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Editorial

Turning knowledge into action

Heather Buchan, National Institute of Clinical Studies, National Health and Medical Research Council, Melbourne

Key words: evidence-based medicine, guidelines.

(Aust Prescr 2007;30:114–15)

Studies of healthcare provision show that many patients do not get care that is consistent with the best available evidence. A study of the care provided to several thousand people in the United States using telephone interviews and chart audit showed that, for a wide range of conditions, people received care consistent with best practice recommendations only 55% of the time. While prescribing showed higher rates of adherence to recommended care than interventions requiring counselling and education (69% vs 18%), substantial numbers of people were not receiving drugs that would be of benefit to them.[1] Similar results have been found when auditing care provided by primary care physicians in the Netherlands.[2] In Australia, more limited studies show that there is widespread underuse of many drugs, such as oral anticoagulants in people with atrial fibrillation, and ACE inhibitors and beta blockers in patients with heart failure. Conversely, there is also overuse of drugs in Australia, such as antibiotics for the common cold and acute bronchitis.[3]

Poor uptake of research findings is not confined to areas where discoveries are recent. It took on average over 15 years for research findings on a number of clinical interventions (such as influenza vaccination, thrombolytic therapy, use of beta blockers after myocardial infarction, and diabetic foot care) to reach a rate of use of 50% in eligible patients seen in clinical practice.[4]

How can the gaps between best evidence and current practice be closed more quickly and more effectively? Traditional approaches aim to improve the knowledge and skills of clinicians through continuing education and training. Over recent years there has also been a focus on making research findings easier for clinicians to access and interpret. Evidence-rating systems, systematic reviews of research, evidence summaries and production of guidelines are all ways of trying to make the enormous research output manageable. However, improved knowledge does not necessarily produce alterations in behaviour or change in long-established habits. This is evidenced by the difficulty that many people have in changing their diet in order to lose weight or attaining recommended levels of exercise despite knowing what they should do and the health advantages that could result.

Barriers other than lack of knowledge that prevent best evidence being applied in practice vary according to the clinical issue, the individual doctor and the environment in which care is delivered. Examples of barriers include a lack of recognition that a gap exists, beliefs or attitudes that research findings are not important or relevant to practice, and established systems of care that make it difficult to change customary processes. In some instances patient beliefs and preferences play an important role in influencing prescribing behaviour. This is one reason for inappropriate prescribing of antibiotics for viral infections.

One approach to improving care is to agree on specific areas where practice should be changed, identify the barriers to change and design interventions to overcome these barriers. For example, one of the aims of a program in Norway was to increase prescribing of thiazides for the treatment of uncomplicated hypertension in general practice.[5] Potential barriers identified were that thiazides were considered old-fashioned, physicians were worried about possible adverse effects and lack of antihypertensive effect, physicians were not familiar with the relevant brand names, and few other clinicians were using these drugs. Established habits of general practitioners and advocacy by pharmaceutical companies were also noted as potential barriers to increased prescribing of thiazides. Interventions designed to overcome these barriers

In this issue …

Patients need information to make the best use of their medicines. While all prescription medicines now have Consumer Medicine Information, Parisa Aslani believes this resource is underused. Sometimes information can be lacking and Anne Sved Williams says the use of antidepressants in pregnancy and lactation has to be largely guided by clinical experience.

Information is also relevant for non-drug therapies. Bronwyn Penny tells us the important components of an exercise prescription for patients with diabetes.

A good example of turning knowledge into action, discussed by Heather Buchan, is the management of jellyfish stings. Geoff Isbister tells us that there have now been prospective trials to guide treatment.

included educational outreach visits, use of opinion leaders, audit and feedback and computerised reminders linked to the medical record system.

Identifying barriers and incentives to change and using this information to tailor implementation strategies seems logical but, at present, while some studies show success using this approach others do not. The interventions used in the Norwegian study significantly increased prescriptions of thiazides for hypertension. However, they were ineffective in improving the risk assessment of patients before prescribing and for achieving treatment goals in patients with hypertension or hypercholesterolaemia.[6]

In some reported studies it is unclear whether the methods used to identify barriers produced accurate information about the most important barriers or whether the implementation strategies were optimally tailored to the identified barriers. An overview of studies of guideline implementation concluded that there was still an imperfect evidence base to make decisions about implementation strategies because of poor reporting of study settings, barriers to change, and the content and rationale of interventions.[7]

The key messages that emerge from experienced researchers running programs to change clinical practice emphasise the importance of:

- using a systematic approach, with careful planning, concrete proposals and targets for change
- ensuring that ongoing practice data are provided to practitioners and used as an integral part of the change process
- providing appropriate leadership and sufficient support for any change program.

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Conflict of interest: none declared

Anaphylaxis wall chart

Accompanying this issue is a new version of the *Australian Prescriber* wall chart on the emergency management of anaphylaxis. This replaces the previous version published in 2001.

The new version has been prepared over many months with the assistance of the Australasian College for Emergency Medicine, the Australian and New Zealand College of Anaesthetists, the Royal Australasian College of Physicians, the Australasian Society of Clinical Immunology and Allergy, the Royal Australian College of General Practitioners, and the Royal Australian and New Zealand College of Radiologists.

The Editorial Executive Committee of *Australian Prescriber* believes that the wall chart will assist health professionals working in the community. While there are other protocols for managing anaphylaxis, the Editorial Executive Committee considers that the *Australian Prescriber* wall chart will be applicable in most situations. As with all protocols, the keystone of drug treatment is to give the patient adrenaline.

Message to all 2007 graduates in medicine, pharmacy and dentistry

If you are graduating in Australia this year and you wish to continue receiving *Australian Prescriber*, please complete and send the distribution form on the inside back cover of this issue, or register online (www.australianprescriber.com at Mailing list).

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.

Varicella vaccination

Editor, – Before the universal varicella vaccination program, 95% of adults in the USA experienced natural chickenpox (usually as school-aged children). Most of these cases were benign and resulted in long-term immunity. This high percentage of individuals with long-term immunity has been compromised by mass varicella vaccination of children, which provides at best 70–90% immunity that is temporary and of unknown duration.[1,2] This shifts chickenpox to a more vulnerable adult population in which chickenpox carries 20 times more risk of death and 15 times more risk of hospitalisation compared to children. This is in addition to the adverse effects of the chickenpox and shingles vaccines[3], as well as the potential for increased risk of shingles for an estimated 30–50 years among adults.

As early as 1965 Dr Hope-Simpson suggested, 'The peculiar age distribution of zoster may in part reflect the frequency with which the different age groups encounter cases of chickenpox...'.[4] A recent study found a 90% overall increase in adult shingles, from 2.77/1000 to 5.25/1000, during a period of increasing varicella vaccine coverage, 1998–2003.[5] If the outcomes in this and other UK studies are due to an immunologically-mediated link (that is, low varicella incidence produces an increase in the incidence of herpes zoster), then the approximate 50% reduction in risk of herpes zoster achieved in a large trial of a zoster virus vaccine, at best reduces shingles incidence back to the prelicensure rate.

The universal varicella vaccination program currently requires a booster vaccine (recommended in children 4–6 years old) and a shingles vaccine (recommended in adults 60 years and older). However, these are less effective than the natural immunity that existed in communities prior to licensure of the varicella vaccine. Routine vaccination against chickenpox has produced continual cycles of treatment and disease.

