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Editorial

Managing arthritis and vascular disease – a rheumatology perspective

Fin Zheng Jun Cai, Rheumatology Registrar, Les Cleland, Professor, and Michael James, Associate Professor, Rheumatology Department, Royal Adelaide Hospital, Adelaide

Arthritis and vascular disease are both very common. Arthritis is often treated symptomatically with non-steroidal anti-inflammatory drugs (NSAIDs), but these drugs can complicate the management of hypertension and congestive cardiac failure. NSAIDs can induce hypertension and cardiac failure in predisposed patients and they can interact with antihypertensives and diuretics. NSAID use can also cause renal impairment, particularly in patients taking diuretics and ACE inhibitors. A lack of functional renal reserve predisposes to this problem. It is important for prescribers to remember these unwanted effects of NSAIDs and therefore monitor blood pressure, watch for increased weight and leg oedema (signs of fluid retention) and check renal function. This monitoring is especially important in the elderly, since cardiac and renal function decline with age.

In patients who have hypertension that is difficult to control, or poor cardiac function or poor renal function (estimated glomerular filtration rate less than 60 mL/min/1.73 m^2), or some combination thereof, it is best to avoid use of NSAIDs. The pharmacological actions of NSAIDs militate against effective management of these problems. Usually an alternative treatment for arthritis is available.

In this issue…

For many children their first encounter with the health system is a painful one. As poorly managed pain in childhood can lead to later avoidance of healthcare, John Murtagh tells us how to minimise the pain of procedures, including immunisation.

The immune system is the target of the new immunosuppressants discussed by Peter Pillans and Paul Trevillian. Immunosuppressants are among the drugs that Fin Zheng Jun Cai, Les Cleland and Michael James say are more appropriate than non-steroidal anti-inflammatory drugs in the early stages of rheumatoid arthritis.

Cancer treatments can affect the immune system, but they have other unpleasant adverse effects such as xerostomia which is reviewed by Ian Olver.

Osteoarthritis is the most prevalent form of arthritis and is increasingly common with advancing years. NSAIDs are used in osteoarthritis for symptomatic relief but have not been shown to retard the anatomical progression to joint failure. Recognising that the usefulness of NSAIDs is limited to analgesic effects helps dampen the enthusiasm of patients for their use, especially when coupled with warnings about the serious and potentially life-threatening adverse effects. These include upper gastrointestinal events and the increased risk of thrombotic cardiovascular events. The risk of these complications is likely to be influenced by an NSAID's half-life and selectivity for the isoforms of cyclo-oxygenase (COX). Drugs with a higher selectivity for COX-2 have a greater risk of cardiovascular adverse events.

The practical limitations of NSAIDs in osteoarthritis help redirect the prescriber to other analgesic options. Paracetamol is the recommended first-line analgesic. Narcotic analgesics may be useful for severe osteoarthritic pain in patients whose cardiac and renal function is compromised. The non-pharmacological therapies for osteoarthritis should not be overlooked. Exercise prescriptions can improve comfort and well-being. The focus needs to be on local exercises, that address muscle imbalances and improve or maintain the range of movement, and more general exercises that improve overall fitness without local aggravation. When indicated, and feasible from a cardiovascular viewpoint, joint replacement surgery can relieve pain, improve function and allow better overall fitness to be achieved. Improved cardiorespiratory fitness and an associated reduction in adiposity can aid blood pressure control. The natural products glucosamine and chondroitin sulfate may reduce symptoms in osteoarthritis and do not appear to compromise blood pressure control or the treatment of heart failure.[1]

In rheumatoid arthritis, NSAIDs are no longer regarded as first-line treatment, except in the sense that they are used to lessen symptoms before starting a disease-modifying anti-inflammatory drug. These drugs include methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, gold sodium thiomalate, cyclosporin and anticytokine 'biological' therapies. The best results are achieved with early implementation of combination therapy with three or more drugs.[2] Glucocorticoids

are enjoying a second vogue as a means of controlling symptoms quickly during the period between starting and responding to a disease-modifying drug. The long-term use of glucocorticoids needs to be weighed against their serious adverse effects, such as their propensity to cause hypertension. When prescribing combination therapy for rheumatoid arthritis, it is important to make dosage adjustments and substitutions in order to achieve objective evidence of disease suppression and to accommodate intolerance to individual drugs or drug-related adverse events. Disease control is of paramount importance in order to reduce cumulative joint damage and the increased cardiovascular mortality[3], both of which have been shown to correlate with unsuppressed disease activity.

There is evidence that fish oil in anti-inflammatory doses can reduce symptoms in rheumatoid arthritis[4] and that fish oil (and other interventions which increase dietary intake of omega-3 fatty acids) generally reduces cardiovascular mortality.[5] Fish oil has also been shown to reduce discretionary NSAID use in rheumatoid arthritis.[4] It also has a number of favourable effects on cardiovascular physiology, including a modest reduction in blood pressure and reduced arterial stiffness.

The important practical point is that a 'need' for NSAIDs in rheumatoid arthritis can be used as a prompt for more intensive application of other therapies. This approach is especially important in patients for whom treatment of other health problems, such as hypertension and heart failure, may be compromised by NSAIDs.

Situations do arise in which it is decided that a patient with cardiovascular disease requires treatment with an NSAID when alternative approaches have failed. If possible the NSAID should be used for second-line analgesia in as small a dose and for as short a period as needed to control symptoms.[6] A short-acting drug is preferable to one with a long half-life. It is important to realise that NSAIDs can perturb cardiovascular homeostasis in ways that run counter, directly or indirectly, to the beneficial actions of drugs used to manage hypertension and cardiac failure. The combination of ACE inhibitors and diuretics with NSAIDs may be especially problematic and should be avoided, if possible. While there are no absolute contraindications to using NSAIDs with cardiovascular drugs, it needs to be recognised that NSAIDs can compromise treatments for cardiovascular disease.

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Professor Cleland and Dr James have a research interest in the health benefits of fish oil. The Royal Adelaide Hospital Preventive Care Centre distributes bottled fish oil for patient use.

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.

Pre-eclampsia

Editor, – I read with interest the article on biochemical tests in pregnancy (Aust Prescr 2006;29:48–52) and wish to comment on the discussion of pre-eclampsia. The author maintains that the diagnosis is based on a triad of hypertension, proteinuria and oedema, yet the Australasian Society for the Study of Hypertension in Pregnancy has issued a consensus statement which asserts otherwise.[1] While hypertension is a requirement, proteinuria (as one of a range of possible end organ effects) is not mandatory to make the diagnosis. Oedema is specifically excluded unless its onset is rapid and generalised. This is important to appreciate as severe forms of pre-eclampsia (and indeed eclampsia) can occur in the absence of the 'triad'. Furthermore, 'routine' urinalysis at each visit in low-risk pregnancies has been discontinued in many centres due to its limited value.

Colin Weatherill

Obstetrician

Mount Gambier, SA

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Associate Professor HA Tran, author of the article, comments:

In pre-eclampsia the detection of hypertension is of utmost importance and blood pressure needs to be rigorously controlled. The presence of proteinuria and oedema is less critical but will further assist in arriving at the correct diagnosis. Although eclampsia can occur in the absence of the 'triad', alternative differential neurological diagnoses need to be considered.

While the clinical utility of 'routine' urinalysis may not be as important in the diagnosis of pre-eclampsia, it is sometimes useful in detecting asymptomatic bacteriuria and glycosuria. Bacteriuria confers an increased risk of pyelonephritis and prematurity[1], and glycosuria may identify unsuspected diabetes other than gestational diabetes. Interventions for both of these conditions can result in better outcomes.[1,2] It is of additional interest that the current British guideline for antenatal care recommends that 'whenever blood pressure is measured in pregnancy a urine sample should be tested at the same time for proteinuria'.[3] The decision to discontinue this practice in low-risk patients is then probably a function of cost versus benefit.

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Deleterious cognitive effects of antimuscarinic drugs

Editor, – I suggest that the article 'Anticholinergic drugs for overactive bladder' (Aust Prescr 2006;29:22–4) gives insufficient prominence to the inevitable occurrence of cognitive impairment from antimuscarinic drugs. There is overwhelming evidence that all antimuscarinic drugs cause cognitive impairment even in healthy people[1], and this is frequently clinically significant in older people.[2,3,4] Any possibility that a treatment will worsen patients' mental function has profound implications and must be regarded with the utmost seriousness.

The therapeutic margin is narrow, or non-existent, and individual variations in blood concentrations and response mean that in practice it will be difficult to achieve a consistently favourable therapeutic effect. Many other commonly used drugs also have antimuscarinic effects so interactions are likely to be frequent. I suggest the average practitioner has insufficient knowledge of these interactions to successfully avoid them.[5]

Ken Gillman
Consultant psychiatrist
Pioneer Valley Private Hospital
North Mackay, Qld

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Associate Professor KH Moore, one of the authors of the article, comments:

Dr Gillman makes an important point regarding the potential for anticholinergic drugs to induce or exacerbate cognitive impairment, especially in the elderly. However, he paints a rather black picture with very broad strokes so an examination of the evidence is needed.

Reference 1 describes a very precise psychometric analysis of scopolamine administration in 24 people, that showed significant decline in performance on spatial and pattern memory tests. This is hardly 'overwhelming evidence that all antimuscarinic drugs cause cognitive impairment'.

Similarly, references 2 and 3 describe studies with 30 and 16 users of a wide range of anticholinergic drugs. The first study showed a 19% attributable risk of mild cognitive impairment for these drugs. In the second paper, all patients were receiving the cholinesterase inhibitor donepezil for Alzheimer's disease. Not surprisingly, donepezil was less

effective for preventing cognitive decline in those on anticholinergic drugs (at two years, but not at one year).

Reference 4 is an interesting review article about the role of anticholinergic drugs in delirium but also discusses studies that included small numbers of patients (n = 15–34).

Reference 5 is a detailed review of the pharmacokinetics of a range of bladder-active anticholinergics. It is very informative but does not appear to support the suggestion that they should be avoided.

Nevertheless, our article could have made greater mention of the risks of anticholinergic therapy in exacerbating or precipitating cognitive impairment, especially in the elderly. These drugs should only be given in conjunction with bladder training at the lowest dose possible to achieve reduced frequency, urgency or urge incontinence, and for the shortest duration possible.

Confessions of a biased reader

Editor, – I wonder how many other people share my obsession about checking declarations of conflicts of interest before they read any letter or article?

I note many well-credentialled academics seem very committed to evidence-based medicine when presenting their arguments. For me, all this effort becomes completely neutralised when I realise that they have received sponsorship associated with the very products they are arguing for. Unfortunately, my bias is so compelling that I cannot take their well presented discussion seriously. How many other people suffer from this problem?

Chris Commens
Dermatologist
Pennant Hills, NSW

Book review

Pocket guide to ECGs. 2nd edition. Duncan Guy.

