determined by the contribution these three factors make to the ulceration. Weight redistribution using specialised orthoses, arterial reperfusion, surgical debridement and antibiotic therapy may all be required. The multidisciplinary approach to the diabetic patient with a foot ulcer is therefore a prerequisite for a successful outcome and saving the limb.

Conclusion

Successful wound healing requires adherence to the principles of wound management. Healing these persistent ulcers will significantly improve the quality of life of long-suffering patients as well as reducing the enormous burden on the health budget. Wound management practices certainly have to improve! Our patients surely deserve optimal healing rates.

Table 5

Diabetic foot examination

Deformity	Charcot's, pes cavus, claw toes, hammer toes
Infection	crepitus, fluctuation, deep tenderness
Atrophic nails	also fungal infection/subungual ulcers
Breakdown of skin	ulcers, fissures, blisters
Edema	pitting oedema lower limbs
Temperature	cold – ischaemic hot – infection
Ischaemia	pulses may be weak/absent
Callosities	plantar surface, metatarsal heads
Skin colour	red – Charcot's/infection pale – ischaemia pink with pain and absent pulses – ischaemia

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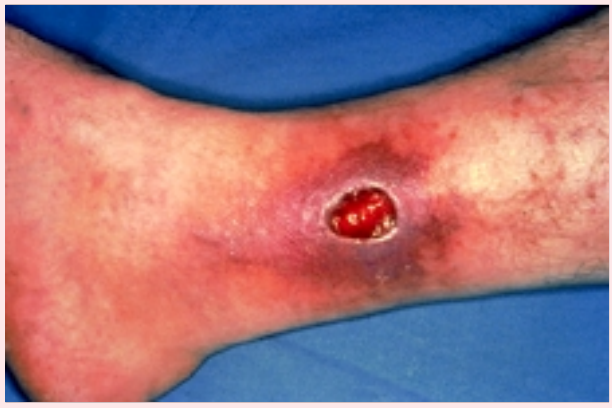
Mixed arterial and venous ulcer



Picture provided by Professor D. MacLellan, Department of Surgery, Canberra Hospital

Self-test questions

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

1. Swabs should be taken regularly from chronic leg ulcers to detect infection at an early stage.
2. Chronic leg ulcers heal more quickly if they are kept dry.

DIAGNOSTIC TESTS

Basic tests of respiratory function

Michael C. F. Pain, Director of Thoracic Medicine, Royal Melbourne Hospital, Melbourne

SYNOPSIS

Respiratory function tests are part of the clinical assessment of many respiratory diseases. The tests can measure individual parts of the respiratory process and, therefore, need to be selected appropriately. Spirometry is the basic screening test for assessing mechanical load problems. Arterial blood gas analysis yields considerable information about gas exchange efficiency while tests of gas transfer assess alveolar-capillary surface function. When specifically indicated, assessing bronchial reactivity and the response to exercise can help in the evaluation of breathlessness.

Index words: pulmonary physiology, spirometry, breathlessness.

(Aust Prescr 2000;23:10–2)

Introduction

In the last 45 years tests of respiratory function have moved from the research laboratories of university departments into the world of everyday practice. This is appropriate as the tests greatly improve diagnostic skills and disease management.

There are many different respiratory function tests, each with strengths and weaknesses. Importantly, a report of respiratory function is only as good as the extent of patient co-operation, the training and skill of the technical staff, the equipment used and the experience of the reporter. Guidelines for the standardisation of testing, equipment performance and normal values have been published and generally accepted.[1,2,3]

Respiratory function tests are an objective measure of abnormal physiology and a means of following a patient's progress (see box). Considerable reliance is placed on respiratory function testing in the assessment of work-related respiratory illness. The tests rarely provide a single clinical diagnosis and must always be interpreted within the full clinical context. They also require co-operation (sometimes maximal performance) from the patient, and this may limit their usefulness in certain situations.

Lung function tests are most useful in the following situations

- the analysis of breathlessness of obscure origin or when the complaint appears out of proportion to the objective clinical evidence
- the quantitation of respiratory impairment (e.g. fitness for surgery, employment or travel)
- following progress or deterioration, either spontaneous or in response to therapy, (e.g. asthma, fibrosing alveolitis, respiratory failure)
- assessment for medicolegal purposes

For the purposes of testing, the respiratory process can be simplified into its major components. Breathing (i.e. *ventilation*) results when a given *respiratory drive* interacts with a certain *respiratory load*. This process requires work and results in *gas exchange*. Inadequacies in gas exchange should lead to attempts at correction by a readjustment of drive. Direct testing of respiratory drive is not easy. Defects in respiratory drive are usually inferred from monitoring the effect of an abnormal load on ventilation.

Simple measurements of respiratory load

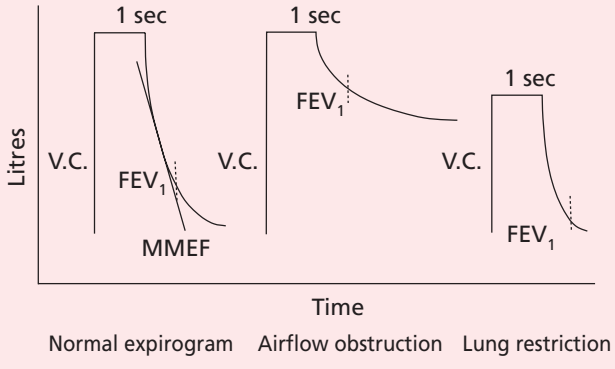
Increases in the respiratory load to breathing are very common. Resistive load increases, such as asthma, obstructive bronchitis, cystic fibrosis and emphysema, impair airflow. Elastic load increases such as interstitial fibrosis, muscle paralysis and obesity impair lung inflation. The quantitation of respiratory load involves determining the vital capacity and the speed of maximal expiratory flow.

The peak flow meter is widely promoted as a simple lung function monitor. Serial measurements in conditions such as

Fig. 1

Volume/time curve

The basic forced expirogram patterns. Usually about 75% of a normal sized vital capacity is expelled in a second. In airflow obstruction, the amount expelled in one second is a much smaller fraction of the vital capacity. In lung restriction the small vital capacity can be mostly expelled in about a second.