Gary S Goldman
Medical Veritas International Inc.
Pearblossom, California
USA

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Influenza vaccination

Editor, – I have an unanswered question after reading the article by Paul Dugdale (Aust Prescr 2007;30:35–7).

I have tended to discourage vaccinating young healthy adults with influenza vaccine as I was under the impression that an occasional bout of influenza in their younger years would prime the immune system and produce much better immune responses for future attacks that would keep them in good stead in their later years.

Is there any evidence for this? Is it a reasonable approach?

Lou Zaninovich
General practitioner
West Perth

Dr Paul Dugdale, author of the article, comments:

There is a health benefit of infection with one subtype of influenza because, like vaccination with that subtype, it will produce immunity to that subtype and can produce partial immunity to other subtypes. However, compared to vaccination, any possible increased efficacy of wild infection in preventing future infection would be more than offset by the health cost of actually having the bout of influenza. Therefore choosing not to be vaccinated on the grounds of possible net future benefit is not reasonable.

It may of course be quite reasonable for a healthy adult to decline vaccination on the grounds that it is not worth their while to reduce their chance of getting wild influenza. A discussion of their particular life circumstances will assist such a decision.

Managing injuries by venomous sea creatures in Australia

Geoffrey K Isbister, Senior Research Fellow, Tropical Toxinology Unit, Menzies School of Health Research, Charles Darwin University, Northern Territory, Clinical Toxicologist and Emergency Physician, Calvary Mater Newcastle Hospital, New South Wales, and Clinical Toxicologist, New South Wales and Queensland Poison Information Centres

Summary

Marine injuries or stings are common, but the majority cause only minor effects and do not require medical intervention. Injuries from venomous marine creatures can be divided into jellyfish stings due to contact with nematocysts, and penetrating injuries from spiny fish, stingrays and sea urchins. Box jellyfish are the most dangerous and may cause severe and potentially life-threatening effects. First aid for jellyfish stings includes removal of the tentacles, and hot water immersion for bluebottles or vinegar for major box jellyfish. In addition to vinegar, major box jellyfish stings are treated with analgesia and local dressings. Early resuscitation is required in the rare severe cases. Irukandji syndrome causes severe generalised pain associated with autonomic effects with little local pain or reaction. Treatment is symptomatic but may require large amounts of analgesia. Spiny fish and stingrays cause a combination of traumatic injury and venom-mediated effects. First aid is hot water immersion and treatment includes analgesia, thorough wound cleaning and regular review for secondary infection. Stingray injuries can be associated with significant trauma and sometimes result in penetrating abdominal or thoracic injury.

Key words: antivenoms, jellyfish, stingray, stonefish.

(Aust Prescr 2007;30:117–21)

Introduction

Injuries from venomous marine creatures are an increasing problem seen by healthcare workers in coastal regions. The majority of injuries are relatively minor and may not require medical intervention. The most frequent marine stings are from jellyfish, mainly bluebottles. Box jellyfish (taxonomic class Cubozoa) are more dangerous and may cause severe and potentially life-threatening envenoming in northern Australia. Injuries from spiny fish and stingrays make up most of the remaining injuries and are a combination of traumatic injury and envenoming. Injuries from sea urchin spines, contact with marine sponges and bites from blue-ringed octopi or sea snakes are less common in Australia.[1,2]

Jellyfish stings

There are over 100 medically important species of jellyfish belonging to the phylum Cnidaria. In Australia, the important groups include:

- *Physalia* (bluebottles or Portuguese Man-of-War)
- *Chironex fleckeri* (major box jellyfish)
- *Carukia barnesi* and other box jellyfish causing Irukandji syndrome.

Bluebottle (Physalia species) stings

Bluebottle stings are common in many parts of Australia. Many thousands of stings occur each summer and a significant proportion of the population has been stung at least once. Stings usually occur in shallow waters in the surf when swarms are washed ashore, so large numbers of cases occur for a short period before the beach is closed. The main clinical effect is immediate and intense local pain which lasts for about an hour, or occasionally longer in more severe cases. This is associated with characteristic linear erythematous raised eruptions. A rash or localised redness at the sting site may remain for hours to days. Uncommonly a delayed localised vesicular reaction occurs within 48 hours, but scarring is rare. Only a few patients develop systemic symptoms such as nausea, vomiting, abdominal pain, myalgia and rarely respiratory distress.[3]

Treatment of bluebottle stings

The bluebottle should be washed off with seawater or carefully removed and then the sting site immersed in hot water. There is now good evidence to support this first aid. An open-labelled randomised controlled trial found that immersion in hot water at 45°C for 20 minutes caused a clinically important reduction in pain in 87% of patients compared to only 33% treated with

ice packs.[3] The venom is heat labile and immersion of the sting in hot water is thought to inactivate the venom and therefore relieve the pain. If hot water immersion is not possible then a constant flow of hot water on the sting site or a hot shower is an alternative. Vinegar is not recommended for bluebottle stings.

Major box jellyfish

Chironex fleckeri is our most dangerous jellyfish. It is found in waters north of the Tropic of Capricorn (from about Gladstone in the east to Exmouth in the west). At least 65 deaths have been attributed to *C. fleckeri* and fatal cases in children occur every few years. Fatalities in the last 15 years have followed rapid envenoming with death due to cardiovascular collapse occurring within 20–30 minutes at remote beaches.[4] Severe envenoming requires skin contact with several metres of tentacle in an adult, but a death has been reported with 1.2 metres of contact in a child.[4]

In the vast majority of cases there is severe local pain and erythematous wheal formation at the sting sites which appear as dark red or purple whip-like lesions. In more severe cases superficial necrosis occurs along the sting lesions. This rarely causes permanent scarring. Delayed hypersensitivity reactions characterised by papular urticarial reactions along the sting sites occur in over half of cases.[4]

Confirmation of jellyfish stings by skin scrapings or 'sticky tape testing' is helpful in patients seen in hospital, particularly after box jellyfish stings. The test is best for tentacle stings such as those of *C. fleckeri*. Sticky tape is placed over the sting site, removed and then placed on a microscope slide for identification of the stinging cells (nematocysts).[5]

Treatment of Chironex fleckeri stings

First aid consists of immediate removal of any tentacles and generous application of vinegar. Vinegar deactivates the remaining nematocysts and therefore prevents further envenoming. Local pain can initially be treated with ice packs, but may require oral or parenteral analgesia. Most skin lesions will heal without any interventions, but more severe and necrotic lesions need local dressings. Delayed hypersensitivity reactions can be treated with topical corticosteroids.

The rapid onset and the almost 'all or none' characteristic of systemic envenoming has meant that almost no-one with severe envenoming arrives in hospital alive unless early basic resuscitation has been successful. Severe *C. fleckeri* envenoming is managed as a medical emergency with immediate basic life support and intervention to manage airway, breathing and circulation. Cardiovascular collapse should be managed with fluid resuscitation, intravenous antivenom (large initial dose of six vials) and adjunctive treatment with inotropes or magnesium in unresponsive cases.[4]

The sheep-derived antivenom specific for *C. fleckeri* has never been tested in controlled trials and its efficacy in humans is unclear.[6] Intramuscular antivenom is not recommended due to delayed and partial absorption, particularly in haemodynamically compromised patients.