Sydney: McGraw-Hill; 2006.
162 pp. Price $37.95

Maros Elsik, Cardiology Fellow, Department of Epidemiology and Preventive Medicine, Monash University, The Alfred Hospital, Melbourne

This book is aimed at general practitioners, medical students, hospital residents and nursing staff. It is now in its second edition so it has clearly found a market. Having read numerous similar books, though not the first edition of this guide, I found it to be useful and practical.

The book is divided into four sections. The first section is devoted to the normal ECG. This describes the usual 'normal' parameters, but also includes a section on the so often ignored but commonly encountered sources of artefact (and misdiagnosis) such as calibration, tremor and lead reversal. The second section describes common abnormalities seen in clinical practice, and provides pathophysiological causes for them. The format is consistent throughout, easy to follow and interspersed with practical and relevant 'clinical tips'. Section

three, the so-called quick reference guide to common cardiac disorders, is logically ordered and sufficiently detailed. In the era of increasing use of devices, it was refreshing to see section four on pacemakers and pacemaker ECGs, stating that significant abnormalities can be detected with a standard ECG, rather than interrogating the device first. The use of real rather than digitally enhanced ECGs throughout the text is of much practical benefit.

A few minor shortcomings of the text include the absence of an index (despite a detailed list of contents), only a brief description of early repolarisation (often a source of confusion), and although not entirely specific, the criteria for differentiating ventricular tachycardia from less serious broad complex tachycardias are not listed. It would have also been useful to include a few examples of commonly encountered and potentially serious electrolyte disturbances as well as digitalis effect and toxicity.

The ECG rulers on the back cover, and the accompanying CD-ROM with self-test ECGs, are additional useful extras, although the CD did not work on my computer.

I found this book easy to follow and packed with useful information. I would recommend it to readers of *Australian Prescriber* as a useful guide and a quick reference.

Managing painful paediatric procedures

John E Murtagh, Department of General Practice, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne

Summary

Prevention of procedural pain in children reduces the risk of subsequent morbidity including pain sensitisation. The primary emphasis for reducing pain should be on appropriate distraction and rapport-building strategies, however the doctor's technique can also assist. Topical anaesthetic preparations supplement the painless suturing of wounds. They can also reduce the pain of injections, including venepuncture. Studies of mass vaccination show that injections into the buttock cause less irritability than injections into the thigh. If the thigh is used then an injection at right angles is preferred to angulation.

Key words: anaesthesia, immunisation, injections, wounds.

Introduction

The treatment of painful procedures in children requires special consideration and planning because pain preventive measures reduce both short-term and long-term morbidity. Current evidence indicates that pain and distress in children is poorly managed and children continue to suffer unnecessarily.[1] This can lead to anticipatory anxiety, needle phobia and the avoidance of health care. Obviously, it is impossible to make many basic procedures such as immunisation and other injections painless, but there are strategies to minimise the pain. Before inflicting pain on a child always consider if the procedure is justified.

General distracting and rapport-building techniques

The strategies used will depend on the age of the child and the support of the parents. For most children, but particularly those of school age, it is wise to establish rapport through showing a genuine interest with considerable eye contact. Make favourable comments including complimentary remarks about their name, a clothing item or a toy or book that they may be carrying. It is good to take time to converse or play games with them including placing stickers on their shirts or transfers on the back of their hands.

A recommended technique for infants (especially under three months) is the 'three S' method:

- swaddling for firm containment
- swaying (where appropriate)
- sucking using a pacifier with 15–50% sucrose.[2]

Practical examples of distraction techniques include the use of novel interactive toys such as a small duck with a rattle or a small animal that plays a drum at the press of a button. Have a bubble-blowing kit on hand to blow bubbles. Party blowers or pinwheels/windmills encourage slow controlled breathing which is relaxing and calming. Another technique when giving an injection is to get the child to take a deep breath followed by a series of rapid blowing, during which the injection is given.[3]

Wound repair

Wherever possible it is worth using a simple painless technique without compromising good healing.

Scalp lacerations

If lacerations are small but gaping, use the child's hair to tie the wound together. This, of course, only applies to children with long hair. **Do not** use this method for large wounds.

Method

- make a twisted bunch of the child's own hair of appropriate size on either side of the wound
- tie a reef knot across the wound and then an extra holding knot to minimise slipping
- as you tie, ask an assistant to drip compound benzoin tincture solution (friar's balsam) or plastic skin on the hair knot
- as this congeals, the knot is further consolidated against slipping.

Leave the tied hair long. The parents can cut the knot about five days later when the wound has healed. The whole procedure is painless unless an injection of tetanus toxoid is indicated.

Reinforced paper adhesive strips (for example, steri-strips)

These strips should be used only for very superficial epidermal wounds or in conjunction with sutures. Despite the temptation, avoid using them in children with open wounds, especially on the forehead. They will merely close the dermis and cause a thin, stretched scar.

Skin glues – an alternative to sutures

Cyanoacrylate tissue adhesives are available for wound closure. These glues act by polymerising with the thin water layer on the skin's surface to form a bond.

Precautions (see box)

The glue should be used only for superficial, dry, clean and fresh skin wounds. It must not be applied for deep wounds or wounds under excessive tension. Contact with the cornea or conjunctiva must be avoided, as this can cause adhesions. It is important that the wound is clean and dry and the wound edges are precisely opposed. No gaps are permissible with the glue method of wound repair.

Wound anaesthesia

There are several methods of achieving relative or absolute anaesthesia of wounds for suturing or debridement. The more important less painful strategies include the use of topical anaesthetic drugs and wound infiltration.

Topical local anaesthesia

Topical anaesthetic drugs that can be used for instilling in minor wounds in children are listed in Table 1. The preparations include a variety of drugs, so toxicity and safety factors have to be considered. Cocaine is very effective, but it is relatively toxic and as a rule should be avoided in open wounds. Adrenaline-containing preparations should be avoided in wounds in end-artery areas such as digits, pinnae, tip of the nose, penis, or on mucus membranes such as inside the mouth where rapid absorption may occur. The recommended topical combinations are ALA and LAT (see Table 1), but these may have to be prepared by a hospital or compounding pharmacy. A variation of LAT and ALA is the readily available preparation EMLA cream. However, this requires at least 60 minutes of skin contact to be effective and is not recommended for open wounds.

Method of use[4]

- thoroughly clean the wound (should be less than 5 cm)
- use LAT or ALA in a dose 0.1 mL/kg bodyweight
- apply this solution on a piece of gauze or cotton wool placed inside the wound and hold in place with an adhesive clear plastic dressing
- leave for 20–30 minutes (an area of blanching about 1 cm wide will appear around the wound).

Anaesthesia is obtained about 20 to 30 minutes after instillation. Test the adequacy of anaesthesia by washing and squeezing the wound or prodding it with forceps – if this is pain-free, suturing will usually be painless.

Improvised topical 'anaesthesia'

It is worth considering the use of a block of ice to chill the lacerated site in children. The child or parent is asked to hold the ice then lift it while a suture is rapidly inserted. Another variation that is especially useful in older children is to use a vapocoolant spray on the skin where anaesthesia is required, such as incising a small abscess.

Injectable local anaesthetic

Injectable lignocaine 1% can be used:

- when LAT or ALA are contraindicated such as areas of end-arteriolar supply
- in adolescents
- to supplement topical anaesthesia if adequate anaesthesia has not been achieved.

Skin glues

- Useful for wounds less than 3 cm
- Must not be used on mucosal surfaces
- Topical anaesthesia helps
- Clean wound with normal saline or aqueous chlorhexidine and let dry
- Apply a small amount to the wound edges with the fine end of the tapered plastic ampoule – squeeze out gently
- Do not allow it to enter the wound
- Hold wound together for 30 seconds
- Apply steri-strips to prevent access to the wound, e.g. picking by the child
- Do not wash the wound for 3–4 days

Follow instructions in product data sheet

Caution: bonds skin and eye tissues in seconds. If spilt on skin, remove with acetone as soon as possible.

Table 1

Topical preparations for local analgesia

Topical preparation	Contents
ALA	adrenaline 1:2000, lidocaine*, amethocaine
LAT	lignocaine 4%, adrenaline 1:2000, tetracaine[†] 2%
TAC	tetracaine[†] 0.5%, adrenaline 1:2000, cocaine 11.8%
AC gel	adrenaline, cocaine
AnGel	amethocaine 4%
EMLA	lignocaine, prilocaine

* lidocaine = lignocaine
[†] tetracaine = amethocaine

Wound infiltration

For a larger wound requiring suturing, infiltrate lignocaine 1% into the wound edges using a small 27 gauge (or smaller) needle with a 3 mL syringe. The pain of injection can be reduced by:

- using topical anaesthesia first
- injecting slowly
- placing the needle into the wound through the lacerated surface, not through intact skin
- passing the needle through an anaesthetised area into an unanaesthetised area
- buffering the acidic solution with 8.4% sodium bicarbonate in a 9:1 ratio, that is 9 mL lignocaine 1% with 1 mL sodium bicarbonate.

Immunisation

Controversy surrounds the optimal method of mass immunisation involving intramuscular injections. An Australian study showed that fewer adverse effects, in terms of irritability and local reactions, resulted from the gluteal approach compared with the anterolateral thigh approach.[5] The Australian Immunisation Handbook does not recommend the gluteal approach because of the theoretical risk of sciatic nerve damage. However, this method is officially recommended in countries such as Japan and Croatia and is widely used in Belgium, Germany, Italy and Denmark.

The World Health Organization (WHO) advises an anterolateral thigh injection with a 25 gauge/16 mm needle inserted at 90° to the skin, while the Australian and USA techniques use a longer and larger bore 23 gauge/25 mm needle inserted at 45° and 60° respectively. The Australian study found that the WHO method 'appears to be the optimal technique for anterolateral thigh injection in children – it ensures that the injection is intramuscular, results in fewer adverse reactions, and is the easiest technique to perform as it does not require angling of the needle to the long axis of the femur'.[6] However, the Australian Immunisation Handbook continues to recommend a 23 gauge/25 mm needle inserted at 45°.

The use of topical drugs such as EMLA has been shown to reduce pain scores in infants receiving immunisation. However, the slow onset and the need to inject into several sites at once may make this approach impractical.

Other procedures

Consider the following strategies for painful and distressing procedures such as venepuncture, intravenous cannulation and lumbar puncture:

- distracting and relaxation skills
- pacifier with 15–50% sucrose in infants up to 3 months
- swaddling and containment of infants

- topical anaesthetic drugs such as EMLA cream or AnGel applied at the recommended time before needling.

There is evidence to suggest that using topical anaesthesia does not make cannulation more difficult. A painless procedure may be more successful than a painful one.[7]

More painful procedures will require the use of sedation involving anaesthetic drugs such as nitrous oxide and midazolam. Ketamine may be used in children over 12 months by staff who are experienced in its use, are able to manage children with compromised airways and are working in an appropriately set up environment.