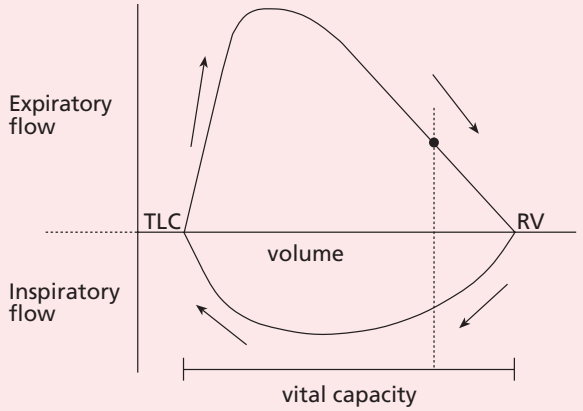
V.C. – Vital capacity

FEV_1 – Forced expiratory volume in 1 second

MMEF – Maximal mid-expiratory flow, which is the slope of the volume/time line drawn over the middle 50% of vital capacity

Fig. 2

Maximal expiratory and inspiratory manoeuvres plotted as a flow-volume curve. The dotted vertical line indicates the point of maximal flow after expelling 75% of the vital capacity.



TLC - Total lung capacity
RV - Residual volume

asthma provide valuable information about disease progress. However, peak expiratory flow (the earliest portion of forced expiration) is very effort-dependent. Also, peak flow measurements give no information about elastic load abnormalities.

Load assessment is best done with spirometry. This provides a written record of slow (VC) and/or forced vital capacity (FVC), forced expired volume in one second (FEV_1) and maximum mid-expiratory flow (MMEF). Most modern electronic spirometers plot volume against flow rate and permit inspiratory as well as expiratory manoeuvres. The machine makes the calculations and corrections and prints out the measured indices.

Expiratory spirometric patterns (Figs. 1 and 2) can be classified as:

Normal	Vital capacity within the statistical normal range for height, age and gender. A normal proportion of the VC can be forcibly expelled within a second (i.e. FEV_1/VC is 70–80%).
Obstructive	FEV_1/VC is below normal. Vital capacity may also be below normal.
Restrictive	Vital capacity below the statistical normal range. FEV_1/VC is higher than normal and may be 100%.
Mixed obstructive and restrictive	Vital capacity below normal and FEV_1/VC below 70%.

In severe obstruction, the vital capacity may be very reduced. Deciding if a restrictive or obstructive process predominates, may need the measurement of static lung volumes (functional residual capacity or residual volume) to assess the degree of hyperinflation. In practice, this distinction can usually be made clinically and static lung volume measurement is only occasionally important.

Diseases predominantly involving the very small airways (bronchiolitis, interval asthma) produce recognisably distinctive spirometric abnormalities. Indices of small airway function include the MMEF and the expiratory flow during the last phase of expiration. On an expiratory flow-volume curve, small airway abnormality is shown as a concavity in the descending limb and a reduction in the measured flow at some point in the expired vital capacity – often the flow at 75% vital capacity. These simple tests of small airway function are only useful if there is not concomitant larger airway obstruction.

Forced inspiratory volume measurements, when contrasted with equivalent expiratory volumes, can detect the presence of upper, extrathoracic airway obstruction such as retrosternal goitre or vocal cord paralysis. This form of obstruction is less during expiratory manoeuvres so that the ratios of FIV_1/FEV_1, MMIF/MMEF and flows at 75% vital capacity on an inspiratory and expiratory flow-volume curve become less than unity.

Asthma

Asthma is a common cause of airflow limitation. The reversibility of the airways obstruction is usually assessed by spirometry before and after a bronchodilator aerosol. An increase of 10% or more in either vital capacity or FEV_1 is taken to indicate significant reversibility, although, of course, not necessarily the maximum reversibility achievable.

When the suspicion of asthma is not confirmed by spirometry, a challenge procedure can be used to assess abnormal bronchial reactivity. This may involve the patient exercising or inhaling histamine, methacholine, hypertonic saline or cold air. Each challenge has its own protocol and risks, and these challenges are best performed in a well-supervised laboratory. Bronchial hyperreactivity is not synonymous with asthma. Although the vast majority of patients with ongoing asthma will have brisk reactivity, most people with a past history of asthma will have intermediate reactivity and some asymptomatic people with no past history will have a degree of bronchial reactivity. Bronchial reactivity is often expressed as the percentage concentration or dose of an agent that produces an acute fall of 20% in FEV_1 (PC_{20} or PD_{20}). Laboratories performing these challenges will usually have established their 'normal reactivity' values.

Simple measurements of gas exchange

Normal gas exchange requires adequate alveolar ventilation, normal ventilation/blood flow relationships and adequate alveolar-capillary membrane surface area. There are tests of varying sophistication which specifically examine each of these functions.

Alveolar ventilation

This is not easy to measure directly, as it is not a simple function of the volume of expired air passing the mouth each minute (i.e. the minute ventilation). The size of the dead space (alveolar dead space, connecting tubing volume and tracheobronchial tree) is often uncertain. This uncertainty, combined with the influence of the breathing pattern, means that minute ventilation may be a very misleading estimate of

alveolar ventilation. To overcome this difficulty, the arterial carbon dioxide tension is used as an inversely proportional index of 'effective' alveolar ventilation. Hence, a normal arterial carbon dioxide tension is taken to indicate satisfactory alveolar ventilation. Elevated or reduced carbon dioxide tensions reflect alveolar hypoventilation or hyperventilation respectively.

Ventilation/blood flow relationships

These are most simply assessed by considering the lungs as a gas exchanger. Its efficiency is rated by the size of the difference between the amounts of oxygen and carbon dioxide in the blood and in the air. If the lungs are working efficiently the differences in composition will be small. Non-uniformity of ventilation/blood flow ratios will result in abnormally wide differences – the alveolar-arterial PO_2 and arterial-alveolar PCO_2 gradients will be abnormal. The oxygen tension gradient is normally less than 10% of the inspired oxygen tension. This simple index can be calculated using the alveolar gas equation (see box).

Alveolar-capillary surface area

This is assessed by one of several techniques measuring the uptake of carbon monoxide, a gas with affinity for blood and which is easily analysed. Although sometimes designated as tests of diffusion, these techniques are much more influenced by effective alveolar-capillary area and therefore are now more commonly termed gas transfer tests. Although many factors influence the result, these tests are usually abnormal in diffuse interstitial inflammatory and fibrotic processes and in emphysema. They are useful in the subclassification of restrictive conditions (those with and without gas transfer impairment) and in determining the probable extent of emphysema in patients with chronic airflow obstruction. They are commonly used in following patients' response to therapy in such conditions as sarcoidosis and fibrosing alveolitis.