Irukandji syndrome

Irukandji syndrome is most commonly reported in northern Australia.[5,7,8] Most clinical studies are of stings by *Carukia barnesi*, but other box jellyfish can cause the syndrome.[7,9] These include *Carybdea xaymacana*, *Alatina* nr *mordens*, *Malo maxima* and an unnamed 'fire jelly'.[9]

Irukandji syndrome is characterised by minor local effects, but severe generalised pain and autonomic effects. The sting may be painless or cause only mild irritation with a patch of erythema. Over 20–30 minutes, severe generalised back, abdominal, chest and muscle pain develop which are associated with tachycardia, hypertension, nausea and vomiting, anxiety, agitation and sweating. In more severe cases there can be cardiac involvement with ECG changes (T wave inversion and ST segment depression), progressing to myocardial depression with elevated troponin and then cardiogenic pulmonary oedema and cardiogenic shock. At least one death has been attributed to Irukandji syndrome.[7] The generalised pain usually takes 6–12 hours to resolve, but cardiac involvement may require supportive care for 2–3 days.

Skin scrapings are required for nematocyst identification. These are placed in 1–4% formalin and then examined under the microscope.[7]

Treatment of Irukandji syndrome

The mainstay of treatment for Irukandji syndrome is supportive care and pain relief. Titrated intravenous opioid analgesia is recommended (fentanyl or morphine). Large and repeat doses are often required. Pulmonary oedema should be treated with supportive care, including oxygen, positive pressure ventilation and inotropes.

Magnesium has recently been used in Irukandji syndrome as an initial bolus and then infusion to treat the pain and hypertension.[8] There has not been universal success and adverse effects due to hypermagnesaemia have been reported.[8] Further study is required before magnesium can be recommended as first-line therapy.

Other jellyfish

Information on other jellyfish in Australia is based on isolated case reports and expert opinion due to the lack of epidemiological studies of definitely identified jellyfish stings. In many cases the clinical effects of local pain and irritation make particular jellyfish stings impossible to distinguish from each other without identification of the jellyfish. Treatment is similar to bluebottle stings although there is little direct evidence for this (Table 1).

Table 1

First aid and treatment of jellyfish stings and venomous fish injuries

Type	First aid	Medical treatment
Bluebottles (*Physalia species*)	■ Wash the sting site with seawater and remove any tentacles ■ Immerse in hot water at 45°C for 20 minutes or hot shower ■ Do not use vinegar	■ The patient rarely requires transport to hospital or medical intervention ■ Severe local stings or bullous wounds may need dressing
Major box jellyfish (*Chironex fleckeri*)	■ Immediately remove any tentacles ■ Apply vinegar immediately and liberally ■ Apply ice packs ■ Resuscitate (airway, breathing and circulation) patients who are unconscious or have cardiovascular collapse	■ All but very minor stings require transport to hospital ■ Give oral and parenteral analgesia for sting site pain ■ For severe life-threatening envenoming: – give first aid – resuscitate – administer intravenous antivenom – consider magnesium therapy
Irukandji syndrome	■ Apply vinegar immediately and liberally ■ Remove any tentacles if present ■ If vinegar is not available wash the area with seawater	■ Transport to hospital for: – parenteral analgesia with titrated intravenous fentanyl or morphine – cardiac monitoring, ECG and cardiac enzymes ■ Cardiac involvement and pulmonary oedema will require supportive care and management of breathing and circulation
Other jellyfish: – mauve stinger (*Pelagia species*) – hair jellyfish (*Cyanea species*) – jimble (*Carybdea rastoni*) – other box jellyfish (*Chiropsalmus bronzeii*)	■ Wash the sting site with seawater and remove any tentacles ■ Consider hot water immersion or ice packs ■ Do not use vinegar	■ Patients rarely require transport to hospital or medical intervention ■ Severe local stings or bullous wounds may need dressing
Venomous fish stings: – stonefish – catfish – other venomous stinging fish	■ Wash the wound site and immerse in hot water about 45°C for a maximum duration of 90 minutes	■ Irrigate the wound and remove foreign debris ■ Radiograph to exclude retained spiny material ■ Give oral or parenteral analgesia and occasionally local or regional anaesthesia for severe pain ■ Stonefish antivenom is available for stonefish stings with severe pain or systemic effects ■ Surgical consultation for involvement of joints or bones
Stingray injuries	■ Wash the wound site and immerse in hot water about 45°C for a maximum duration of 90 minutes ■ Apply local pressure for bleeding and resuscitate if there are thoracic or abdominal injuries	■ Irrigate and debride the wound ■ Titrate intravenous analgesia and/or local or regional anaesthesia ■ Surgical consultation for deep injuries, injuries to the chest or abdomen, or with retained material ■ Resuscitation and surgical intervention for major trauma from thoracic or abdominal injuries
Sea urchin injuries	■ Wash the wound site and immerse in hot water about 45°C for a maximum duration of 90 minutes	■ Radiograph or ultrasound to identify any retained spines ■ Remove spines close to the surface ■ Review regularly until resolved ■ Wound may require further spine removal and further radiographic imaging or ultrasound

Mauve stingers (*Pelagia* species) cause local pain and skin irritation and have been confused with bluebottle stings in southern waters.[3] Hair jellyfish (*Cyanea* species) also occur in southern waters and are named for their hair-like tentacles. Skin contact results in minor and transient pain associated with spreading erythema. There have been numerous reports of corneal stings by this jellyfish. The eye should be irrigated with large amounts of fluid and topical steroids instilled.

Other species of box jellyfish occur in Australia but cause less severe effects and may present similarly to other jellyfish stings. One large box jellyfish, *Chiropsalmus bronzeii*, occurs in far north Queensland and causes only local pain and skin reactions. The jimble (*Carybdea rastoni*) is well-known in southern and western waters and will cause local pain and erythema.

Venomous fish

The important groups of fish with venomous spines include catfish, stonefish and scorpion fish.[2,10] They cause puncture wounds with localised pain, which can be severe and persistent with significant envenoming such as with stonefish, bullrout or marine catfish. There is usually associated erythema and oedema occurs in more severe cases. Uncommonly the fish spine may break off and require removal. The most important complication is secondary infection with marine or aquatic organisms.

Stonefish camouflage themselves on the sea floor and most commonly cause injuries when trodden on. The spines are covered by sheaths that push back as the spine covered in venom enters the tissues. This causes immediate severe pain which may radiate from the injury site with associated swelling and erythema. Although systemic effects are often described these are more likely secondary to pain rather than systemic envenoming. Bullrout occur in tidal estuaries and slow-moving streams of eastern Australia. They are also bottom-dwellers which commonly cause injuries to the feet with similar severity to those of stonefish.

Catfish are a common cause of spiny injuries although many catfish do not have venom associated with the spines in their dorsal and pectoral fins. More severe injuries occur with the oriental or striped catfish (*Plotosus lineatus*), which possesses potent toxins. Most injuries occur in fishermen trying to pull the fish off lines.

There are numerous other venomous or spiny fish, such as red rock cod in New South Wales, and soldier fish and cobblers in southern Australia. Most of these cause injuries when they are handled, for example by fishermen. Scats are less well known but occur in the Indo-Pacific ocean. They cause immediate severe pain that lasts for up to an hour with minimal other effects.