Acknowledgement: Dr Jane Munro, Royal Children's Hospital, Melbourne

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Further reading

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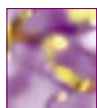
Conflict of interest: none declared

See **Dental notes** page 108

Self-test questions

The following statements are either true or false (answers on page 115)

1. Neonates exposed to painful procedures may later develop neurobehavioural dysfunction.
2. The use of topical anaesthesia before an injection of local anaesthetic is contraindicated.

Xerostomia: a common adverse effect of drugs and radiation

Ian N Olver, Chief Executive Officer, The Cancer Council Australia, Sydney

Summary

Xerostomia is the subjective sensation of dry mouth. Many drugs, especially those with anticholinergic effects, can cause xerostomia, particularly in the elderly. Another major cause is radiotherapy to the head and neck damaging the salivary glands. Newer techniques to target radiotherapy and protective drugs, such as amifostine, could decrease the incidence of xerostomia. Treatment is based on either stimulating the flow of remaining salivary tissue with lollies or sialogogues such as pilocarpine, or wetting the mucosa with water or artificial saliva containing glycerine or compounds such as carboxymethylcellulose. Patients need regular dental examinations because of the effect of xerostomia on intra-oral health.

Key words: pilocarpine, radiotherapy, salivary glands, sialogogues.

Introduction

Xerostomia is the subjective feeling of having a dry mouth. It is associated with dysfunction of the salivary glands. These glands normally produce 1–1.5 L of saliva each day. Saliva has a fluid component (responsible for lubrication) released by parasympathetic stimulation and a protein component released from secretory vesicles by sympathetic stimulation. Not only is lubrication a necessary part of chewing food prior to swallowing, but saliva impacts on the oral microbial environment, the maintenance of the oral immune system and also the mineralisation of teeth.

Causes

A variety of drugs can cause xerostomia. They include diuretics, beta blockers, tricyclic antidepressants, antihistamines, anticonvulsants and antipsychotics. Xerostomia is also reported with oral morphine. There is a greater likelihood of taking these drugs as patients age which explains the correlation of xerostomia with age.

Diseases such as Sjogren's syndrome with sicca symptoms, or endocrine conditions such as hypothyroidism can result in xerostomia. It is important to also consider psychological factors. Both anxiety and depression have been associated with decreased salivary flow rates.

Radiotherapy to the head and neck is a major cause of xerostomia. The prevalence of xerostomia post-radiation is over 90%. It was found to be severe in 30% of patients with advanced cancer starting a palliative care program.[1] Often patients with cancer become dehydrated, which will exacerbate the symptom of dry mouth.

Nerve damage during head and neck surgery may both compromise the function of the salivary glands and alter oral sensation. Chemotherapy can also decrease salivary flow.

The secretory cells of the parotid gland are very radiosensitive and radiation causes inflammation and vascular damage in the parenchyma. A decrease in salivary flow can occur within the first week of radiation, with the saliva becoming more viscous and acidic. There are also changes in the electrolyte and protein content of the saliva which in turn affects the microbial flora and the propensity for tooth decay. The degree of damage depends on how many of the major glands are in the radiation field and the damage increases with total dose of radiation.[2] The initial volume, particularly of the parotid glands, will also affect the degree of xerostomia post-radiation. If only one side is irradiated some recovery will occur over the following year as a result of compensatory hypertrophy of the remaining glands.

Symptoms

The most frequent symptoms of xerostomia are the need to keep the mouth moist with water, particularly at night, and difficulty with speech. There is also a loss of taste and difficulty chewing and swallowing dry foods. This can in turn cause loss of appetite and weight. Patients find it difficult to tolerate dental prostheses and are more prone to dental caries. Burning and tingling sensations on the tongue are reported. Fissuring of the lips and mouth ulcers increase the chance of secondary fungal infections in the mouth.

Evaluation

History and examination, including palpation of the salivary glands, are most important. On inspection the buccal mucosa may be dry and sticky, or red if there is a secondary infection with *Candida albicans*. There is no pooled saliva. Lipstick adhering to the front teeth can be a sign of xerostomia as there is no saliva to clean their surfaces.

Sialometry is a specialist test which can be used to aid in the diagnosis of Sjogren's syndrome. Saliva is collected from the salivary gland orifices and the response to stimulation with citric acid can be measured, although this test is complex and can be inaccurate. The glands may be imaged with sialography or by

nuclear medicine techniques. Salivary gland biopsy can be used to diagnose conditions such as Sjogren's syndrome.

Prevention

General nutrition and hydration are important to help reduce the severity of xerostomia. Avoiding or decreasing the doses of the many drugs which are associated with xerostomia, particularly in the elderly, is a useful precaution.

Patients are encouraged to regularly practice oral and dental hygiene, and if they wear dentures, not to leave them in at night. They should avoid sugary or acidic foods or irritating spicy foods.[3] Stopping alcohol and smoking will help to decrease dental disease.

Pre-radiation

Before radiotherapy, patients should be reviewed by a dentist and have any necessary dental treatment, for example the application of fluoride gels. Antifungal drugs may be used to prevent candidiasis in patients at high risk of infection.

Another major strategy to try to prevent xerostomia is to better target the radiotherapy. Newer techniques including three-dimensional planning and intensity-modulated radiation, where the dosage can be varied across the treatment volume, aim to spare the normal tissues including the salivary glands. In very specific cases, such as a head and neck cancer with no neck nodes involved where only one side of the neck is being irradiated, a submandibular gland can be surgically transferred to a shielded area in the submental space to protect it from the radiation.

Drugs are being developed to try to protect normal tissues from chemotherapy or radiation damage. Amifostine, a thiol free radical scavenger, has been shown to reduce the damage to salivary glands when given concomitantly with radiation such as radioiodine for treating the thyroid gland. The adverse effects of amifostine include nausea and hypotension and it needs to be injected daily.[4]

Treatment

The initial strategy to treat xerostomia is to try to stimulate any remaining salivary gland tissue. This may be achieved by chewing gum or by sucking sugarless lollies.

Sialogogues are drugs which stimulate saliva production. They are essentially muscarinic-cholinergic analogues which act on smooth muscle and exocrine glands. Pilocarpine can increase salivary flow after radiotherapy, but is associated with adverse effects such as perspiration, flushing and increased bowel and bladder motility.[5] Its peak effects are within one hour of administration. Sialogogues are contraindicated in patients with asthma, congestive heart disease and narrow angle glaucoma. Recent studies of pilocarpine do not show that it improves salivary flow or quality of life.[3] Cevimeline is more selective of M_1 and M_3 receptors and thus may minimise cardiac and pulmonary adverse effects. However, clinical trials will be

needed to confirm its preclinical activity in radiation-induced xerostomia.[6] Another drug used to stimulate salivary flow is interferon alfa lozenges as trialled in Sjogren's syndrome. The literature is equivocal on whether acupuncture has a role in alleviating xerostomia.

Some of the discomfort of xerostomia may be relieved by wetting the oral mucosa. This may be simply achieved by regular sips of water, but other substitutes for saliva contain mucin, glycerine or carboxymethylcellulose, hydroxypropylcellulose or hydroxyethylcellulose. These artificial salivas mimic the physical characteristics of saliva but do not have any of its antimicrobial properties. Trials have been conducted of intra-oral reservoirs containing artificial saliva to try to simulate salivary flow.[7]

Conclusion

Xerostomia is a common adverse effect associated with drugs and cancer therapy, particularly radiation to the head and neck. Appropriate drug therapy, good oral hygiene and better targeting of radiation may help prevent the disease. Strategies to alleviate symptoms include stimulating the remaining glands or using substitutes for saliva.

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Further reading

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See **Dental notes** page 108

Immunosuppressants – mechanisms of action and monitoring

Peter Pillans, Associate Professor and Medical Specialist, Director of Clinical Pharmacology, Princess Alexandra Hospital, Brisbane

Summary

Although corticosteroids and drugs such as azathioprine still have a role, there is increasing use of newer potent immunosuppressants. Many of these drugs act on T-lymphocytes. Tacrolimus is a calcineurin inhibitor which has a similar mechanism of action to cyclosporin, reducing T-cell differentiation. Sirolimus and everolimus bind to the same protein as tacrolimus, but have a different mechanism of action. As some of these drugs have a narrow therapeutic range, drug concentrations must be monitored. Mycophenolate is an inhibitor of purine synthesis. Another approach is to block the receptors on T-cells with immunosuppressant antibodies such as basiliximab, daclizumab and muromonab-CD3.

Key words: azathioprine, cyclosporin, everolimus, sirolimus, tacrolimus.

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Introduction

Immunosuppressants are essential for successful organ transplantation and the treatment of many autoimmune disorders. They suppress rejection and dampen the autoimmune process, but they also lead to the undesired consequences of immunodeficiency, such as infection or malignancy, and non-immune toxicity.[1] Glucocorticoids and thiopurines such as azathioprine are still widely used, but newer potent drugs have become the cornerstone of many treatments.

Azathioprine

Azathioprine is a prodrug which is converted to 6-mercaptopurine and metabolised to cytotoxic thioguanine nucleotides which are responsible for immunosuppression and inhibiting DNA synthesis. Both cell-mediated and antibody-mediated immune reactions are depressed. Although its use in transplantation has declined, azathioprine is still widely used as an immunosuppressant or corticosteroid-sparing drug in immune disorders. The main toxicities are bone marrow suppression (particularly agranulocytosis) and hepatotoxicity.

Improved understanding of its pharmacogenetics has led to the safer use of azathioprine. A major influence on thiopurine therapy is the inherited activity of thiopurine methyltransferase. This enzyme shunts thiopurine to relatively inactive compounds. A deficiency of thiopurine methyltransferase is associated with grossly elevated concentrations of thioguanine nucleotides and severe haematological toxicity (agranulocytosis). Where laboratory assays are available, measuring thiopurine methyltransferase activity before starting azathioprine therapy may be advisable to identify patients at risk of acute haematological toxicity.[2] The other major purine metabolic pathway involves xanthine oxidase. In patients taking azathioprine, use of a xanthine oxidase inhibitor such as allopurinol may result in severe myelotoxicity.

Calcineurin inhibitors

Calcineurin catalyses some of the intracellular processes associated with the activation of T-lymphocytes. When calcineurin inhibitors bind to intracellular proteins called immunophilins, they block the effect of calcineurin. This results in reduced production of interleukin-2 and reduced proliferation of T-cells.

The nephrotoxicity of calcineurin inhibitors has emerged as an increasing cause of late renal allograft loss. The pathogenesis appears to be multifactorial and includes calcineurin-induced vasoconstriction, calcineurin-induced release of endothelin-1 (a potent vasoconstrictor), decreased production of the vasodilator nitric oxide, and increased expression of transforming growth factor beta$_1$ (a key cytokine associated with interstitial fibrosis).[3] Reducing the dose of calcineurin inhibitor, or using protocols including mycophenolate and sirolimus, may minimise the risk of nephrotoxicity and improve allograft and patient survival.