Example: simplified calculation of the alveolar-arterial oxygen tension gradient

Given data: arterial oxygen tension = 55 mmHg
arterial carbon dioxide tension (P_aCO_2) = 55 mmHg
inspired oxygen concentration = 21% (room air)

hence inspired oxygen tension (P_IO_2) = 150 mmHg
(21/100 of (barometric pressure – 47*)
or multiply concentration by 7.1 if at sea level)

Derive alveolar oxygen tension (P_AO_2) from the alveolar gas equation

$$P_AO_2 = P_IO_2 - P_aCO_2/R$$

(R is the gas exchange ratio and is assumed to be 0.8)

$$= 150 - 55 \times 1.25$$

$$= 81 \text{ mmHg}$$

Hence the **alveolar-arterial PO2 gradient** is 81 – 55 = **26 mmHg**

Interpretation: As well as ventilatory failure, as demonstrated by the alveolar hypoventilation, there is also a degree of ventilation/blood flow mismatching since the gradient is greater than normal (<15 mmHg).

* 47 mmHg is the water vapour pressure at 37°C

Simple exercise testing

Tests performed during exercise provide information about overall fitness and the appropriateness of cardiorespiratory responses. They can be elaborate procedures following cardiac output, pulmonary haemodynamics, gas exchange and anaerobic metabolism measurements at varying grades of exercise, but this type of study has little place in everyday practice. Observations made during a six-minute walk test can provide useful objective information provided the subject is induced to co-operate fully. The actual distance walked, the degree of breathlessness experienced and the change in blood oxygen level (assessed by portable oximetry) are data which can be obtained simply. These data are required before some authorities will agree to provide portable domiciliary oxygen. The extent of exercise limitation due to mechanical load excess agrees reasonably well with the degree of impairment on spirometry.[4]

When to use respiratory function tests

The most common reason for studying pulmonary function is in the analysis of breathlessness. The application of simple tests of load (spirometry[3]), gas exchange (arterial blood gas analysis[5]) and gas transfer will usually allow conclusions as to whether or not the complaint is reasonably based.

In hospital practice, the gas exchanging aspects of pulmonary function become important in the assessment and management of acute respiratory failure.

Respiratory function tests are also widely used to assess fitness for surgery, fitness to undertake certain occupations or to assess the degree of impairment in work-related lung conditions.

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Self-test questions

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

3. Healthy adults usually cannot forcibly expel more than 60% of the vital capacity within one second (FEV_1).
4. To be meaningful, spirometry demands total co-operation from the patient.

The perioperative management of anticoagulation

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SYNOPSIS

The perioperative management of patients on long-term warfarin therapy poses particular problems. This situation is exacerbated by the absence of randomised trials. The strategy used is based on the assessment of each patient's thromboembolic and bleeding risks. These determine the need for withholding warfarin and switching to heparin. Most patients having minor procedures can continue to take warfarin, provided that they are closely monitored and local measures are used to ensure adequate haemostasis.

Index words: thromboembolism, heparin, warfarin, haemostasis.

(Aust Prescr 2000;23:13–6)

Introduction

The most common indications for long-term oral anticoagulation with warfarin are venous thromboembolism, mechanical cardiac valves and atrial fibrillation. When patients with these conditions need surgery, the perioperative management of their warfarin therapy poses a major problem. Withholding warfarin increases the risk of thromboembolism, particularly in the context of surgery which itself increases the thrombotic risk. To minimise the risk of perioperative thrombosis, alternate anticoagulation with heparin is often used. Perioperative anticoagulation is accompanied by an increased risk of postoperative bleeding. There is no consensus on the optimal approach to anticoagulation in the perioperative period. In each individual patient, rational decisions must be made after weighing up the haemorrhagic and thrombotic risks.

Risks of temporarily withholding warfarin

The risks are difficult to quantify due to the lack of randomised trials examining this issue. They vary according to the indication for the warfarin therapy.

Patients with cardiac valve replacement

In patients with mechanical heart valves, the thromboembolic risk increases 3.7 fold when anticoagulation is stopped.[1] The incidence of thrombotic complications is higher in patients with the following risk factors:

- patient related:
  - advanced age
  - left atrial enlargement
  - history of thromboembolism
  - increased fibrinogen
  - atrial fibrillation and/or cardiomyopathy
  - congestive cardiac failure
- valve related:
  - mechanical versus tissue valves
  - first generation valves (Starr-Edwards, Bjork Shiley) versus later generation valves (St. Jude, ATS, Carbomedics)
  - mitral position

The rates of thromboembolic events differ with valve position and type. In a study of 1608 patients with mechanical valves, the lowest event rate was seen in patients with a prosthetic aortic valve.[2] Bileaflet valves (e.g. St. Jude) had the lowest thromboembolic event rate followed by the tilting-disc (Bjork Shiley) and caged-ball (Starr-Edwards) valves.

Do the benefits of anticoagulation outweigh the risks?

The approach to the management of anticoagulation in patients with prosthetic valves undergoing non-cardiac surgery remains controversial. The need for perioperative anticoagulation in patients with mechanical heart valves has been questioned in a recent review. The authors argue that for every 10 000 patients with mechanical heart valves who are given perioperative intravenous heparin, three thromboembolic events are prevented at the cost of 300 major postoperative bleeding episodes.[3] These figures are calculated by assuming an average thromboembolic rate of 8% per year in patients with mechanical heart valves, an anticoagulation-free period of four days and a 3% risk of major postoperative bleeding with intravenous heparin. In light of these calculations, a risk-benefit analysis would preclude the use of *full dose* anticoagulation during the perioperative period in patients with mechanical valves, except in patients with very recent arterial embolism who have a high risk of recurrence in the absence of anticoagulation. In the absence of recent embolism, the authors recommend, for hospitalised patients, the use of subcutaneous low dose unfractionated or low molecular weight heparin at doses used for *prophylaxis* against venous thromboembolism, with no prophylaxis for outpatients.

There are limited prospective data to support or contradict these recommendations. The available literature consists mainly of small, non-randomised trials from which no definitive conclusions can be drawn. In one of the few prospective studies, 45 patients with mechanical heart valves underwent

non-cardiac surgical procedures.[4] No thromboembolic events were seen in 26 patients with *aortic* prostheses in whom warfarin was withheld for a total of 6–10 days perioperatively. In 19 patients with *mitral* prostheses, the warfarin effect was reversed with vitamin K on the day of surgery. A heparin infusion was started 12 hours after the operation and warfarin was resumed on the third postoperative day. No thromboembolic events were observed in this group.