Treatment

First aid for venomous fish stings is hot water (45°C) immersion of the affected limb for up to 90 minutes.[1] The temperature must be tested with an unaffected limb first. Anecdotally hot water provides symptomatic relief, but the pain may recur when the affected limb is removed from the water.[10] With more severe or non-responsive pain, oral and occasionally parenteral analgesia is required. Infiltration of the wound with local anaesthetic or a regional nerve block is often more effective. However, the patient must be warned that hot water treatment should not be used after the limb is anaesthetised because of the risk of thermal injury. All wounds must be thoroughly cleaned and irrigated. Any pieces of spine should be removed and radiographic or ultrasound imaging may assist in identifying foreign bodies.

Stonefish antivenom should be used in any stonefish sting that does not respond to hot water immersion and adequate analgesia. This horse-derived antivenom is likely to be more effective if given intravenously and soon after the injury.

Swabs from obviously infected wounds should be cultured and antibiotics prescribed. The role of prophylactic antibiotics is unclear. Large series of cases and experience in the aquarium and catfish industries suggest that prophylactic antibiotics are not required.[10] However, all penetrating marine injuries must be regularly reviewed so that any emerging infection can be treated early. Confirmed infection requires antibiotic therapy and the opinion of an infectious diseases specialist should be sought.

Stingrays

Although stingrays have venom in their tail, the trauma of the injury is usually more important than venom-mediated effects. Stingrays usually rest on the bottom of the water and most commonly cause an injury when they are unwittingly trodden on. This makes the stingray reflexively whip its tail upward and into the person's foot or ankle. Injuries to the hands can occur if the fish are handled and rarely divers can sustain injuries to the chest or abdomen that cause serious trauma or death. The sharp bony spine produces a laceration and simultaneously leaves venom in the wound. The major effects of the venom are intense local pain and slowly developing necrosis. Systemic effects are uncommon and most likely secondary to severe pain. The most important complication is secondary infection, especially in wounds that penetrate a joint space or tendon sheaths, or wounds that are not cleaned or debrided when appropriate.

Treatment

The treatment of stingray injuries is similar to spiny fish injuries (Table 1) except there is often more trauma. First aid may require control of haemorrhage as well as hot water immersion. Lacerations should be left open for delayed primary closure, ensuring adequate drainage. Wounds containing foreign material, or which enter sterile body cavities, or present late, usually require surgical exploration and debridement. Again,

there is controversy over prophylactic antibiotics and they should be considered with large wounds, retained foreign material or delayed presentation.[10]

Sea urchins

Most sea urchin injuries are from non-venomous spines and the main problem is removal of broken-off spines. Venomous spines are less common but cause more intensely painful puncture wounds. Hot water immersion is appropriate first aid. Treatment consists of radiographic or ultrasound examination to locate retained spines. Some spines are a chalky material that breaks easily, making removal difficult, while others are stronger. It is reasonable to remove spines close to the surface and then follow the patient until the symptoms resolve. Patients with persistent pain may require surgical removal of the remaining spines.

Sponges

Sponge contact reactions are uncommon and may be difficult to diagnose if they are delayed. Only a few Australian species produce toxic secretions, including fire sponges (*Tedania* species) and *Neofibularia* species.[11] Initially there may only be a mild sensation with localised itchiness and stinging developing after minutes to hours. In some cases this sensation increases and can cause intense symptoms for 2–3 days. Usually there is only erythema, but occasionally vesicles and bullae, local swelling and joint stiffness develop. Fire sponges are reported to cause delayed reactions and desquamation can occur after 2–3 weeks.[11]

No specific treatment has been recommended except washing the sting site. The effects resolve over days to weeks irrespective of treatment. Symptomatic relief with analgesia or antihistamines can be used.

Blue-ringed octopus bites

A number of species of blue-ringed octopi occur in tidal areas around Australia. Their saliva contains tetrodotoxin, a potent sodium channel blocker. They will only bite when disturbed or handled. The bite is often painless and associated with small puncture marks. Generalised paraesthesia, nausea, dizziness and malaise may develop, but the majority of cases do not progress. In severe cases there is rapid progression to a flaccid paralysis and respiratory failure. Early basic resuscitation to provide ventilatory support is essential in severe envenoming. Medical management is supportive and the effects usually last 2–5 days. Pressure immobilisation is recommended for first aid.

Conclusion

Minor injuries from venomous marine creatures are common but most people do not seek medical attention. This is typified by the thousands of bluebottle stings that occur annually which are treated by first aid stations and where hot water immersion has now been shown to be effective. Major injuries are less common and range from severe box jellyfish stings that occur mainly in northern Australia to trauma and secondary infections from penetrating injuries from fish such as stingrays.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 135)

1. Bluebottle stings should be washed off with vinegar.
2. Lacerations from stingray injuries should be left open for delayed primary closure.

Consumer Medicine Information conundrums

Parisa Aslani, Senior Lecturer in Pharmacy Practice, Faculty of Pharmacy, The University of Sydney

Summary

People have a right to receive accurate and up-to-date information about their medicines from their health professionals. Providing written and verbal medicine information can improve consumers' use of medicines, but it can also have a negative impact. Consumer Medicine Information is standardised written information about prescription and pharmacist-only medicines in Australia. It is a tool which can be used by health professionals during their consultations to explain about the treatment they are recommending, including its harms and benefits. If used effectively and appropriately, Consumer Medicine Information could become an important vehicle in ensuring the quality use of medicines. Although some consumers are receiving Consumer Medicine Information from their health professionals, the documents are generally underutilised.

Key words: drug information, drug therapy, patient information.

(Aust Prescr 2007;30:122–4)

Introduction

There have been increasing demands for information about medicines from consumers who consider written information to be useful[1,2] and have been in favour of receiving it.[3,4] In Australia consumer organisations drove the development of Consumer Medicine Information (CMI) which is now available for all prescription medicines. Some consumers prefer to receive this information from their doctors[5] while others prefer pharmacists[3,5], however many health professionals have been doubtful about the value of CMI.

Research shows that there is limited interaction between consumers and health professionals when written medicine information is provided.[2,5] This is unfortunate because, when received with verbal advice, written information has many positive impacts on consumers[6], including improved adherence to therapy.[7,8,9] Medicines information specifically written for consumers should therefore have an important role in consultations and support the quality use of medicines.

What is a CMI and how is it distributed?

It is a legal requirement that CMI is available for all prescription (S4 and S8) and pharmacist-only (S3) medicines, and that it is consistent with the approved product information. The content of a CMI is defined by legislation and includes headings such as how to take your medicines, side effects and a description of the product. Australian CMIs are unique because they were developed to enable consumers to easily locate the information they need and the current design and content have been tested to ensure this.

The name 'Consumer Medicine Information' is intended to show clearly that the information is about medicines. It is therefore a concern that the consumer section of the Pharmaceutical Benefits Scheme website (PBS Online) uses the term 'Consumer fact sheet' to describe CMIs. Pharmaceutical industry, health professional and consumer organisations have been battling to increase consumer awareness of 'CMIs'. The use of an additional term that does not specifically refer to medicines may create confusion.