Cyclosporin

Since the early 1980s, cyclosporin has been the primary immunosuppressant used in transplantation. It binds with cyclophilin to inhibit calcineurin.

Cyclosporin has a narrow therapeutic range with large inter- and intra-subject pharmacokinetic variability. Target concentration strategies are therefore used to monitor its use. Traditionally, trough concentrations (C_0) are measured, but measurement of whole blood concentrations two hours post-dose (C_2 monitoring) has been recently promoted. There is no good evidence that C_2 monitoring is superior to C_0 monitoring. Timing of the blood sample for cyclosporin monitoring is critical and, generally, less convenient with C_2 monitoring.

Cyclosporin is a substrate for cytochrome P450 3A4 and the multidrug efflux pump, P-glycoprotein. Absorption and subsequent elimination may therefore be influenced by drugs that affect CYP3A4 or P-glycoprotein. Inhibitors of P-glycoprotein may decrease the efflux of drug from intestinal cells and therefore increase blood concentrations. The whole blood concentration of cyclosporin should be carefully monitored whenever inducers or inhibitors of CYP3A4 are concurrently administered and following their discontinuation. Important inhibitors and substrates of CYP3A4/P-glycoprotein include the azole antifungals (ketoconazole reduces cyclosporin dose requirements by up to 80%), calcium antagonists (diltiazem), ergots, fluvoxamine, HMG CoA reductase inhibitors (atorvastatin and simvastatin), protease inhibitors and macrolides such as erythromycin and clarithromycin. Important CYP450 inducers which may be associated with a significant fall in calcineurin inhibitor concentrations include rifampicin, isoniazid, carbamazepine, phenytoin, barbiturates and St John's wort.

Although some brands of cyclosporin are bioequivalent on a population basis and therefore interchangeable, cyclosporin has a narrow therapeutic range. There is therefore a potential that individual variations in pharmacokinetics could lead to significant alterations in blood concentrations if the patient is prescribed a different preparation. Unplanned generic substitution should not occur. For transplant patients in particular, consult an appropriate specialist before any substitution is considered. If patients are switched from one brand to another brand of cyclosporin, increased monitoring is indicated.

Concentration-related adverse effects include nephrotoxicity, hypertension, gingival hyperplasia, hirsutism, tremor and hyperlipidaemia. Haemolytic uraemic syndrome and post-transplantation diabetes mellitus may also occur.

Tacrolimus

Tacrolimus (FK506) is a macrolide antibiotic but is also a calcineurin inhibitor. It is more potent than cyclosporin and binds to a different immunophilin (FK-binding protein) to inhibit calcineurin.

Adverse effects in common with cyclosporin include hypertension, nephrotoxicity and the haemolytic uraemic syndrome. Tacrolimus is less likely to cause hyperlipidaemia, hirsutism and gingival hypertrophy, but diabetes is more

commonly associated. Trough whole blood concentrations should be monitored along with renal and hepatic function. As with cyclosporin, tacrolimus is also a substrate of CYP3A4 and subject to the same interactions.

Antiproliferative drugs

Sirolimus (rapamycin) and everolimus are structurally very similar and have the same mechanism of action. Like tacrolimus, they bind to FK-binding protein, but they have no effect on calcineurin. Instead, the complex inhibits a protein kinase that is critical for cell cycle progression. This kinase is known as the mammalian target of rapamycin (mTOR). Inhibition of mTOR suppresses cytokine driven T-lymphocyte proliferation and activation, resulting in immunosuppression.

The main difference between sirolimus and everolimus is that the half-life of sirolimus (60 hours) is approximately double that of everolimus (30 hours). Both drugs are cleared by hepatic metabolism and, like cyclosporin and tacrolimus, they are substrates for cytochrome P450 3A4 and P-glycoprotein, so have similar interactions.

As with tacrolimus, monitoring of whole blood concentrations of sirolimus and everolimus is essential because of their significant toxicity, narrow therapeutic window, large inter-individual variations in bioavailability and clearance and the potential for drug-drug interactions. Furthermore, efficacy in preventing acute rejection correlates with blood concentrations. Whole blood is the preferred medium because the concentration in red blood cells is 10–30 times higher than in plasma. For sirolimus (and tacrolimus) the effective therapeutic concentrations can be less than 5 microgram/L, so HPLC-mass spectrometry provides the most specific and accurate results.[4] Enzyme-linked immunosorbent assay and microparticular enzyme immunoassay are non-specific and less precise methods.

Mycophenolate

Mycophenolate is the prodrug of mycophenolic acid which inhibits purine synthesis by inhibiting inosine monophosphate dehydrogenase. Currently two products are available in Australia – mycophenolate mofetil and mycophenolate sodium. Both are converted to mycophenolic acid.

Mycophenolic acid is 97–98% protein bound and it is the unbound or free mycophenolic acid that is pharmacologically active. Multiple factors, including hypoalbuminaemia, uraemia and the accumulation of the inactive glucuronide metabolite influence the protein binding of mycophenolic acid in renal failure, and thus alter the free fraction. As with other highly protein-bound drugs, the free fraction of mycophenolic acid inversely correlates with albumin concentrations. The free fraction is increased by reduced renal function and mycophenolic acid glucuronide (which displaces mycophenolic acid from albumin).[5]

Mycophenolate is currently used in a fixed dosage regimen. However, the pharmacokinetics of mycophenolic acid are complex with up to a 10-fold variation in the area under the concentration time curve (AUC) for a given dose. The AUC for mycophenolic acid has a predictive value for the risk of acute rejection.[6] Concentrations of mycophenolic acid can be measured by some laboratories and can be considered if efficacy or toxicity are in question. A limited four-point AUC with samples at 0, 1, 3 and 6 hours can be used, but this test can only be realistically performed with inpatients.

Immunosuppressant antibodies

Antithymocyte globulin

This is a polyclonal IgG antibody from horses or rabbits immunised with human thymocytes. Infusions of antithymocyte globulin cause profound T-cell depletion and the lymphopenia typically persists beyond one year. An unwanted effect is the release of cytokines. This is associated with the 'cytokine release syndrome' characterised by fever, rigors and hypotension.

Antibodies against CD25

Basiliximab and daclizumab are monoclonal antibodies against CD25, a receptor on the surface of T-lymphocytes. They are indicated for prophylaxis of acute rejection in renal transplantation. The antibodies bind to and block the interleukin-2 receptor α-chain (CD25 antigen) on activated T-cells. This results in inhibition of interleukin-2 induced T-cell activation. These antibodies appear to be relatively well tolerated and hypersensitivity reactions are uncommon. No monitoring is required.

Muromonab-CD3

This is a mouse-derived monoclonal antibody which binds to the CD3 component of the T-cell receptor complex leading to T-cell depletion. Muromonab is also associated with the cytokine release syndrome which can range from a mild self-limiting flu-like illness to more serious manifestations including pulmonary oedema and neuropsychiatric adverse reactions. Neutralising antibodies can develop which block the effect and limit the re-use of muromonab-CD3. A longer-term concern is the increased incidence of lymphoma.

Conclusion

Advances in transplantation and the treatment of immune disorders have paralleled the development of immunosuppressant drugs. While the newer drugs are associated with superior efficacy, this may come at the cost of a greater incidence of opportunistic infections and malignancy, and adverse effects such as chronic allograft nephropathy, hyperglycaemia and hyperlipidaemia. Accurate concentration monitoring of cyclosporin, tacrolimus, sirolimus, everolimus and probably mycophenolate is necessary to improve outcomes and minimise toxicity.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 115)

3. Sirolimus and tacrolimus bind to the same protein, but have different mechanisms of action.

4. Sirolimus, tacrolimus and everolimus are all substrates for cytochrome P450 3A4.

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Immunosuppressants – clinical applications

Paul Trevillian, Senior Staff Nephrologist and Transplant Physician, Department of Nephrology, John Hunter Hospital, Newcastle, New South Wales

Summary

Immunosuppressants are used to control severe manifestations of allergic, autoimmune and transplant-related diseases. Some drugs have a diffuse effect on the immune system while others have specific targets. Drugs with diffuse effects are more likely to cause damaging adverse effects, but the effectiveness of the more specific drugs may be reduced if their action can be bypassed by alternative metabolic pathways. Treatment protocols therefore frequently use drug combinations to minimise adverse effects and to prevent resistance to treatment. Although protocols are essential to allow scientific evaluation, the clinician must be prepared to tailor treatment based on the ongoing assessment of drug effects, disease activity and the robustness of the individual patient.

Key words: calcineurin inhibitors, corticosteroids, transplantation.

Introduction

Many of the currently available immunosuppressants were developed for use in oncology or transplantation. As this treatment is potentially life-saving desperate measures can be justified. However, there are now over 80 autoimmune diseases and several common allergic conditions in which immunosuppressants could play a role although they may not be life-saving.

Some immunosuppressants act through immunodepletion of effector cells, while others are predominantly immunomodulatory, affecting the activity of cells, usually through cytokine inhibition. Immunosuppressants can be categorised as glucocorticoids, small molecules or proteins.[1]

Glucocorticoids

Corticosteroids are the mainstay of most immunosuppressive regimens in both the induction and maintenance phases. In high intravenous pulse doses (methylprednisolone 250–1000 mg daily for 1–3 days) they are directly lymphocytotoxic. In smaller doses, they are immunosuppressive and anti-inflammatory by limiting cytokine production. The required dose and duration of treatment therefore tends to be disease specific.

Some diseases, for example asthma, respond to a short course which can be abruptly stopped, but most rheumatic diseases require the dose to be very slowly tapered over months, especially when single figure milligram doses of prednisone are reached. Abrupt cessation runs the risk not only of relapse of disease, but also hypoadrenocorticism. (Adrenal suppression can be confirmed by a one-hour synthetic ACTH stimulation test if there is clinical concern.) In the withdrawal phase, non-specific polyarthralgias and myalgias are common, but generally respond to a small dose increment followed by a renewed, slower taper.

Second-line drugs, usually antiproliferative drugs such as azathioprine, mycophenolate or methotrexate, may have a steroid-sparing effect in the maintenance phase of treatment. However, they also have their own toxicities.

Patients prescribed corticosteroids should be told to expect the common early adverse effects, such as sweatiness, hoarse voice, loss of diurnal sleep patterns, and appetite stimulation. Rarely, more serious acute psychiatric disturbances are seen such as agitation, aggression or psychosis. Long-term, and less reversible, adverse effects include Cushingoid appearance, proximal myopathy, hypertension, hyperlipidaemia, diabetes, cataract formation, peptic ulceration, osteopenia and aseptic necrosis of bone.

Small molecules (Table 1)

The small molecule immunosuppressants include calcineurin inhibitors, such as cyclosporin, and antiproliferative drugs, such as sirolimus.