Besides being a small non-randomised trial, the other drawback of this study was the lack of long-term follow-up. Valve thrombosis, especially with the tilting-disc (Bjork Shiley) valves, develops slowly and insidiously and may not be evident for 1–2 months. Hence, an uneventful early postoperative period may provide false reassurance that the perioperative anticoagulation has been safe and successful.

A recent review evaluated retrospectively the risk of perioperative bleeding during non-cardiac surgery in 235 patients with mechanical prosthetic heart valves.[5] A variety of perioperative anticoagulation strategies was used. On multivariate analysis, only a tilting-disc valve in the mitral position and surgery for tumour were found to be predictive factors for a thromboembolic event. Discontinuation of warfarin less than 48 hours before surgery and reinstitution of intravenous heparin within four hours following surgery significantly increased the risk of bleeding. No embolic or haemorrhagic events were detected in 22 patients treated with perioperative low molecular weight heparin.

What to do

The lack of adequate data makes it difficult to give firm recommendations. Patients on warfarin for *tissue* valves (usually mitral) are usually managed preoperatively by cessation of their warfarin without heparin replacement. In contrast, common practice in Australia has been to admit patients with *mechanical* valves prior to surgery for full dose anticoagulation with intravenous heparin. There are preliminary data to suggest that subcutaneous low molecular weight heparin may be substituted safely for intravenous unfractionated heparin. The evidence suggests that anticoagulation with either heparin may not be required for all patients. The final decision should take into account individual patient factors such as the surgical procedure, the type and location of the prosthetic valve and whether or not there are other indications for anticoagulation.

Patients with prior venous thromboembolism

The risk of withholding warfarin therapy in patients with venous thromboembolism depends on the timing of the thrombosis and the patient's history.

Time interval following the thromboembolic event

The risk of recurrence in the absence of anticoagulation is highest in the first month following a deep vein thrombosis (DVT) and declines sharply over a three month period. Although the risk of withholding warfarin in the immediate post-thrombotic period has not been quantified, it is estimated to be 40% over a one month interval i.e. greater than 1% for each day without anticoagulation.[3] This suggests that, if possible, surgery should be avoided in the first month following an acute DVT and, if surgery is imperative, full dose intravenous heparin should be used.

History of recurrent DVT

Discontinuation of warfarin is associated with a risk of thromboembolism of approximately 15% per year. These patients should receive perioperative heparin, especially if they are having urological or orthopaedic surgery.

Patients with atrial fibrillation

In patients with non-valvular atrial fibrillation, the average risk of systemic embolism in the absence of anticoagulation is approximately 4.5% per year.[6] The risk is higher in individuals with a history of systemic embolism in the past 12 months. The risk appears to be higher in the first month following an arterial thromboembolic event. However, the overall risk of thrombosis is so low that the risk of bleeding following major surgery probably outweighs the benefits of postoperative heparin even in prophylactic doses.

Strategy for perioperative anticoagulation

The anticoagulation strategy selected depends upon an evaluation of the thromboembolic risk and the haemorrhagic risk of the surgical procedure.

Minor procedures

Oral anticoagulants may be continued at a lower therapeutic level (INR 1.5–1.8) for minor procedures with a low risk of bleeding.[7] These include excision of skin lesions, bone marrow biopsies, cataract surgery and procedures in which the bleeding can be controlled readily by local measures. This approach is not recommended for laparoscopic surgery and ultrasound or CT-guided biopsies.

Major procedures

The strategy for perioperative anticoagulation in patients undergoing major surgery is based more on the assessment of the risk of thromboembolism than the risk of haemorrhage. Patients can be divided into two risk groups (Table 1). In the low-risk group warfarin is withheld for five days before surgery, but no alternate anticoagulation is given (Table 2). High-risk patients should receive aggressive alternate anticoagulation with unfractionated or low molecular weight heparin (Table 2).

Low molecular weight heparins are commonly used as prophylaxis against venous thromboembolism prior to and after major surgery. They are more effective than low dose heparin in orthopaedic patients who are at high risk for venous thromboembolism. Low molecular weight heparins do not increase the risk of bleeding any more than low dose heparin and are more convenient to use as laboratory monitoring is generally not required.

There is considerable variability amongst individual surgeons as to an acceptable upper limit of the INR on the day of surgery. In particular, neurosurgeons generally prefer a near normal INR, while vascular surgeons may accept an INR of 1.5–2.0.

Table 1

Risk of thromboembolism if anticoagulation is withdrawn

	Low	*High*
Atrial fibrillation and/or cardiomyopathy	Without stroke or systemic embolisation in the last 12 months	With stroke or systemic embolisation within the last 12 months
Biological heart valves	Except during first three months	During first three months
Prosthesis	Vascular grafts	Cardiac mechanical valves (mitral>aortic)
Venous thrombosis	Not within the last three months and without a confirmed hypercoagulable state	*Within the last three months, or recurrent venous thrombosis
Systemic arterial emboli	Non-recurrent	Recurrent

Note: two low-risk factors = high risk

* The risk in patients with a confirmed hypercoagulable state but no venous thrombosis within the previous three months, and no recurrent thrombosis, has not been established.

The acceptable INR will also depend on the individual surgical characteristics of each patient.

Insertion of a vena caval filter should be considered if (a) the patient has had a pulmonary embolism or proximal DVT within a month or (b) the risk of bleeding from anticoagulation is unacceptable in a high-risk patient.

Anaesthetic considerations

There are concerns about the possibility of extradural haematoma formation in patients receiving heparin and undergoing epidural/spinal anaesthesia. Unfractionated heparin should be ceased at least six hours prior to such an anaesthetic and low molecular weight heparin ceased a minimum of 12 hours (and preferably 16–18 hours) beforehand, at which time anti-Xa values (the best laboratory test for activity of such heparins) fall to low levels. A longer delay is advisable in patients with renal insufficiency in whom excretion of low molecular weight heparin is reduced. If a low molecular weight heparin is used the night prior to epidural/spinal anaesthesia planned for the next morning, the dose preferably should be the thromboprophylactic dose rather than the full anticoagulation dose.