Health professionals have a duty of care to provide information, whether verbal, written or both, to ensure that consumers can use their medicines correctly and safely. While they are not legally obliged to provide CMI with every medicine prescribed or supplied, Box 1 shows how CMI can be used with consumers.[10]

In 2003, and as part of the Medicines Information for Consumers program, community pharmacists in Australia began to receive financial incentives for distributing CMI.[11] Participating pharmacists therefore have an obligation to provide CMI following the guidelines of the Pharmaceutical Society of Australia.[12]

Box 1

Using Consumer Medicine Information[10]

CMI can be used to:

- educate consumers and their carers about the medicine and how to take it effectively
- support verbal information
- inform and reassure about adverse effects, and monitor adverse events
- improve adherence to therapy.

The vast majority of CMIs are distributed from health professionals' computers. Currently more than 1200 (about 88% of all CMIs) are available electronically. The websites of pharmaceutical companies and health professional and consumer organisations are increasingly including CMIs (Box 2).

The consumer experience

Anecdotally, very few Australian consumers are receiving CMI with their prescription medicines. Moreover, when CMI is given, it tends not to be discussed as part of the consultation. Those consumers who are aware of CMI, who receive it from pharmacists and who read it[5,11], do not know how it differs from other forms of written information.[13]

In a survey of 226 consumers in community pharmacies in metropolitan Sydney, 58% reported receiving CMI on the day of the interview, and 82% said that they had received CMI in the past.[5] Their main reasons for reading CMI were to gain knowledge about their medicines, and concerns about adverse effects. The most commonly cited impact of reading the CMI was being informed, followed by being more confident about the medicine and its importance. Fear of experiencing adverse effects made 11 consumers (5%) stop taking their medicine. A further 20 reported having concerns, the majority of whom contacted their health professional. Only two of the 20 ceased taking their medicine, and three reported changing it.[5]

The Medicines Information for Consumers program was evaluated in 2003 and 2004.[11] The first survey of 200 consumers showed that 94% had received a computer-generated CMI from their pharmacist on at least one occasion. Two later telephone surveys of 1000 consumers indicated that 24% and 29% of the respondents had remembered receiving a computer-generated CMI from their pharmacist, sometime in the past. Some reported that the CMI caused them to be anxious about their medicines.

There is contradictory evidence regarding the impact of written medicine information on the adverse effects experienced by consumers who read the information. Some studies show a direct relationship between fear of adverse effects and stopping medicines after reading written information.[14,15] Other studies have shown no relationship.[7,16,17] The reluctance of some health professionals to provide CMI to consumers for fear that the information can lead to perceived or actual experience of adverse effects and consequent non-adherence to therapy may not be fully justified. However, the negative impact is real and this is why it is preferable to discuss CMI with the consumer rather than just handing it out.

Although there is some discrepancy between the actual research and the anecdotal evidence, there is confusion among consumers about what a CMI leaflet is and what it contains. CMI is not meant to be a stand-alone document, but an important tool that should be part of the interaction between health professionals and consumers. Health professionals have the responsibility to ensure that consumers understand the information in the CMI and know what action to take should they experience adverse effects.

Use by health professionals

Consumers want to receive information from their health professionals, some from their doctors[5] and others from their pharmacists.[3,5] It is therefore in the best interests of consumers if health professionals are aware of CMI and how to use it.

The first guidelines for health professionals were published in 1995.[18] They contained recommendations on the provision of CMIs, their use in counselling about the treatment and the action to be taken in special circumstances, such as emergencies. The guidelines suggested that health professionals provide CMIs to non-English speaking people, but take reasonable steps to ensure that they understand the information

Box 2

Some websites with Consumer Medicine Information

Website	URL and navigation to CMI
National Prescribing Service, consumers section	www.nps.org.au/consumers Go to: Consumer Medicine Information
Royal Australian College of General Practitioners, patients section	www.racgp.org.au/patients Go to: Consumer Medicine Information
Australian Prescription Products Guide	www.appco.com.au/appguide Go to: Consumer Medicine Information
Better Health Channel (Victoria)	www.betterhealth.vic.gov.au Go to: Medicines guide
Pharmaceutical Benefits Scheme, consumers section	www.pbs.gov.au/html/consumer/home Go to: (name of drug) then go to Consumer Fact Sheet
Healthinsite	www.healthinsite.gov.au Go to: (name of drug) then go to Healthinsite Information Partner Results

content, such as seeking assistance from a family member, friend or interpreter who can read and translate the CMI for the consumer.

Pharmacy and nursing specific guidelines have since been developed to encourage the use of CMIs by these professionals. There is also a guide for consumers and health professionals which provides information about CMIs, how they can improve health care and how they can be used.[10]

Despite all this activity, there is limited knowledge among health professionals of what CMIs are (with the exception of pharmacists who are paid a fee to distribute them) and how they can be used for the benefit of consumers. Pharmacists and doctors may feel that they are too busy to include CMI in their consultations or they may not provide it because they are uncertain what to do with it.

How can a CMI be used in practice?

In using CMI with consumers (Box 1), it is important that health professionals are familiar with its structure and content.[10] It is also important to note that while areas within a CMI can be highlighted for increased consumer attention, no sections of a CMI should be deleted or crossed out as this de-emphasising of information might increase the health professional's liability should any problems occur.[12]

Health professionals can increase consumer awareness of CMI by encouraging their patients to ask for CMI for their current and new medicines.

Conclusion

Consumers have a right to receive information about the medicines they are taking. Although some consumers are receiving CMI, there is a need to increase its provision. The challenge for all health professionals is to integrate the CMI into their consultations. Consumers, too, should be made aware of CMI and that they can ask for a CMI about their medicine.

There is also a need to evaluate CMI receipt and use by consumers, and to assess the impact of CMI on the healthcare system. There is an expectation that CMI will promote the quality use of medicines, but there is no evidence currently available to confirm this.

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Antidepressants in pregnancy and breastfeeding

Anne Sved Williams, Psychiatrist, Clinical Senior Lecturer, University of Adelaide, and Director, Perinatal and Infant Mental Health Services, Children, Youth and Women's Health Services, South Australia

Summary

Maternal depression and anxiety during pregnancy and the early years of an infant's life cause substantial problems to the mother, her infant and her family. Suicide is an ever-present risk with depression along with adverse effects on infant growth and birth weight. Balancing these risks against accumulating evidence of the effects of selective serotonin reuptake inhibitors on the fetus and infant presents a challenge to the treating doctor. Careful explanation to the woman and her partner of the risks of both the condition and the treatment, using a biological, psychological and social treatment approach, is likely to provide the most benefit.

Key words: depression, infants, lactation, selective serotonin reuptake inhibitors.

(Aust Prescr 2007;30:125–7)

Introduction

Depression in pregnant and lactating women is a common problem. In attempting to find the best treatment options for these women, doctors work with less knowledge and more risks than with other patients. Drug trials always exclude pregnant and lactating women and therefore practice is guided by data accumulated from clinical experience. Clinicians must consider the risk of damage from the medications and the effects of the illness itself on both the mother and the baby.

Harmful effects of maternal depression

There is increasing evidence that antenatal and postnatal anxiety and depression potentially have enduring effects on offspring.

Pregnancy

Although some studies differ, most document maternal antenatal depression as causing slightly shorter gestational length and lower birth weight in newborns.[1] Antenatal anxiety has shown a strong association with raised cortisol levels in 10-year-old offspring, with the potential for increased vulnerability to psychopathology in these children.[2] Boys whose depressed mothers show ambivalence to them in early months have increased rates of behavioural problems and learning difficulties by the age of five years.[3]

Lactation

The relationship between postnatal depression and breastfeeding is emerging as complex. Women who develop postnatal depression are more likely to stop breastfeeding than women who are not depressed. Likewise, women who establish and maintain breastfeeding are less likely to develop depression than women who have difficulties with breastfeeding.