Calcineurin inhibitors

Since the 1980s, calcineurin inhibitors have been the main contributors to the success of solid organ transplantation, especially kidneys. By blocking interleukin-2 synthesis, they prevent activation of T-lymphocytes and are therefore useful in disorders of cell-mediated immunity. Calcineurin inhibitors have a proven role in the prevention of acute cellular rejection of transplanted organs, in psoriasis and in nephrotic syndrome.

Table 1

Small molecule immunosuppressant drugs in current use

Class of drug	Generic name	Potential clinical uses	Drug monitoring	Main adverse effects
Immunophilin-binding drugs				
Calcineurin inhibitors	cyclosporin	organ transplants, nephrotic syndrome, psoriasis, atopic eczema, rheumatoid arthritis	TDM(C_0 or C_2), creatinine, potassium, magnesium, glucose, lipids	nephrotoxicity, hypertension, tremor, hirsutism, gum hypertrophy, diabetes, haemolytic uraemic syndrome
	tacrolimus	organ transplants	TDM(C_0), creatinine, potassium, magnesium, glucose, lipids	as for cyclosporin but more tremor, diabetes, less hypertension and fewer cosmetic effects
Mammalian target of rapamycin (mTOR) inhibitors	sirolimus everolimus	organ transplants	TDM(C_0), lipids, FBC, UA	delayed wound healing, mouth ulcers, acne, pancytopenia, hyperlipidaemia, interstitial pneumonitis, peripheral oedema, proteinuria
Inhibitors of nucleotide synthesis				
Purine synthesis inhibitors	mycophenolate mofetil mycophenolic acid	organ transplants, vasculitides, SLE	TDM not widely used, FBC	diarrhoea, dyspepsia, neutropenia, anaemia, viral infections
Purine analogue	azathioprine	organ transplants, rheumatoid arthritis, SLE, inflammatory bowel disease	FBC, LFTs	neutropenia, macrocytosis, liver dysfunction, skin cancers, interaction with allopurinol
Pyrimidine synthesis inhibitor	leflunomide	rheumatoid arthritis, organ transplants	FBC, LFTs	diarrhoea, nausea, rash, alopecia, hepatitis, pancytopenia
Antimetabolites				
Dihydrofolate reductase inhibitor	methotrexate	rheumatoid arthritis (may be used in parallel with TNF inhibitors or leflunomide), psoriasis, psoriatic arthritis, inflammatory bowel disease	FBC, LFTs	anaemia, neutropenia, nausea, hepatitis, pulmonary fibrosis
Alkylating drugs				
Prodrug of phosphoramide mustard	cyclophosphamide	systemic vasculitides, especially Wegener's granulomatosis, SLE, membranous glomerulonephritis	FBC, MSU, UA	neutropenia, anaemia, alopecia, haemorrhagic cystitis, sepsis, infertility, bladder cancer

TDM	therapeutic drug monitoring	TNF	tumour necrosis factor
	C_0 = trough concentration	MSU	midstream urine for microscopy and culture
	C_2 = concentration 2 hours after a dose		
FBC	full blood count		
UA	urinalysis		
SLE	systemic lupus erythematosus		
LFTs	liver function tests		

They have been used in many other autoimmune conditions but have a diminishing role in rheumatoid arthritis. While they are good at maintaining autoimmune diseases in remission, withdrawal often leads to relapse.

In solid organ transplantation, combinations of calcineurin inhibitors, mycophenolate mofetil and prednisone give better results than monotherapy. Ironically, calcineurin inhibitors are nephrotoxic and may contribute to long-term renal failure, both in transplanted organs and normal kidneys. They also aggravate hypertension and hyperlipidaemia thereby inducing an unfavourable cardiovascular profile. There is also an increased risk of diabetes.

Mycophenolate mofetil

Since it was introduced into Australia in 1996 mycophenolate mofetil has largely replaced azathioprine in organ transplantation. One advantage over azathioprine is that allopurinol can be used for gout prophylaxis without the need to reduce the dose of mycophenolate. Possibly because of its anti-B cell properties[2] mycophenolate seems particularly effective in severe forms of systemic lupus erythematosus. It is also gaining favour as a steroid-sparing drug in the maintenance phase of a number of immune disorders, particularly the vasculitides.[3]

The main adverse effects are haematological and gastrointestinal. On higher doses a third of patients will develop diarrhoea. An enteric-coated formulation of mycophenolate has been developed to try and reduce gastrointestinal adverse effects. Therapeutic drug monitoring is available but not widely used.

Sirolimus and everolimus

These potent antiproliferative drugs have gained acceptance in renal transplantation as a strategy to minimise the use of calcineurin inhibitors in low immunological risk patients.[4] They have a decreased likelihood of causing hypertension and glucose intolerance. Although these drugs are associated with less nephrotoxicity than calcineurin antagonists, they potentiate the renal toxicity of cyclosporin and regular monitoring of renal function is recommended. Sirolimus and everolimus are generally avoided perioperatively because they can severely delay wound healing. They are potent inhibitors of intimal hyperplasia in arteries, and sirolimus-eluting intra-arterial stents are now used to reduce re-stenosis rates. However, they can increase serum cholesterol and lipids. The balance of the harm and benefit of continued treatment should be re-evaluated in patients who develop severe refractory hyperlipidaemia. Therapeutic drug monitoring is essential because of the risk of toxicity such as anaemia, leucopenia and thrombocytopenia.

Cyclophosphamide

Cyclophosphamide is a cytotoxic drug. It is the drug of choice for Wegener's granulomatosis, but is also used in other vasculitides such as microscopic polyangiitis and systemic lupus erythematosus.[5] Monthly intravenous pulses are as effective as daily oral use in systemic lupus erythematosus, but allow a reduced total dosage. Cyclophosphamide is also used to induce sustained remission in relapsing nephrotic syndrome. Marrow suppression with neutropenia is common after six weeks of treatment and continuing more than six months runs the risk of gonadal suppression and infertility in both sexes.

Methotrexate

This antimetabolite is used in some autoimmune diseases including psoriasis, psoriatic arthritis, rheumatoid arthritis and Crohn's disease. As a disease-modifying antirheumatic drug, its use in combination with tumour necrosis factor inhibitors (such as infliximab or etanercept) or leflunomide has been shown to markedly improve symptoms in rheumatoid arthritis.[6]

Proteins (Table 2)

Polyclonal antilymphocyte (antithymocyte) antibodies have been used in Australia since the 1960s. More recently, hybridoma technology has produced a plethora of monoclonal antibodies against molecules expressed by human immune effector cells.

T-lymphocyte depleting antibodies such as muromonab-CD3 have been widely used to prevent or treat acute rejection of organ transplants. The main drawback is a 'cytokine storm' reaction to the first dose, which can cause life-threatening pulmonary oedema.

Basiliximab and daclizumab are monoclonal antibodies against the interleukin-2 receptor (CD25). They are used as induction drugs in transplantation as they significantly reduce the acute rejection rate, with little or no increase in morbidity. They are not yet significantly used in autoimmune diseases.

The anti-B cell antibody (anti-CD20), rituximab, is licensed for use against B-cell lymphomata, but there are now published anecdotal reports of its effectiveness in 29 different autoimmune diseases.[7] Randomised controlled trials are proceeding in systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis and in renal transplantation of highly sensitised recipients.

A new monoclonal antibody, alemtuzumab, is directed against a surface molecule (CD54), which is widely distributed on lymphocytes, macrophages and dendritic cells, thereby causing severe and long-lasting depletion of these cell lines. As a result, the risk of serious infection is increased. The use of this antibody is cautiously making the transition from immunoprophylaxis in transplant recipients to a wider use in immune diseases.[8]

Two monoclonal antibodies against tumour necrosis factor, infliximab and adalimumab, and etanercept which prevents tumour necrosis factor binding to its receptor, are licensed for use in rheumatoid arthritis. They are also being used in ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disease.[9] Infusion reactions are common.

Table 2

Protein-based immunosuppressant drugs in current use

Drug	Potential clinical uses	Adverse effects
Lymphocyte depleting antibodies		
Polyclonal antithymocyte globulin	prevention and treatment of allograft rejection treatment of moderate to severe aplastic anaemia	cytokine-release syndrome (fever, chills, hypotension), thrombocytopenia, leucopenia, serum sickness
Muromonab-CD3	prevention and treatment of allograft rejection in transplant patients	severe cytokine-release syndrome, pulmonary oedema, acute renal failure, gut upset, neurological disturbances
Alemtuzumab	treatment of B-cell chronic lymphocytic leukaemia, immunoprophylaxis for renal transplants, GVHD, multiple sclerosis, rheumatoid arthritis	mild cytokine-release syndrome, neutropenia, anaemia, pancytopenia, immune thrombocytopenia, thyroid disease
Rituximab	treatment of B-cell non-Hodgkin's lymphoma antibody-mediated transplant rejection, SLE, vasculitis	infusion reactions, hypersensitivity reactions (uncommon)
Non-depleting antibodies and fusion proteins		
Basiliximab Daclizumab	prevention of allograft rejection in transplant patients	hypersensitivity reactions (uncommon)
Belatacept (LEA29Y)	prevention and treatment of allograft rejection in transplant patients	clinical trials still in progress
Tumour necrosis factor inhibitors		
Etanercept	rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis	injection site and infusion reactions, heart failure, opportunistic infections including fungi and tuberculosis, lymphoproliferative disease, demyelinating disease – reactivation of multiple sclerosis, SLE-like illness
Infliximab Adalimumab	rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease	
Pooled immunoglobulin		
Intravenous immunoglobulin	Kawasaki disease, CIDP, multiple sclerosis, Guillain-Barré, ITP, bone marrow transplants, myeloma, chronic lymphocytic leukaemia with hypogammaglobulinaemia, transplant rejection	rash, headache, abdominal pain, haemolysis (especially in patients with blood groups A, AB), thromboses, liver dysfunction, aseptic meningitis, acute renal failure

GVHD	graft versus host disease
SLE	systemic lupus erythematosus
CIDP	chronic inflammatory demyelinating polyneuropathy
ITP	idiopathic thrombocytopenic purpura

Pooled intravenous immunoglobulin was introduced to restore immunocompetence to patients with congenital acquired immune deficiency syndrome. Paradoxically, the discovery of its ability to inhibit the production and binding of auto- and allo-antibodies means that it is now more widely used as an immunomodulatory drug in the treatment of debilitating autoimmune diseases and antibody-mediated allograft rejection.[10] The fact that immunoglobulin also provides passive immunity means that it is regarded as having a low risk of infectious complications compared to other immunosuppressants. Consequently, it has been used in many conditions without good supportive evidence of efficacy, so the Australian National Blood Authority guidelines now restrict its use.[11] Nevertheless, it is likely that immunoglobulin use will continue to rise as knowledge about its mechanisms of action accumulates.

Using immunosuppressants – strategies and protocols

Treatment protocols are designed to:

(a) remove/suppress the predominant immune effectors and/or

(b) resolve acute inflammation

(c) prevent relapse.