Table 2

Recommendations for perioperative anticoagulation of patients undergoing major elective surgery

Day	*Low-risk patients*	*High-risk patients*
– 5 (pre-op)	Cease warfarin	
– 4	No anticoagulation	Cease warfarin Measure INR Start full dose UFH as inpatient ***OR*** LMWH* as outpatient. Continue daily until day –1.
– 1		Stop LMWH a minimum of 12 hours and UFH six hours before surgery.
0 (surgery day)	Measure INR and if >2.0 on the morning of surgery, options include: postponement of surgery, fresh frozen plasma. Consult haematologist.	
+ 1	Start warfarin as soon as oral fluids tolerated using the preoperative maintenance dose. A lower dose may be required if INR >1.2 or if other drugs are being used.	Once haemostasis secured, and generally after at least six hours post surgery: • recommence LMWH (preferred) or UFH (do not commence with bolus dose) • start warfarin as soon as oral fluids tolerated using the preoperative maintenance dose. A lower dose may be required if INR >1.2 or if other drugs are being used. • cease UFH/LMWH when INR >2.0 on at least two consecutive days • if patient discharged before INR >2.0, use LMWH as an outpatient

UFH = standard unfractionated heparin
LMWH = low molecular weight heparin

* Alternatives include enoxaparin 1.5 mg/kg once daily, dalteparin 100 IU/kg twice daily or nadroparin (weight adjusted). At present, these drugs have Pharmaceutical Benefits Scheme listing for treatment of deep venous thrombosis and for prophylaxis of hip surgery. These doses are those approved, as at February 2000, for full-dose anticoagulation for venous thromboembolism.

Notes:

- Insertion of a vena caval filter should be considered if (a) the patient has had a pulmonary embolism or proximal DVT within a month or (b) the risk of bleeding from anticoagulation is unacceptable in a high-risk patient.
- These guidelines may not necessarily be applicable to neurosurgical procedures or for patients with mechanical valves undergoing cardiac surgery. Generally, each department has established their own individual guidelines.

Dental surgery in the anticoagulated patient

Non-surgical dental procedures (professional cleanings, fillings, crowns, etc.) are not associated with a significant bleeding risk and can be performed safely while the INR is in the therapeutic range.

Traditionally, many dentists have withdrawn warfarin before some dental surgical procedures. Recent evidence, however, suggests that the recommended approach is not to discontinue warfarin. In the English language literature, there are reports of approximately 2014 dental surgical procedures including multiple and full mouth extractions, alveoectomies and surgical extractions in 774 patients taking warfarin.[8] Less than 2% of these patients had serious bleeding problems, defined as bleeding uncontrolled by local measures. Another study compared postoperative bleeding following dental extractions in 106 patients on warfarin and 106 normal patients. It found no difference in the incidence or severity of bleeding.

In contrast, in 542 dental procedures in 493 patients in whom warfarin was withheld for the procedure, five (1.0% of patients; 0.9% of procedures) had serious embolic complications (including four deaths). Although suggestive, a direct cause and effect relationship between withholding warfarin and a thromboembolic event is unproven.

Approach to dental surgery

1. Check INR the day before the procedure to ensure it is within the therapeutic range for the patient. If above this, delay surgery until the INR is within the therapeutic range.
2. In the majority of cases, continue warfarin therapy throughout the dental procedure and postoperative period. This may need to be reassessed for multiple and complex dental extractions, particularly if infection is a concern, in which case an INR of under 1.6 may be desirable. Table 3 is an example of a patient information sheet for use in this situation.
3. Daily or alternate day monitoring of the INR may be required, especially if the patient is receiving antibiotics.
4. Judicious use of local measures to ensure adequate haemostasis e.g. packs soaked in 5% tranexamic acid placed over the extraction site.
5. In patients with excessive oozing, tranexamic acid mouthwash (10 mL of 5% solution) held in the mouth for two minutes is helpful when used six hourly for 3–5 days. Practically, this preparation may be difficult to obtain other than from major teaching hospital pharmacies.

Table 3

Instructions for patients on warfarin for multiple and complicated surgical tooth extraction *

1. Cease your warfarin two nights before procedure and do not take it again until the evening of the day on which you have the extraction.
2. Have an INR test performed on the morning of the extraction before the procedure. This result will be telephoned to your dentist.
3. If the INR is >1.6 (normal <1.3), it is suggested that, if possible, the extraction be deferred for another occasion.
4. Start taking warfarin tablets again the night after the procedure, with the same dosage you had been taking previously before the extraction, and continue each day until the next INR test.
5. If you are prescribed antibiotics for the procedure, have an INR test 3-4 days afterwards to check warfarin dose. Do this earlier if excessive bleeding occurs.

Dental procedures of a less traumatic nature, provided infection is not present, generally do not require alterations in warfarin dosage.

* Reproduced with permission from Associate Professor A. Street, Alfred Hospital, Melbourne

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Self-test questions

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

5. Patients taking warfarin should stop their treatment two days before any routine dental procedure.
6. The risks of bleeding probably outweigh the benefits of anticoagulation with heparin when patients with non-valvular atrial fibrillation have major surgery.

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Everyday drug therapies affecting the kidneys

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SYNOPSIS

The kidney is exposed to many potential toxins because of its anatomy and physiology. Prerenal factors affecting cardiac output, drugs altering intrarenal haemodynamics and those directly toxic to the renal parenchyma may cause life-threatening renal impairment. Comorbidities and pre-existing renal disease increase the risks. Careful assessment before prescribing commonly used drugs, dosage adjustment when indicated and close follow-up are required to avoid the potential iatrogenic pitfalls.

Index words: nephrotoxicity, analgesic nephropathy, acute tubular necrosis.

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Introduction

The normal kidney receives approximately 25% of resting cardiac output. Glomerular filtration produces approximately 180 L of ultrafiltrate daily. While most is reabsorbed, filtration allows the excretion of waste products, minerals, acids and drugs, or their metabolites. Excretion may expose the vasculature, tubules and interstitial tissues to very high concentrations of these substances. The kidneys, therefore, quite commonly suffer adverse effects of drug therapy (see box). Comorbidities and co-administration of other drugs increase the likelihood of adverse drug reactions.

Prerenal factors

An adequate cardiac output is an essential requirement for normal renal function. If renal function is impaired by a decreased cardiac output the increase in the concentration of urea is more marked than the increase in the concentration of creatinine. This characteristic laboratory finding results from avid reabsorption of tubular fluid, accompanied by urea which is freely permeable through cell membranes, but not creatinine which is impermeable to renal tubular cells. To maintain cardiac output, the requirements are:

- sufficient blood volume
- effective cardiac pump
- appropriate peripheral resistance.

Blood volume

Diuretics, particularly the more potent loop diuretics (frusemide, ethacrynic acid, bumetanide), may cause volume depletion. This decreases cardiac output, particularly in patients who already have decreased 'effective' blood volume, such as those suffering cardiac failure, liver failure or nephrotic syndrome.