Harmful effects of antidepressants

Antidepressant use in Australia has changed in the last two decades. Tricyclic antidepressants have fallen from favour and many have been withdrawn. Their adverse effects and risk of fatality from overdose make them hazardous. However, some doctors continue to prescribe them after considering the risks and the benefits. There have been few documented problems arising from their use, but this is perhaps due to lack of extensive research. A small study on the use of dothiepin in lactation suggested better outcomes for children of depressed mothers taking the drug compared to those whose mothers chose no medication.[4] Case reports suggest that doxepin may be harmful to infants and should be avoided in breastfeeding.[5]

Data on mirtazapine are sparse and therefore this drug should not be used as a first-line treatment in pregnancy. Recent work cautiously suggests that levels of mirtazapine are low in breastfed infants.

Venlafaxine use in early pregnancy has been associated with increased rates of spontaneous abortion but not fetal abnormality. There are also now many case reports of neonatal effects so it should be used with great caution in pregnancy. Venlafaxine has the potential to accumulate in the breastfed baby with prolonged treatment.[6]

Drugs used to treat bipolar depression include sodium valproate which is highly teratogenic and is best avoided in the first trimester. However, it is probably safe to use during lactation. Lithium may also cause fetal abnormalities and is generally advised against in early pregnancy and during lactation. However, a recent review of its use in the first trimester has shown lower rates of cardiac abnormalities than previously documented. Its use in lactation has suggested it is relatively safe in compliant mothers with healthy babies.[7] Infants must be monitored for lithium concentrations in serum as well as renal

and thyroid function. Specialist advice is highly recommended with lithium. This is also the case for lamotrigine.

SSRIs during pregnancy

First trimester: Early prospective trials on SSRIs suggested they were safe with no teratogenic effects. However, recent data have challenged this and suggest a small increase in birth defects. These results were not statistically significant and should be interpreted with caution.[8,9] Paroxetine has been associated with cardiovascular abnormalities[10], although recent analysis suggests this risk is only at doses greater than 25 mg per day.[11]

Second and third trimesters: Recent studies show a small but significant risk of shorter gestational length and lower birth weight in infants of mothers who used SSRIs in later pregnancy even compared to babies of untreated mothers with depression.[1]

Third trimester: Increases in mild respiratory distress, irritability and feeding problems have been observed in infants of mothers taking SSRIs in late pregnancy. Some but not all research suggests that paroxetine may cause more neonatal difficulties.[12] These effects are self-limiting and have generally settled by 14 days. It is unclear whether these neonatal effects are withdrawal or toxic effects.[13]There have also been reports of persistent pulmonary hypertension of the newborn[14] and possibly intraventricular haemorrhage.[12]

SSRIs during lactation

Many SSRIs are highly protein bound and little drug is transferred from the mother to the infant during lactation. We can therefore be more confident in prescribing SSRIs in lactation.[5] However, there is individual variability in infant levels of SSRIs and there are occasional case reports describing adverse effects.[15] Less data are available on the use of other antidepressant drugs during lactation.

So what is a doctor to do?

When a woman presents early in pregnancy with depression a very careful assessment should be made, preferably with her partner or other family member as additional historian. An assessment of risk of self-harm or suicide is vital. Other risks such as poor antenatal care are increased with depression. Once safety issues and general self-care have been addressed, a biological, psychological and social treatment plan should be explored relating to the patient's needs and wishes, and the severity of the depression. Sufficient information should be provided to the patient so they can make an informed decision about their treatment. Careful documentation of these discussions is important for medicolegal reasons.

Pre-conception counselling for women already taking antidepressants must explore the relative risks of the depression itself compared to the risks of using antidepressants in pregnancy. Anxiety about medication use in pregnancy may be high. For a woman whose depression has receded, a trial of slow cessation of medication before conception may be successful, but her mental state should be monitored in case of a relapse.

Unplanned conceptions for women on antidepressants can cause alarm and some women will abruptly cease their medication. Unfortunately, up to 75% of women who do so may develop a recurrence of their depression before delivery.[13] Careful reassessment of relative risks will reassure many women that continuation of their medication is appropriate.

If a pregnant woman decides to continue taking the drug, doctors should be aware that pharmacokinetics change during pregnancy. In the event of a relapse, a woman might need higher doses of many drugs including SSRIs to maintain clinical improvement.

Later in pregnancy, concerns over neonatal toxicity and withdrawals guide some doctors to lower SSRI doses until after delivery. Anecdotally, many women can manage this well, provided good psychosocial support is available. Some women will choose to continue on current doses with support, and appropriate management of the neonate.

Which antidepressant to use?

Experts differ in their assessments of the relative risks of the antidepressants, but in general, SSRIs are preferred to tricyclic antidepressants, combined serotonin and noradrenaline reuptake inhibitors and mirtazapine. Every antidepressant has been associated with some neonatal effects, and different studies show differing results. The data on paroxetine in higher doses cause concern.[11] While some perinatal psychiatrists prefer fluoxetine with its longer half-life and potential for slower neonatal withdrawal effects, many prefer the shorter-acting SSRIs, either citalopram, fluvoxamine or sertraline as the maternal response may be faster.

Useful sources of information

It is essential to frequently update information about best practice in this area as new information rapidly changes practice. Reliable websites such as the Organisation of Teratology Information Specialists (OTIS) (www.otispregnancy.org) and the Canadian www.motherisk.org are valuable to both doctors and patients. Most large Australian obstetric facilities also provide a pharmacy information service (see box), and if in doubt, a telephone call is appropriate. Telephone advice from a psychiatrist can be obtained privately or through GP PsychSupport on 1800 200 588. Pharmaceutical companies may have additional data about the effects of antidepressants on pregnancy and lactation.

Conclusion

The risks of the depression and its consequences must be weighed against the risks of the medications to both mother and

Pregnancy drug information centres

New South Wales

MotherSafe

Tel: (02) 9382 6539 / 1800 647 848 (toll free for NSW callers)

Queensland

Queensland Drug Information Centre (health professionals)

Tel: (07) 3636 7098

South Australia

Women's and Children's Hospital

Tel: (08) 8161 7222

Victoria

Royal Women's Hospital

Tel: (03) 9344 2277

Western Australia

Women's & Newborn Health Service

Tel: (08) 9340 2723

infant during the different phases of pregnancy and lactation. Careful history taking, close monitoring and good psychosocial care may be sufficient for many women with depression during pregnancy. When antidepressants are needed, the baby should be monitored postnatally for feeding, neurological and respiratory difficulties. Prescription of SSRIs postnatally appears less hazardous than in antenatal use, and potentially of benefit to mother and child.

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Self-test questions

The following statements are either true or false (answers on page 135)

3. It is safe to prescribe sodium valproate during early pregnancy.
4. Generally, SSRIs are safe to use during lactation.

Abnormal laboratory results

Cell markers

Kimberly Cartwright, Consultant Haematologist, Wollongong Hospital, New South Wales

Summary

Cell markers serve as a monogram to help identify and classify cells. The majority are molecules or antigens within the plasma membrane of cells. Specific combinations of markers are unique to different cell types. These molecules are not merely markers, but also have important functional roles. Knowing which molecules are present can help in the diagnosis of disease or in directing treatment.