To achieve (a) and (b), high doses are often used initially ('induction phase'). To achieve (c), lower doses of safer drugs are often chosen for the longer term ('maintenance phase').

Withdrawal of therapy is usually only considered after achieving clinical and laboratory evidence of sustained remission. Drugs are withdrawn gradually, one at a time and in the case of corticosteroids only after a long taper.

Empiricism vs controlled trials

Many protocols have evolved empirically from an understanding of the putative immune mechanisms operating in a particular disease. Sometimes the protocols were derived from what had been seen to work in conditions with apparently similar immunopathology. Randomised controlled trials of immunosuppressive protocols are available in the more common conditions such as rheumatoid arthritis or organ transplantation, but as new drugs emerge, the combinations for comparison become bewildering. Today's 'gold standard' treatment can be very quickly outdated, perhaps even before it has been optimised. Tailoring of immunotherapy to the individual is desirable, but this approach makes protocol comparisons difficult.

Similarly, the disease being treated may be so pleomorphic that finding like populations to compare in trials becomes very difficult. For example, lupus nephritis has five distinct histological subtypes, each with their own prognosis.

Choosing immunosuppressive regimens

In order to make sound judgements when choosing a treatment protocol the clinician has to consider the clinical trial evidence and then decide:

■ Is the aim to pre-empt an anticipated immune response (for example, after organ transplantation) or to suppress an established immune-mediated inflammation (for example, acute glomerulonephritis)?

■ In the case of an immune disease, how much immunosuppression will be required and for how long (that is, an assessment of disease activity)? Consider:

 – the natural history of the untreated disease

 – is the disease multiphasic (for example, polyarteritis nodosa) or 'single shot' (for example, microscopic polyangiitis)

 – the extent and severity of the disease in this particular patient

 – is the affected organ beyond recovery

 – the likelihood of relapse

 – the ability to monitor disease parameters long term

■ Is this patient likely to withstand the treatment I will recommend (host fitness parameters)? Consider:

 – age (older patients are easier to immunosuppress but have a greater risk of infection)

 – sepsis risk

 – cancer risk

 – cardiovascular/diabetes risk

 – presence of comorbidities

 – patient compliance and availability for follow-up.

In choosing the dose and duration of immunosuppressive treatments, one must always weigh disease activity versus host fitness. For example, an elderly patient with perinuclear-ANCA positive microscopic polyangiitis, confined to the kidneys, with crescents in 10% of glomeruli, will not need as aggressive an approach as the same disease in a young patient, with 80% crescents, lung haemorrhage and mononeuritis multiplex.

Managing and monitoring patients taking immunosuppressants

Patients need to be under constant surveillance, usually by a partnership between the specialist and the general practitioner. Frequency of visits depends on perceived level of risk, but typical parameters to monitor are summarised in Table 3. Patients may need prophylaxis against the adverse effects of their treatment (Table 4).

Therapeutic drug monitoring is available now for a number of drugs, for example cyclosporin, tacrolimus, sirolimus and mycophenolate. This allows for 'concentration-controlled' regimens. Some common drugs, for example corticosteroids, still have no good measure of individual bioavailability.

Infection risk

Immunosuppression increases susceptibility to infections which can become life-threatening in a matter of hours. At first, common bacterial infections of wounds, chest or urine predominate, but after 1–2 months of therapy opportunistic infections emerge, particularly herpes viruses, pneumocystis pneumonia, fungi and atypical mycobacteria.

Vaccinations against influenza (injected) and pneumococcus are recommended in chronically immunosuppressed patients.[12] They are safe and reasonably effective when given in the stable maintenance phase. In general, live attenuated virus vaccines, such as varicella or measles, should not be given to immunosuppressed patients (or to close family contacts).

Cancer risk

In patients taking immunosuppressants, early cancers are often viral induced. They include lymphoproliferative disorders and

Table 3

Routine monitoring of patients taking immunosuppressant drugs

Monitoring of immune system	Acute phase reactants (e.g. C-reactive protein, erythrocyte sedimentation rate)
	Disease-specific auto-antibodies (e.g. antineutrophil cytoplasmic antibody, anti-double-stranded DNA antibody)
	Immunoglobulin and complement concentrations
	Organ function and histology
	Neutrophil and lymphocyte counts, and T-cell subsets
Monitoring of adverse effects	Haemoglobin, platelets, lipids, blood glucose
	Blood pressure
	Skin cancer surveillance, rectal examination, pap smear and possibly prostate specific antigen
	Bone densitometry
	Cataract screening
Therapeutic drug monitoring	Meeting therapeutic targets (where known)
	Defines poor absorption
	Helps assess compliance

Table 4

Common prophylactic treatments for patients taking immunosuppressant drugs

Infection prophylaxis	'Heavy' immunosuppression may warrant prophylaxis for cytomegalovirus (valganciclovir), *Pneumocystis jiroveci* pneumonia (cotrimoxazole) and candidiasis (oral nystatin)
	Influenza and pneumococcal vaccines
Anticoagulation	Immune diseases are frequently associated with thrombophilia requiring antiplatelet drugs or warfarin
Cardiovascular/ diabetes risk	Corticosteroids, calcineurin inhibitors and mammalian target of rapamycin inhibitors all have adverse cardiovascular risk profiles. 'Statins' and antidiabetic drugs are often indicated.
Bone preservation	May require calcium, vitamin D and bisphosphonate supplements
Ulcer prophylaxis	Consider H_2 antagonist or proton pump inhibitor especially with steroid use

cervical cancer. In the long term, nearly all common cancers are increased, but particularly skin cancers. After 20 years of immunoprophylaxis following renal transplant, 80% of Australian patients will have developed skin cancer.

Conclusion

Advances in our understanding of the immune aetiology of many debilitating diseases have resulted in wider use of immunosuppressant drugs in common clinical practice. The last two decades have seen the development of several useful small molecule drugs but also a profusion of monoclonal antibodies targeting the immune system. Increasingly, primary care physicians are involved in the supervision of patients taking these drugs. This task has been made easier and safer by the establishment of therapeutic targets for drug monitoring and the obligatory use of prophylactic drugs to prevent common adverse effects. Good clinical judgement, supported by laboratory investigations, is needed to differentiate the patients who are over-immunosuppressed (and therefore at risk of infections and cancer) from those experiencing relapse of their underlying disease.

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Conflict of interest: none declared

Dental notes

Prepared by Dr M McCullough of the Australian Dental Association

Painful paediatric procedures (see page 94)

Dental procedures can be one of a child's most uncomfortable experiences if not handled correctly. They can have adverse psychological effects for the remainder of the child's life with regard to both future dental experiences, and how they relate to other healthcare professionals. Dentists need to be acutely aware of a child's feelings of vulnerability and fear of the unknown when coming to the dentist for the first time. Ideally the dentist should follow guidelines such as the standards of care of the Australasian Academy of Paediatric Dentistry.

Children should be introduced to the dental surgery in a non-threatening manner, ideally when only an examination is necessary. However, on occasion a child requires treatment after they have been in pain for some time, and the expectation of treatment is overlayed by previous experience or embellished accounts of the experiences of their friends, siblings and most importantly the attitudes portrayed by adults, particularly their parents. The concerns and procedures outlined in the medical article (page 94) are generally applicable to dental practice. Establishing rapport with the child and communicating at the appropriate developmental level leads to the use of behaviour management techniques such as 'tell, show, do', distraction and systematic desensitisation which should result in an atraumatic dental visit for the child.

Local anaesthesia has, in the past, been considered by some practitioners to be unnecessary for deciduous teeth; however it should be stressed that if a procedure is predicted to be painful anaethesia should be provided. Topical anaesthesia should be used, with the material localised onto dry mucosa for 60 seconds, minimising the amount that the child may taste by using the end of a cotton roll. Local anaesthesia should be introduced through tight mucosa for inferior alveolar blocks and buccal infiltrations. For palatal tissues, the needle can be inserted in the already anaesthetised buccal papilla and gently forwarded until the solution can be deposited into the palatal tissues. Care should be taken regarding dosage and toxic concentrations and practitioners should be aware of the signs of toxicity. Occasionally, referral to a specialist paediatric dentist and the use of sedation or general anaesthesia for lengthy and involved procedures may be the best approach for the long-term psychological well-being and positive health behaviour of the child.

Xerostomia: a common adverse effect of drugs and radiation (see page 97)

Xerostomia (dry mouth) is a relatively common condition and is due to salivary dysfunction. It has multiple causes, including developmental, inflammatory and neoplastic disorders. Common causes are anxiety, an adverse effect of drugs, and radiotherapy in the head and neck region. A decrease in the quantity or quality of saliva has a profound effect on the oral environment. This results in extensive and recurrent smooth surface dental decay, increased periodontal disease, significant worsening of any underlying mucosal disease and an increased likelihood of oral candidosis and difficulty with the retention of dentures. Ideally, before patients start taking drugs that can cause xerostomia or undergoing radiotherapy in the head and neck region, they should have a detailed dental check-up followed by treatment of any active disease. Topical agents can be very useful in reducing decalcification and promoting mineralisation of teeth. Dentists can advise patients on methods for the care of their teeth as well as methods to diminish the feeling of oral dryness that so profoundly affects patients' quality of life. Patients with xerostomia must have regular dental reviews and excellent oral hygiene as the removal of any teeth may result in them being unable to cope with dentures. Patients with Sjogren's syndrome also require long-term follow-up as they have a significantly higher incidence of lymphoma in their salivary glands.

Psychostimulant poisoning

Dan McCormack, Emergency/Toxicology Registrar, The Canberra Hospital, and Nicholas A Buckley, Department of Clinical Pharmacology and Toxicology, Australian National University Medical School, Canberra

Summary

Psychostimulants are sympathomimetic activators of the central nervous system. Licit examples include caffeine, decongestants, methylphenidate, dexamphetamine and some drugs for weight loss. While these have the potential for abuse, the major problem in Australia is illicit use of amphetamines, ecstasy (3,4-methylenedioxymethamphetamine) and cocaine. These substances are taken to produce feelings of euphoria and well-being, increased energy and alertness. Potential problems with toxicity range from tachycardia and hypervigilance to seizures, psychosis and serotonin syndrome. Management is primarily directed at reversing the excitation of the central nervous system by sedation with benzodiazepines, but more specific treatments are occasionally indicated.

Key words: amphetamines, drug abuse, overdose.

Introduction

In the 2004 national drug survey, over 9% of Australians over the age of 14 years had tried amphetamine/methamphetamine, 7.5% had tried ecstasy and nearly 5% had tried cocaine. From this survey, it is estimated that over half a million people used ecstasy at least once in 2004, and a similar number had used amphetamines. In contrast, only 1% had used cocaine in the previous year.[1]

These drugs have a long history of use and abuse. Cocaine was first isolated in 1860, amphetamines were first synthesised in 1887, ecstasy was first patented in 1914, and methamphetamines were produced in 1919. Each drug has had a variety of licit indications at various times. Methamphetamine was prescribed for a range of conditions including depression and obesity. Amphetamines were used as decongestants (Benzedrine) and have been given to soldiers to increase energy and alertness. They are still used for disorders like narcolepsy and attention deficit hyperactivity disorder, while cocaine is still in limited use as a topical anaesthetic. Even ecstasy has been used as an adjunct to psychotherapy in the USA.