Effective cardiac pump

Drugs with negative inotropic effects, such as beta blockers and some calcium channel antagonists, have the potential to impair renal function, especially if cardiac output is already compromised. In clinical practice, the adverse effects on the heart usually predominate so the drug is often stopped before the renal dysfunction becomes clinically relevant.

Peripheral resistance

Vasodilator drugs, such as minoxidil and prazosin, rarely cause deterioration of renal function themselves. However, they may be associated with marked salt and water retention, requiring the addition of loop diuretics. Calcium channel blockers, while causing oedema of the eyes and ankles, are actually natriuretic and do not cause salt and water retention.

Intrarenal circulation

The intrarenal circulation is controlled by many factors including prostaglandins and the 'renin angiotensin' system. These systems are able to vary the relative degrees of vasoconstriction or dilatation of the afferent or efferent arterioles of the glomerulus. This alters intraglomerular pressure and therefore the glomerular filtration rate. These systems are particularly activated in disease states where there is already underlying renal impairment or abnormalities of cardiac output. They are also affected by many drugs. Fortunately, stopping the offending drug usually restores renal function fairly promptly.

Non-steroidal anti-inflammatory drugs (NSAIDs)

All the NSAIDs inhibit prostaglandin synthesis, leading to unopposed, intrarenal vasoconstriction. This decreases the glomerular filtration rate. This results in fluid retention, with the risk of increasing cardiac failure in patients with pre-existing cardiac dysfunction, and resistance to antihypertensive therapy in patients with normal cardiac function.

Commonly-used drugs which can affect renal function

- Diuretics
- Beta blockers
- Vasodilators
- Non-steroidal anti-inflammatory drugs
- ACE inhibitors
- Aminoglycosides
- Radio contrast media
- Compound analgesics
- Antiviral agents
- Lithium

Angiotensin converting enzyme (ACE) inhibitors

By interfering with the production of angiotensin II, the ACE inhibitors decrease efferent arteriolar regulation. Clinically significant alterations in renal function may result, particularly in low perfusion states, such as renal artery stenosis to a solitary kidney, or if there is bilateral renal artery disease. If the ACE inhibitor adversely affects renal function you should consider the presence of functionally significant renovascular disease, however the absence of such an effect does not rule out the presence of a renal artery lesion. Furthermore, a small deterioration in renal function may occur in patients who have no renovascular disease, but have a pre-existing mild elevation of serum creatinine when they start an ACE inhibitor. This deterioration will often reverse in time if the ACE inhibitor is continued.

Parenchymal damage

Many drugs can cause structural damage to the renal parenchyma. This usually presents as acute tubular necrosis.

Aminoglycosides

The aminoglycoside antibiotics remain a relatively common cause of acute deterioration in renal function. They have the potential to cause significant morbidity and even mortality. Even when cautiously administered, therapy for more than seven days has been reported to cause a rise in serum creatinine in up to 30% of patients. Other factors, such as pre-existing impaired renal function, hypovolaemia, concomitant diuretic use, and reduced serum potassium or magnesium, can all increase the nephrotoxicity of aminoglycosides. Clinically, the onset of renal failure may be quite insidious because oliguria is not usually present. A warning sign may be the development of hypokalaemia which precedes the rise in serum creatinine resulting from the aminoglycoside-induced acute tubular necrosis. Although measuring trough concentrations of aminoglycoside may assist in guiding dosage, many studies have failed to show that monitoring decreases the incidence of nephrotoxicity significantly. Once-daily dosing has, in a number of studies, been shown to decrease the incidence of nephrotoxicity without impairing antibiotic efficacy.

Aminoglycosides are eliminated by glomerular filtration. About 5% of the filtered drug is actively reabsorbed by proximal tubular cells and can reach high concentrations in these cells. The drug is then slowly eliminated, unchanged, over a period of days. Toxic damage to the tubular cells is believed to be related to the ability of the aminoglycoside to disrupt plasma membranes, but additional poorly understood factors are also implicated. A decreased dosage or increased intervals between doses must be prescribed for patients with known impairment of renal function.

Lithium

When serum concentrations are high (e.g. above 1.2 mmol/L), urine output increases and glomerular filtration rate decreases mildly. Urinary concentrating ability is decreased.

Acute renal failure has been reported with lithium intoxication, but the mechanism is uncertain and it may be due to factors such as volume depletion, direct nephrotoxicity or a combination of both.

Whether chronic renal failure results from lithium-induced interstitial nephritis remains controversial. It is an uncommon complication of this drug. For instance, in 1997 in Australia, out of 1468 new patients entered into the End-Stage Renal Failure Programs, only five patients were listed with a diagnosis of lithium-induced disease. Nevertheless, patients should have their serum creatinine checked every 6–12 months in addition to the monitoring of their lithium concentrations every 3–4 months.

Contrast media

In patients with pre-existing impairment of renal function due to diabetic nephropathy, a common cause of acute renal impairment is contrast media-associated nephrotoxicity. The pathogenesis is poorly understood, but alterations in intrarenal haemodynamics and direct tubular epithelial cell toxicity may be primary factors. Clinically significant contrast-induced nephrotoxicity is uncommon in non-diabetics and is rare in patients with normal renal function. Whilst the use of non-ionic contrast media is less likely to cause renal impairment, it is still not risk-free. The amount of the contrast given may be important, with volumes of more than 30 mL being more likely to be associated with toxicity. A prospective multicentre trial studied 1196 patients, of whom 213 had diabetes mellitus and 509 had serum creatinine of more than 141 micromol/L. In the azotaemic non-diabetic patients, 4% showed evidence of nephrotoxicity, but in those with both azotaemia and diabetes, the incidence was 12% even when non-ionic contrast materials were used.

Diabetic patients with pre-existing impaired renal function are more likely to develop toxicity and are also more likely to require dialysis. Some cases may suffer irreversible renal failure.

A variety of prophylactic measures have been tried. Mannitol, frusemide and dopamine can increase the risk of nephrotoxicity. Calcium channel blockers may be beneficial, but intravenous saline loading appears to be the most successful in reducing the risk. Intravenous normal saline, 80 mL/hour for 6–10 hours before and after the procedure, is recommended providing there are no contraindications such as incipient cardiac failure. NSAIDs and diuretics should be withdrawn 24 hours before an elective investigation.