Key words: flow cytometry, immunocytochemistry, immunophenotyping.

(Aust Prescr 2007;30:128–9)

Introduction

Most cell markers are molecules in the cell membrane which can be used to identify cell types. They are classified by their clusters of differentiation (CD) which are recognised by specific antibodies.

How does the laboratory analyse cell surface markers?

There are two common immunophenotyping methods used to analyse cell markers. These are flow cytometry, which is performed on fresh, unfixed cell suspensions, and immunohistochemistry which is performed on fixed specimens. These tests can be performed on blood, bone marrow, lymph nodes and other tissues.

An understanding of these tests and the necessary specimen preparation is important for practitioners collecting fine needle aspirates and surgical biopsies, to ensure optimal processing and interpretation.

Flow cytometry

Flow cytometry uses a laser light source to analyse the size, complexity and physical properties of fresh viable cells in suspension after labelling with fluorescent monoclonal antibodies. One to two thousand cells can be analysed per second.

The advantages of flow cytometry include the ability to rapidly and simultaneously analyse multiple cell parameters. The disadvantage is the inability to directly assess the cellular morphology of the cell population under analysis. A smear of the specimen must be stained and reviewed microscopically in correlation with flow cytometry to ensure analysis of the correct cell population, to assess cell viability and to guide the selection of antibodies to be tested. Flow cytometric analysis may be severely compromised if the samples contain insufficient material or too many dead cells.

Although the acquisition of data can be automated, the interpretation of the results and their clinical significance requires substantial input and critical judgement from trained haematologists or pathologists. Results should be analysed in conjunction with the clinical presentation, cellular morphology and cytogenetics when appropriate.

Immunohistochemistry

Immunohistochemistry is the phenotyping method of choice for tissue biopsies and is an integral component of routine diagnostic histopathology. It allows direct visualisation of labelled cell surface antigens and cellular morphology via light microscopy. The selection of antibodies available for use on paraffin section is more limited and the turnaround time is slower than for flow cytometry. Results may be severely compromised if the samples are too small or inadequately fixed.

When are these tests useful?

To assess abnormal cell populations

Generally this analysis is requested by haematologists or pathologists to further investigate aberrant cell populations found during microscopy of blood, marrow, lymph nodes or other tissues. Flow cytometry is now an essential tool in the diagnosis of haematological malignancies such as leukaemia and lymphoma.

For example, immunophenotyping may be recommended to investigate persistent peripheral blood lymphocytosis. Lymphocytosis may be due to a reactive state such as resolving viral infection, prior splenectomy or due to an underlying lymphoproliferative disorder such as chronic lymphocytic leukaemia. CD8 T lymphocytes predominate in reactive lymphocytosis whereas B-chronic lymphocytic leukaemia has a distinctive immunophenotype characterised by the expression of mature B cell markers (CD19, CD20 and CD23),

weak expression of monoclonal surface immunoglobulin and co-expression of the T cell marker, CD5. Recent studies suggest that expression of other markers such as CD38, ZAP70 and p53 correlates with a poor prognosis. The routine use of these assays requires further study and standardisation.[1]

Flow cytometry is not useful in the diagnosis of Hodgkin's lymphoma and other fibrotic tumours. This is because there are a low number of viable malignant cells in the sample compared to the numerous surrounding reactive cells.

To monitor for minimal residual disease

Flow cytometry is one of several methods used to detect minimal residual disease in patients with no clinical or morphological evidence of disease. In patients with a known haematological malignancy such as acute lymphoblastic leukaemia, flow cytometry may be useful to detect low levels of persistent disease following therapy.

To quantify cell populations

Clinicians may also request the analysis of specific markers to help guide therapy, for example using flow cytometry to measure CD4 lymphocyte counts in immunosuppressed or HIV positive patients. Patients with low CD4 counts are at greater risk of opportunistic infections. This is particularly true when the CD4 lymphocyte count in peripheral blood falls below 200 cells/microlitre or 0.2 x 10^9/L.

To assess cell proliferation

Ki-67 (MIB1) is an important marker of cell proliferation which can be assessed by immunohistochemistry or flow cytometry to assist diagnosis and guide therapy.[1] For example, Burkitt's lymphoma is characterised by a very high growth fraction with nearly 100% of cells positive for Ki-67. This is much higher than seen in other lymphomas. Because of this high proliferative index, Burkitt's lymphoma can frequently be cured with intensive chemotherapy.

To identify disease-specific targets for therapy

Rituximab, an antibody specific to CD20, is an important advance in the treatment of non-Hodgkin's lymphoma. Similarly, trastuzumab, which targets the human epidermal growth factor receptor 2 protein (HER2), is a new therapy for breast cancer. Testing appropriate patient specimens for these antigens helps to determine whether patients may benefit from the use of these targeted therapies. CD20 may be found on B lymphocytes by either immunophenotyping or immunohistochemistry. HER2 is found by immunohistochemistry or by the DNA-based technique fluorescent *in situ* hybridisation.

To identify foreign cell populations

In some laboratories the Kleihauer assay, used to detect fetomaternal haemorrhage, is now performed by flow cytometry. Similar methodologies have been developed to detect blood doping in athletes by identifying homologous blood cell antigens.[2]

To detect paroxysmal nocturnal haemoglobinuria

Paroxysmal nocturnal haemoglobinuria is a rare haematological disorder characterised by marrow aplasia, intravascular haemolysis and an increased risk of venous thrombosis. It is due to an acquired inability to produce a molecule which anchors certain cell membrane proteins. This leads to a deficiency in specific membrane proteins. Flow cytometric analysis can detect clonal populations of blood cells deficient in these proteins, greatly simplifying the diagnosis.

Conclusion

Analysis of blood and tissue for cell surface markers is a widely accepted and useful tool. It assists clinicians in diagnosing and managing a variety of conditions, particularly haematological malignancies.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 135)

5. Flow cytometry is a useful technique for diagnosing Hodgkin's disease.
6. Immunosuppression in patients with HIV can be assessed by flow cytometry.

Prescribing exercise for diabetes

Bronwyn Penny, Exercise Physiologist, Diabetes Australia – NSW, Sydney

Summary

Prescribed effectively, regular exercise is extremely safe, effective and essential in managing diabetes and its complications. It can play a significant role in reducing associated cardiovascular and lifestyle risk factors. The cornerstone of effective exercise prescription lies in the consideration of the various barriers, motivators and medical concerns that face people with diabetes and understanding how exercise may impact both positively and negatively upon these factors.

Key words: cardiovascular disease, stress testing.