Current patterns of use and abuse

The predominant amphetamine available during the 1980s was amphetamine sulphate. Introduction of legislative controls over the precursor materials has meant that in recent times over 90% of amphetamines seized have been methamphetamines. Methamphetamines are produced by reduction of ephedrine or pseudoephedrine, found in decongestants and other household products, making them relatively simple drugs to produce. Ecstasy is 3,4-methylenedioxymethamphetamine (MDMA) and is mostly smuggled into Australia because of the lack of local expertise in production, although local production may be increasing. Cocaine is purified from a plant and is imported.

Formulations and cost

Amphetamines and ecstasy are commonly taken as tablets. The tablets can also be crushed and injected. Ecstasy costs between $30 and $50 a tablet.

There are several different kinds of methamphetamines available (see box). 'Speed' is methamphetamine powder, generally manufactured in Australia, and is usually low quality. 'Pills' are tablets of methamphetamine produced in Australia which are often sold as ecstasy. 'Base' is an oily, damp powder that is made in Australia and is generally of high purity. 'Ice' or 'crystal meth' is high quality methamphetamine crystals, generally imported from Asia. Methamphetamines can be smoked, injected or swallowed. The cost of methamphetamine varies in different parts of Australia and with its form, from $50 for a 'point' (0.1 g) of crystal to $55 for a gram of speed.[2]

Cocaine can be snorted, smoked or injected. It costs approximately $200/g.

■ 'speed'	methamphetamine powder
■ 'pills'	methamphetamine tablets
■ 'base'	oily damp methamphetamine powder
■ 'ice' or 'crystal meth'	methamphetamine crystals
■ ecstasy	3,4-methylenedioxymethamphetamine (MDMA)

Adulteration of tablets should be considered in regard to potential adverse effects. While ecstasy tablets usually contain a single drug, it frequently is not MDMA. Up to 80% of ecstasy tablets sold in Australia are actually methamphetamine. Sometimes ketamine is added to mimic the effects of MDMA. Other chemicals sold as ecstasy include ephedrine, other amphetamine analogues with similar pharmacological effects such as 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine (MDEA) and paramethoxyamphetamine (PMA). PMA or 'death' is more toxic than MDMA and has been associated with a spate of deaths in Australia and Canada.

'Herbal ecstasy' preparations usually contain the Chinese herb *Ma huang*, which contains ephedrine, and caffeine derived from the cola nut. Ephedrine is similar to amphetamines but less potent. *Ma huang* can also be found in energy drinks and dietary supplements. Experience from overseas does not suggest 'herbal ecstasy' is any safer than MDMA, with over 800 reported adverse events related to ephedrine-containing substances, including myocardial infarctions, strokes and seizures.

Toxicokinetics and pharmacology

Oral amphetamines and MDMA have an onset of action within 30 minutes, with peak concentrations being reached in 1–3 hours. The elimination half-life of these drugs ranges between 6 and 12 hours. Cocaine has an extremely rapid onset of action taken intravenously or inhaled, and between 30 and 60 minutes orally or intranasally. It has a short half-life of 30–90 minutes.

Psychostimulants cause an overall increase in the effects of monoamine neurotransmitters – noradrenaline, dopamine and serotonin – by increasing their release and blocking reuptake. Amphetamines, MDMA and cocaine have the greatest effect on noradrenaline, serotonin and dopamine respectively.[3] Ecstasy primarily increases serotonergic activity while methamphetamine primarily increases adrenergic activity. Cocaine also blocks fast sodium channels, causing local anaesthetic and pro-arrhythmic effects.

Clinical presentations

The majority of ecstasy users do not experience adverse events that precipitate a hospital visit. Serious complications are rare and partly dependent on individual susceptibility and circumstances. The common adverse acute physiological and psychological effects that psychostimulants elicit are an exaggerated 'fight or flight' response. Signs include tachycardia and hypertension, hypervigilance, dilated pupils, rapid speech, clenched jaw and bruxism, diaphoresis, peripheral vasoconstriction and being generally restless with repetitive movements.

More serious acute sequelae can be grouped by the affected organ systems:

- central nervous system – haemorrhagic and non-haemorrhagic stroke, seizures, coma, cerebral vasculitis
- cardiovascular – hypertension, arrhythmias, cardiac ischaemia (cocaine in particular) and aortic dissection
- psychiatric – aggression, delirium, paranoid psychosis
- respiratory – non-cardiogenic pulmonary oedema, pulmonary hypertension
- gastrointestinal – diarrhoea, mesenteric ischaemia, hepatotoxicity
- renal – acute renal failure
- musculoskeletal – rhabdomyolysis
- other – serotonin toxicity, hyperthermia, syndrome of inappropriate antidiuretic hormone, obstetric complications, urinary retention.

MDMA and amphetamines can cause serotonin toxicity. This is particularly likely if they are taken in conjunction with monoamine oxidase inhibitors including moclobemide.

Extreme dehydration and water intoxication have been associated with MDMA toxicity. Dehydration is due to a lack of awareness of thirst in the setting of extreme physical activity. Water intoxication can be a consequence of increased antidiuretic hormone secretion and drinking too much water (to prevent dehydration), leading to complications associated with hyponatraemia. Cardiac ischaemia can occur with any of these drugs, but is particularly associated with cocaine. It is due to a combination of increased myocardial demand, coronary vasoconstriction, and increased thromboxane A_2 activity and thrombus formation. The risk of a myocardial infarction is 24 times greater in the first hour after cocaine ingestion, even in persons otherwise of low risk.

Assessment

A history of the ingested substances needs to take into account possible substitutions or the addition of other substances to illicit tablets. Past history should focus on medication (due to concerns about potentiating drug interactions), psychiatric history and other risk factors for serious adverse effects (for example cardiovascular disease or epilepsy). Alternative medical diagnoses need to be considered.

A full set of physical observations is important, particularly temperature, blood pressure and pulse. Relevant investigations include an electrocardiogram (ECG), serum electrolytes, liver function tests and creatine kinase concentration. Screening for drugs of abuse in the urine may confirm exposure to particular drugs, but is not useful in acute management which is based on the detection and prevention of complications.

Management

While some patients can just be observed, others will need management of specific complications.

Psychiatric complications

Psychiatric sequelae need to be managed in a calm, non-confrontational manner, as for any agitated, potentially aggressive disorder. Either oral or intravenous sedation may be needed if further assessment is required and the patient is unco-operative. The primary aim is to ensure that the patient is not a risk to themselves or the staff. Benzodiazepines are preferred and have the added benefit of decreasing the likelihood of seizures. Antipsychotics such as haloperidol may be useful for patients with severe psychosis. 'Chemical sedation' should only be given in a monitored environment where rapid intervention is possible in the event of respiratory compromise or hypotension.

Depressive symptoms can occur in the days following stimulant use. These may progress to overt depressive illness possibly warranting antidepressants. Suicidal ideation and suicide attempts may occur.

Cardiovascular complications

Hypertension associated with amphetamine and cocaine abuse is mostly transient and will not require specific management. Benzodiazepines will generally provide adequate control of blood pressure in the agitated patient. Severe hypertension in the setting of possible neurovascular pathology may require vasodilators such as phentolamine or hydralazine.

If cardiac chest pain is suspected in someone who has taken cocaine it should be treated with aspirin, oxygen and nitrates. Beta blockers are contraindicated as unopposed alpha-receptor stimulation can worsen vasoconstriction and increase blood pressure. Most cocaine-related chest pains do not result in infarction and the risk of subsequent ischaemic events without further drug abuse is relatively low.[4] Standard chest pain protocols including monitoring cardiac enzymes and ECGs can be followed. If there are confounding factors then a semi-urgent exercise stress test should be organised.

Neurological complications

An acute neurological deterioration such as a severe headache, seizures, localising signs or ongoing confusion requires a CT scan of the brain to exclude haemorrhagic or non-haemorrhagic stroke and traumatic injury secondary to the confused state. Seizures can be controlled in the first instance with benzodiazepines and then phenobarbitone if persistent or recurrent. Phenytoin has no role in the treatment of drug-induced seizures.

Serotonin syndrome

The diagnosis of serotonin toxicity is based on clinical findings – in particular clonus and hyperreflexia.[5,6] Treatment is essentially supportive, with intravenous hydration and close monitoring. Severe serotonergic crises with marked hyperthermia and development of pyramidal rigidity require admission to intensive care for active cooling, paralysis and ventilation to prevent development of rhabdomyolysis and disseminated intravascular coagulation. There are case reports of moderate to severe serotonin syndrome being treated with cyproheptadine 4–8 mg three times a day, in addition to supportive measures.

Chronic sequelae

The most commonly repeated findings in studies of MDMA, methamphetamine and cocaine use have been problems in the area of learning and memory. There is both animal and human evidence of neurotoxicity, but the evidence as to whether this is reactive but reversible, or permanent and irreversible in humans is inconclusive.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 115)

7. The most common substance found in ecstasy tablets currently available in Australia, other than 3,4 methylenedioxymethamphetamine (MDMA), is methamphetamine.

8. Cocaine use increases the risk of myocardial infarction in otherwise healthy people.

9. Chest pain following cocaine use is managed with beta blockers.

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.

Deferasirox

Exjade (Novartis)

125 mg, 250 mg and 500 mg dispersible tablets

Approved indication: iron overload

Australian Medicines Handbook section 4.2

Patients who require frequent transfusions of blood, such as those with thalassaemia, are at risk of chronic accumulation of iron. This excess iron is deposited in the tissues such as the heart and liver resulting in damage and diminished function. To prevent organ failure these patients require the iron to be removed by chelating agents such as desferrioxamine. As desferrioxamine has to be given parenterally, oral chelating agents are being developed. Deferiprone was approved in Australia in 2003.

Deferasirox is another oral chelating agent. After absorption two molecules of deferasirox bind one atom of iron. The complex is then excreted in faeces. Deferasirox is metabolised and has an elimination half-life of 8–16 hours.

A short-term study of 24 adults with thalassaemia found that increasing doses of deferasirox increased iron excretion.[1] This led to a one-year study of 586 patients with a mean age of 17 years (range 2–53 years). They were randomised to take deferasirox or have subcutaneous desferrioxamine with the doses determined by the concentration of iron found on liver biopsy. (Patients randomised to desferrioxamine could remain on their previous dose.) Depending on the dose, both chelating agents reduced serum concentrations of ferritin. The mean reductions in liver iron concentration, when liver biopsies were repeated at the end of the study, were 2.4 mg/g with deferasirox and 2.9 mg/g with desferrioxamine. Overall 53% of the patients taking deferasirox achieved the target liver iron concentration compared with 66% of the patients given desferrioxamine.