Clinically, if toxicity occurs, the serum creatinine begins to rise within 24–48 hours, peaks within 3–5 days and then returns to baseline within 7–10 days. Oliguria is uncommon and urine examination usually shows tubular epithelial cells, coarsely granular casts and mild proteinuria.

Analgesic nephropathy

Compound analgesics

Chronic interstitial nephritis and papillary necrosis can develop as a consequence of long-term abuse of combination analgesics, particularly those containing phenacetin.[8] Possibly as a result of decreased compound analgesic abuse, this disease appears to be decreasing in prevalence in Australia. Two decades ago,

it accounted for 12–15% of patients presenting with end-stage renal failure. More recently, the proportion has dropped to less than 5%, occurring predominantly in an older age group, compared with 20 years ago.

Analgesic abuse may be difficult to diagnose because of patient denial and often non-specific symptoms, signs and laboratory findings. High use is generally defined as use of one or more doses of analgesic daily, for at least five years and a minimum total dose of approximately 3000 doses. To establish the diagnosis, CT scanning without contrast is most useful for detecting papillary necrosis.

Following removal of phenacetin from compound analgesics, there has been a clear decline in the prevalence and incidence of analgesic nephropathy. However, it is still uncertain if phenacetin, or a metabolite, e.g. paracetamol, is the main aetiological agent. The decreased availability of compound analgesics as well as altered consumption habits occurred around the same time making the cause difficult to identify. There have been documented cases of analgesic nephropathy occurring in patients who abuse non-phenacetin-containing compound analgesics. On the other hand, reports of analgesic nephropathy, in association with consumption of single analgesics, are quite rare. In particular there is insufficient evidence to indicate that chronic paracetamol ingestion is nephrotoxic. There is little evidence that regular analgesic consumption increases the progression of renal disease due to other causes, such as glomerulonephritis or diabetes mellitus.

NSAIDs

NSAIDs can cause an acute, usually reversible, deterioration in renal function due to inhibition of renal vasodilatory prostaglandins in the kidney. The risk factors include older age, hypertension, pre-existing impaired renal function, diabetes, diuretics and volume depletion. NSAIDs may also exacerbate salt and water retention in patients with congestive heart failure.

More rarely, NSAIDs may cause an acute interstitial nephritis, characterised by acute renal failure and heavy proteinuria. The renal failure may be severe enough to require dialysis. The syndrome may occur sooner or later after commencing NSAIDs, but the patient usually recovers gradually after the drug is stopped.

Although chronic administration of NSAIDs to experimental animals can induce papillary necrosis, there are no convincing data that prolonged consumption of NSAIDs in humans is a significant risk factor for analgesic nephropathy and chronic renal failure.

Conclusion

The kidney is exposed to many medications. Patients with comorbidities, particularly the aged and those with pre-existing renal disease, diabetes and cardiac failure, are especially at risk of renal impairment. With the increasing availability of computer access to the relevant medical literature, it is wise to check the list of precautions and adverse effects before prescribing for these patients.

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Self-test questions

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

7. Non-steroidal anti-inflammatory drugs reduce the glomerular filtration rate.
8. Renal impairment due to decreased cardiac output causes a more marked increase in plasma urea concentrations than in creatinine concentrations.

The story of the painting

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

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

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

Patient support organisations

Australian Kidney Foundation

The Australian Kidney Foundation is a non-profit organisation that relies on community funding and support, with minimal government funding. Through its branches the Foundation aims to increase public awareness and understanding of kidney-related diseases, and to fund research to understand better the causes and treatment of kidney and urinary tract diseases.

The Foundation conducts broad-based education programs for patients, potential organ donors, medical practitioners, the general community and school students. It aims to improve patient services and preventative medicine, by informing government of patients' needs and commenting on relevant public issues, as well as raising funds. The Foundation encourages and promotes organ donation, and makes available information on kidney-related conditions.

'Kidney Care', a recent initiative, is a support network and monthly education session for people living with kidney disease. Volunteers support people living with kidney disease through:

- public speaking about kidney disease, organ donation and transplantation
- a telephone support register
- practical support to people on dialysis, their families and friends.

Contacts

The Australian Kidney Foundation
GPO Box 9993 in each capital city
Web site: www.kidney.org.au
Kidney Health Information Line: Freecall 1800 682 531

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Email: akf@hobart.kidney.org.au

Northern Territory
Room 4, Casuarina Plaza
CASUARINA NT 0810
Tel: 08 8945 4047 Fax: 08 8945 4037

National Renal Resource Centre
Sydney Dialysis Centre
37 Darling Point Road
DARLING POINT NSW 2027
Tel: 02 9362 3995; 02 9362 3121
Freecall: 1800 257 189
Fax: 02 9362 4354
Email: d.oshaughnessy@hcn.net.au

Dental implications

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

Basic tests of respiratory function (page 10)

Respiratory function can be affected during dental treatment. Dentists need to be aware if their patients have any respiratory conditions especially as most treatment takes place in the airway. Medication used for treatment of chronic obstructive respiratory disease should be considered when planning dental treatment. Some drugs used in dentistry, sedatives, narcotics and large doses (taking into consideration patients' age and physical status) of local anaesthetics are capable of producing transient respiratory depression.

Patients with a history of asthma may have an acute episode during treatment. A pre-operative assessment should consider the treatment needed if an attack occurs. Patients are usually well informed about emergency treatment and often carry an inhaler prescribed for such an emergency.

An increasing number of dental surgeries are equipped with oxygen and oximeters. The stress of treatment on patients with chronic obstructive pulmonary disease can be reduced with supplemental oxygen. These patients need to be placed in a position of comfort, without being too far reclined. A nasal mask or canula delivering 2–3 litres of oxygen per minute readily increases peripheral oxygen saturation to above 96%, providing improved physiological conditions for dental anaesthesia and improved patient comfort during the procedure. It can be shown that an additional supplement of one litre per minute of nitrous oxide (a mixture of 75–80% oxygen) improves physiological function and in particular heart rhythm, should minor irregularities in rhythm be present.

Unless there is a specific contraindication, adrenaline or other catecholamine vasoconstrictors can be used in dental local anaesthetics. Respiratory disease itself is not a contraindication to the use of catecholamine vasoconstrictors.

If there is any doubt concerning treatment of these patients, the physician managing their pulmonary condition should be consulted and treatment jointly managed.

New drugs

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

Daclizumab

Zenapax (Roche)

vials containing 25 mg/5 mL

Approved indication: renal transplant

Australian Medicines Handbook Section 14

Despite advances in immunosuppression, acute rejection remains a major problem for patients receiving a kidney transplant. The chances of a successful transplant may be increased by interfering with cellular immunity. Monoclonal antibodies such as basiliximab (see 'New drugs' Aust Prescr 1999;22:95) and daclizumab inhibit the proliferation of T lymphocytes by binding to the interleukin-2 receptor on these cells.

Daclizumab is infused before surgery. The dose is then repeated every two weeks for a total of five doses with the aim of saturating the receptors. The half-life of daclizumab is 20 days, resembling that of IgG.

In one trial, 126 patients given daclizumab were compared with 134 who received an intravenous placebo. Both groups were also given cyclosporin, azathioprine and prednisone. Acute rejection occurred in 35% of the patients given a placebo, but in only 22% of patients given daclizumab. After a year, the graft survival was 90% in the placebo group and 95% in the daclizumab group.[1]

The toxicity of the other immunosuppressive drugs is not increased by daclizumab. Treatment did not cause significantly more adverse effects than placebo.[1]

While daclizumab reduces the incidence of acute rejection its long-term effectiveness requires further study. Although 90% of the daclizumab molecule contains a human antibody sequence this does not appear to make it significantly superior to basiliximab.

REFERENCE

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Leflunomide

Arava (Hoechst Marion Roussel)

10 mg, 20 mg and 100 mg tablets

Approved indication: rheumatoid arthritis

Australian Medicines Handbook Section 14

Disease modifying antirheumatic drugs, such as gold and methotrexate, are increasingly prescribed for patients with rheumatoid arthritis. These drugs are toxic and may not slow the progression of the disease. Leflunomide is an attempt to produce an effective, well tolerated treatment. It is an immunomodulating drug which inhibits the pyrimidine synthesis that is associated with cell proliferation. Leflunomide also has a weak anti-inflammatory action.

Patients begin taking leflunomide with a loading dose for three days. This is because the drug has a long half-life (2–3 weeks). There is extensive first pass metabolism which converts leflunomide to its active form. The active metabolite is slowly excreted into the urine and faeces. Smoking increases clearance.

Leflunomide has been compared with placebo and sulfasalazine, a drug with the capability of retarding disease progression. A total of 359 patients were randomised to be treated for 24 weeks. Although many patients did not complete the study, the arthritic symptoms and signs responded to treatment in 20% of the patients in the placebo group compared with 55% of the leflunomide group and 56% of the sulfasalazine group. X-rays revealed that there was less disease progression in the active treatment groups. The study did not have enough power to show a difference between leflunomide and sulfasalazine.[1] Other studies suggest the efficacy of leflunomide and methotrexate may be similar.

While 96 of the 133 patients taking leflunomide completed the trial, 19 (14%) had to withdraw because of adverse events.[1] Common problems were diarrhoea, nausea, rashes and alopecia. Other adverse effects include headache, dizziness, leucopenia and altered liver function. Regular white blood counts and liver function tests are recommended.

In October 1999 the European Medicines Evaluation Agency issued a statement warning the public about serious adverse reactions to leflunomide. There was particular concern about reports of pancytopenia and serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Few significant drug interactions have emerged, but live vaccines are not recommended until six months after the conclusion of treatment. Leflunomide is contraindicated in pregnancy.

Until more information is available about leflunomide it will probably be reserved for patients with severe active rheumatoid arthritis who cannot tolerate or do not respond to other disease modifying drugs.

REFERENCE

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Temozolomide

Temodal (Schering-Plough)

5 mg, 20 mg, 100 mg and 250 mg capsules

Approved indication: brain tumours

Australian Medicines Handbook Section 14.1.3

The primary brain tumours include anaplastic astrocytoma and glioblastoma multiforme. Both of these tumours have a poor prognosis. Patients may be treated with surgery followed by radiotherapy and chemotherapy. Temozolomide has been developed as an option for treating patients who relapse after this therapy.

Temozolomide is an alkylating agent, with similarities to dacarbazine. It is taken once a day at least one hour before food for five days each month. The drug is rapidly absorbed and crosses the blood-brain barrier. Most of the drug is metabolised with less than 10% being excreted unchanged in the urine.

In 162 patients with anaplastic astrocytoma there was a response rate of 33% with temozolomide. The median survival time for these patients was 14.6 months. In the more common glioblastoma multiforme, the median survival time was much shorter. When the drug was compared with procarbazine in the treatment of 225 patients, the median progression-free survival was 2.7 months for temozolomide and 1.8 months for procarbazine.

In the few months that they survive, most patients will have adverse effects from the treatment. Myelosuppression is very common, so patients must have their blood count checked before each monthly treatment. Nausea and vomiting are also common and some patients will need antiemetic drugs.

While temozolomide has been approved for both types of tumour in Australia, the evidence of its effectiveness in glioblastoma multiforme was insufficient to warrant an accelerated approval in the U.S.A.

NEW FORMULATIONS

Loratadine/pseudoephedrine sulfate

Clarinase 24 Hour Relief (Schering-Plough)

10 mg loratadine/240 mg pseudoephedrine sulfate sustained-release tablets

Omeprazole magnesium

Acimax (AstraZeneca)

20 mg tablets

Losec (AstraZeneca)

10 mg and 20 mg tablets

Topiramate

Topamax (Janssen-Cilag)

15 mg and 25 mg sprinkle capsules

NEW COMBINATIONS

Interferon alfa-2b and ribavirin

Rebetron Combination Therapy (Schering-Plough)

composite packs containing

interferon alfa-2b 18 million IU/pen

ribavirin 200 mg capsules

Loperamide hydrochloride/simethicone

Imodium Advanced (Janssen-Cilag)

2 mg loperamide hydrochloride/125 mg simethicone

NEW PROPRIETARY BRANDS

Betamethasone

Antroquoril (Schering-Plough)

200 microgram/g cream and ointment

Captopril

Captopril (Douglas)

12.5 mg, 25 mg and 50 mg tablets

Metoprolol tartrate

SBPA Metoprolol (Schein Bayer)

50 mg and 100 mg tablets

Naproxen sodium

Crysanal (Syntex)

550 mg tablets

Ranitidine

Ranoxyl (Douglas)

150 mg and 300 mg tablets

Ranitidine hydrochloride

SBPA Ranitidine (Schein Bayer)

150 mg and 300 mg tablets

Salmonella typhi Vi

Typherix (SmithKline Beecham)

25 microgram/0.5 mL pre-filled syringes

Answers to self-test questions

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

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