In the main clinical trial serious adverse events such as infections affected approximately 9% of both groups. The most frequent adverse events associated with deferasirox were fever, headache, abdominal pain, nausea, vomiting and diarrhoea. In 11% of patients serum creatinine increased and 19% developed proteinuria. Renal function should therefore be monitored monthly. Monthly liver function tests are also recommended because there is a risk of drug-induced hepatitis. As deferasirox may cause cataracts and reduced hearing, annual eye examinations and hearing tests are advised.

Depending on how the results of the main trial are analysed, the efficacy of deferasirox may be inferior to that of desferrioxamine. In children aged 2–5 years it is only approved for use if desferrioxamine is ineffective or not tolerated.

There does not appear to be a published comparison of deferasirox and deferiprone. Deferasirox only needs to be taken once daily, but it is unknown if it has any other advantages.

T T   manufacturer provided some data

Reference *

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Epoetin beta

Neorecormin (Roche)

Pre-filled syringes containing 1000 IU, 2000 IU, 3000 IU, 4000 IU, 5000 IU and 6000 IU per 0.3 mL, and 10 000 IU, 20 000 IU and 30 000 IU per 0.6 mL

Approved indication: specified anaemias

Australian Medicines Handbook section 7.6

Erythropoietin is a hormone which stimulates the production of red blood cells. A recombinant form, epoetin alfa, has been available for several years. Australian clinicians now have the option of prescribing recombinant epoetin beta, a form which has been available in Europe since 1990.

Like epoetin alfa, epoetin beta is genetically engineered using Chinese hamster ovary cells. Its protein sequence is indistinguishable from natural erythropoietin.

Following injection there is a dose-related response in the bone marrow. The dose is adjusted according to the packed cell volume or haemoglobin concentration. In the anaemia of chronic renal failure the regimen consists of a correction phase and then a maintenance phase.

Epoetin beta can be given by subcutaneous injection or by intravenous injection over two minutes. The bioavailability of the subcutaneous injection is less than half that of intravenous doses, but the half-life is longer (8–22 hours vs 4–12 hours) and lower doses can be used. In the correction phase of renal anaemia epoetin is given three times a week, but the subcutaneous injection can be given daily. It may be possible

during the maintenance phase to give a subcutaneous dose once every two weeks.

There have been several studies of epoetin beta for the anaemia of chronic renal failure. Most patients reach their target haematocrit after 12 weeks of treatment. Patients can successfully maintain their haematocrit with self-administered injections.[1] (This study used a pen injector which is not available in Australia.) While most of the patients will be on dialysis, epoetin beta can be used if patients with chronic renal insufficiency develop a symptomatic anaemia before starting dialysis.

Anaemia is common in patients with cancer particularly if they have been subjected to chemotherapy. In a placebo-controlled study of 349 patients with haematological malignancies, injecting epoetin beta subcutaneously three times a week for 16 weeks significantly reduced the need for blood transfusions. The patients' quality of life improved as their haemoglobin increased.[2] Another study of 241 patients with lymphoproliferative malignancies found that a once-weekly injection was as effective as three times a week.[3]

In addition to treating chemotherapy-induced anaemia in non-myeloid malignancies, epoetin beta, like epoetin alfa, is approved for increasing the yield of autologous blood donations, for example when people donate their own blood before undergoing surgery. Epoetin beta is also approved for preventing anaemia in premature babies.

As the packed cell volume increases the patient's blood pressure may rise. The risk of thrombosis may increase, particularly if there is a rise in platelet production. There is also a possibility that epoetin could stimulate tumour growth.

Iron studies and electrolytes should be regularly checked. Most patients will require iron supplements. Neutralising anti-erythropoietin antibodies can develop. If this results in red cell aplasia treatment must stop.

The pain of subcutaneous injections of epoetin beta has been compared with that of epoetin alfa. In a small study patients were injected with both products for four weeks. Pain scores were significantly lower with epoetin beta.[4] Another study compared epoetin beta with buffered formulations of epoetin alfa, and saline, by giving 60 patients four simultaneous injections. Epoetin beta was more acceptable than epoetin alfa and some patients felt it was no more painful than the saline injection.[5]

When indicated, epoetin beta will help to ameliorate the anaemia in most patients, but it may not improve long-term outcomes, at least in malignant disease. During a median follow-up of 27–28 months in 343 patients with lymphoproliferative malignancies, the median survival was 18 months with placebo and 17 months with epoetin beta.[6]

T T T manufacturer provided all requested information

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Rotavirus vaccine (Rotarix)

Rotarix (GlaxoSmithKline)

vials containing powder for reconstitution

Approved indication: prevention of rotavirus gastroenteritis

Australian Medicines Handbook section 20.1

Rotaviruses are a common cause of gastroenteritis in children. This can result in dehydration and, particularly in developing countries, death.

There are different strains of the virus. This vaccine has been developed from the common G1 serotype (89-12 strain). The production process results in a live attenuated vaccine which can be given orally (on the inside of the cheek).

A phase II trial in Singapore involved 2464 babies aged 11–17 weeks. They were given three different concentrations of the vaccine or a placebo. The seroconversion rate was 75–86% after a month. A second dose was then given and this resulted in 76–91% of the babies having antirotavirus antibodies one month later.[1]

A trial in South America gave three different concentrations of the vaccine to 1618 babies 6–12 weeks of age. Another group of 537 babies was given a placebo. Two months after the second dose of vaccine 61–65% of the babies had seroconverted. During the first year of life there were 1635 episodes of gastroenteritis but rotavirus was only isolated in 109 babies. Rotavirus gastroenteritis affected 3.58% (58/1618) of babies randomised to the vaccine group and 9.49% (51/537) of babies randomised

to the placebo group. Vaccine efficacy against rotavirus gastroenteritis was calculated to be 56–70%.[2]

Another South American trial gave the vaccine to 31 673 babies at the ages of two and four months. Compared to a control group of 31 552 given a placebo, the vaccinated babies had a significantly reduced rate of severe gastroenteritis. In the cohort of 20 169 babies followed until they were one year old, nine vaccinees needed hospital admission, compared with 59 of the placebo group. The vaccine efficacy against severe gastroenteritis was 85%.[3]

Adverse events which had a higher incidence with the vaccine than with placebo included irritability, flatulence, diarrhoea, reduced appetite and fever.

The vaccine can be given at the same time as other vaccines. Although it can be given with oral polio vaccine, a gap of two weeks is suggested. As viral antigen is excreted in the stools there is a potential for transmission to other people.

A different rotavirus vaccine marketed in the USA was withdrawn in 1999 after it was associated with intussusception. During the large South American study there were nine cases of intussusception following vaccination compared with 16 in the placebo group. Although the difference was not statistically significant, 56 deaths occurred after vaccination compared with 43 in the placebo group.[3]

The vaccine is most likely to be of benefit in communities with a high incidence of severe rotavirus gastroenteritis. Whether the multivalent vaccines under development will have greater effectiveness than this monovalent vaccine is currently uncertain.

T T   manufacturer provided some data

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Rotavirus vaccine (RotaTeq)

RotaTeq (Merck Sharp & Dohme)

tubes containing 2 mL suspension

Approved indication: prevention of rotavirus gastroenteritis

Australian Medicines Handbook section 20.1

Rotavirus is a leading cause of severe gastroenteritis in young children worldwide. Rotavirus-induced disease is responsible for the hospitalisation of approximately 10 000 Australian children each year. Between July 2004 and June 2005, the most prevalent serotypes in Australia were G1 (48.3%), G3 (36.7%) and G9 (6.9%), with G2 and G4 serotypes also causing some infections (less than 1%).[1] However, the prevalent serotype can change over time and in 2002–03, G9 was the dominant strain causing almost 75% of cases, with G1 responsible for only 11% of infections.[2]

This live oral pentavalent vaccine contains five types of rotavirus. The viral surface proteins correspond to human rotavirus serotypes G1, G2, G3, G4 and P[8]. The P[8] antigen was included in the vaccine to potentially provide protection against other G-serotypes that may contain P[8], for example serotype G9.

Safety and efficacy data for the vaccine were examined in a placebo-controlled trial of 68 038 babies. The vaccine was given to healthy infants with the first dose administered between 6 and 12 weeks of age then followed by two more doses at 4–10 week intervals. All infants had been immunised by the age of 32 weeks. Oral polio vaccine was not permitted to be given at the same time; however other childhood vaccines were allowed.[3]

Serum antibody responses were measured in a sub-group of 189 babies 14 days after the third dose. The seroconversion rates for neutralising antibody (specific to serotypes contained in the vaccine) and antirotavirus IgA were higher in the vaccine group compared to the placebo group. However, it is not known if these antibodies are responsible for protection against rotavirus gastroenteritis.

The number of hospitalisations or emergency department visits due to infections with G1–4 and G9 serotypes was evaluated. There were 383 cases in the 28 646 babies given the placebo compared to only 20 cases in the 28 488 babies given the vaccine. Depending on the serotype, the vaccine efficacy against hospitalisation or emergency department visits varied from 87.6% to 100%. Although these findings were statistically significant, the incidence of infections with some of the serotypes was very low.[3]

In an efficacy sub-group analysis, vaccine efficacy against G1–4 and G9 rotavirus gastroenteritis of 'any severity' was evaluated during the first rotavirus season. There were 318 cases of infection among the 2305 babies in the placebo group compared to only 83 cases in the 2207 vaccinees.[3]

There is an indication that the efficacy of this vaccine may decline in subsequent seasons since during the second rotavirus

season the efficacy dropped from 71.3% (first and second season) to 62.6%. Protection beyond a second rotavirus season was not evaluated in this trial.

A previous rotavirus vaccine, which was shown to be highly efficacious against rotavirus infection, was voluntarily withdrawn in 1999 because of an association with intussusception in babies after the first dose. In the trial of the new vaccine, all 68 038 babies were monitored for at least 42 days after each dose for serious adverse effects. Overall, there were 30 cases of intussusception – 12 of these occurred in the vaccine group and 18 in the placebo group. Only six cases occurred within 42 days of vaccination compared to five in the placebo group. There were ten cases of rectal bleeding in the vaccine group compared to three cases in the placebo group. The number of serious adverse events (fever, vomiting and diarrhoea) and deaths were similar in the vaccine and placebo groups. Dermatitis was more common among vaccine recipients.[3]

This vaccine can be given at the same time as other vaccines except oral polio vaccine.

It seems likely that this pentavalent vaccine will reduce hospitalisations due to prevalent rotavirus serotypes that cause gastroenteritis in Australia. It is not known if this vaccine will be more effective than the monovalent vaccine currently being marketed.

T T manufacturer provided some data

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The T-score (T) is explained in 'Two-way transparency', Aust Prescr 2005;28:103.

* At the time the comment was prepared, information about this drug was available on the website 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 website of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int)

Answers to self-test questions

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

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