(Aust Prescr 2007;30:130–3)

Introduction

Regular physical activity has been shown to significantly improve the health outcomes for people with diabetes. Physically active patients with diabetes have lower rates of all cause mortality and cardiovascular heart disease.[1] Regular exercise assists in maintaining good blood glucose control which in turn helps to decrease the risk of developing diabetes complications such as neuropathy and nephropathy.[2,3,4] It can also enhance quality of life and reduce stress, anxiety and depression.[5]

Prescribing exercise should be considered one of the essential components of diabetes care. Unfortunately, it is still largely underused.[4]

Pre-exercise screening and testing

Certain exercise intensities and modalities may be contraindicated or inappropriate for some people.[3,4,6] Before prescribing an exercise program for a person with diabetes it is imperative that the patient is screened and assessed for cardiovascular disease risk factors or other conditions that may pose significant health risks.[3,6] The patient should be asked about any symptoms of cardiovascular disease including unusual shortness of breath, chest pain with exertion, dizziness, light-headedness, swelling of the ankles and pain in the calves that is not associated with muscle pain. If these symptoms are present, further investigation is needed before the patient can begin an exercise routine.[7] Other cardiovascular risk factors that should be assessed include blood pressure, cholesterol and lipid profiles, resting heart rate, weight, body mass index, waist circumference, family history and previous cardiac history.[6]

The presence of cardiovascular risk factors and other complications does not preclude a person with diabetes from undertaking an exercise program.[6] Screening provides a useful risk stratification tool to guide exercise prescription or identify those who should undergo cardiac stress testing before starting to exercise.[3,6] Currently there are no clear-cut guidelines.

Stress testing allows definitive management of patients with cardiovascular disease before exercise is prescribed. However, there is no evidence that stress testing should be routinely performed before exercise of moderate intensity if cardiovascular disease risk is low. Stress testing may be impractical and expensive.[3] Conversely, ECG stress testing is recommended for sedentary individuals with high cardiovascular disease risk (greater than or equal to 10% risk of cardiovascular disease over 10 years) who wish to participate in aerobic activities that exceed demands of daily living, or patients with several cardiovascular disease risk factors.[3,6]

Other conditions that should be screened for include proliferative and non-proliferative retinopathy, peripheral neuropathy, autonomic neuropathy, nephropathy and microalbuminuria as well as musculoskeletal limitations such as rheumatoid arthritis, severe osteoarthritis, osteoporosis and other joint problems.

High intensity exercise is contraindicated in people with proliferative retinopathy due to the risk of retinal haemorrhage.[3] High intensity exercise, while not contraindicated, is not recommended for people with nephropathy and microalbuminuria. High impact and weight-bearing modalities such as running and jumping are inappropriate and not recommended for people with peripheral neuropathy, arthritis and osteoporosis as they are at greater risk of falls, injuries and foot damage due to poor peripheral sensation.[3]

To develop an individualised program, simple easily performed exercise tests requiring little specialised equipment, such as the six-minute walk test or one-minute sit-to-stand, may provide an insight into the patient's current physical capacity. This will assist the practitioner to successfully develop a program that matches the needs of the patient to the prescribed exercise intervention.[6] Exercise testing is also useful for assessing the efficacy of the exercise program. It is important to consider the appropriateness of any exercise test used as it needs to accommodate the patient's physical abilities and limitations.[7]

Exercise prescription

Various medical and physical concerns will govern the type, intensity and duration of exercise an individual is capable of performing safely.[3,4,6] Several lifestyle and socio-economic issues such as motivation, personal goals and preferences, stage of change and cultural influences will also affect the type

of exercise intervention developed and its implementation.[2,4,5] Finally, availability and access to services and facilities such as exercise professionals, exercise facilities and safe exercising options will vastly influence the design and implementation of an exercise program.[4] It is important that any exercise program be tailored towards the individual.

Written exercise instructions may help with adherence to an exercise program. However, of more importance is the level of support the physician gives to the patient regarding the uptake of physical activity. Physician support, patient consultation, specific advice regarding the type, time and intensity of the exercise program and the setting of appropriate and realistic goals appear to be the strongest predictors of adherence along with the patient's readiness to change a perceived limitation. Regular monitoring, assessment and goal setting will greatly assist the patient's ability to achieve long-term behaviour change.[8]

Aerobic activity

Regular aerobic exercise improves blood lipid profiles, blood pressure and resting heart rates, body composition and glycaemic control as well as reducing cholesterol. In addition, it helps patients to lose weight.[3,4]

For health benefits, current guidelines recommend that aerobic activity should be performed for at least 30 minutes at a moderate intensity on most, if not all days of the week with no more than 72 hours between exercise sessions. If weight loss is desired, then 60 minutes of exercise or more is recommended.[3,4,6] It is often difficult for most people to begin at this level, therefore the exercise prescription should initially begin at a level the patient can manage, with the aim of gradually increasing exercise duration and intensity as the patient progresses.[4]

Exercise should be continuous in nature and could include activities such as walking, swimming or cycling.[3,4,6] However, the type of exercise will depend on the patient's safety and physical activity preferences.[6]

Exercise intensity should be at least moderate to vigorous in nature. Moderate intensity exercise is described as a level of activity that elicits a heart rate response of 55–70% maximal heart rate or 12–13 on a 20 point rating of perceived exertion using the Borg scale (see Box 1).[3,6,9] While moderate intensity is preferred, some patients, especially very obese patients, may be unable to cope for sustained periods of exercise. In this scenario, interval type training and alternating periods of high and low exercise intensities may be more useful. With regard to monitoring exercise intensity, while heart rate monitoring has its benefits, rating of perceived exertion requires no additional equipment, is easy to use and teach to patients and correlates strongly with exercising heart rates. The Borg scale is useful in monitoring exercise intensity for those with autonomic neuropathy where heart rate responses may be disproportionate to actual exercise intensities.[6]

Resistance training

Resistance training is another vital component of any exercise program for people with diabetes. This refers to exercise that requires the body's musculoskeletal system to work against an opposing force, such as gravity or weight. Resistance training has positive effects on insulin resistance, glycaemic control, weight loss and management, maintenance of lean body mass, strength, balance and functional capabilities.[2,3]

Very obese individuals, those with balance and mobility issues, foot health problems and peripheral vascular disease often find this form of training easier to cope with and may be more likely to adhere to the program.[2]

Current research and guidelines recommend resistance training be performed at least 2–3 times a week in conjunction with an aerobic training program to obtain the greatest benefits.[2,3,4,6] Heavy resistance training provides the biggest impact on glycaemic control and insulin sensitivity. Previously, only light weight resistance training was recommended because of safety concerns for the patient. The major concern was possible harmful effects from large acute spikes in blood pressure associated with heavy resistance exercise. However, recent evidence suggests the myocardial demands of heavy resistance training are comparable to the cardiovascular demands placed on the body when performing some occasional activities of daily living such as stair climbing.[3] Recent research has also shown the safety and efficacy of heavy resistance strength training even for older adults.[2,3]

Provided there are no contraindications, heavy resistance training targeting all major muscle groups should be included and consist of heavy loads lifted 8–10 times, progressing to 2–3 sets for each exercise. While there are no set guidelines, a 1–2 minute break between sets will give better strength benefits.

Box 1

Borg's ratings of perceived exertion scale [9]

6	
7	very, very light
8	
9	very light
10	
11	fairly light
12	
13	somewhat light
14	
15	hard
16	
17	very hard
18	
19	very, very hard
20	

The load should not be able to be lifted more than 8–10 times each set (that is 8–10 repetitions maximum strength).[2,3] Regardless of exercise intensity, it is imperative that good exercise technique is emphasised throughout the program to reduce the risk of injury and maximise health outcomes.[3,4]

Exercise programs

There are specific exercise programs for people with diabetes (see Box 2). You can also contact Diabetes Australia (phone 1300 136 588) for information on exercise programs in your local area.

Special considerations

The effects of exercise on patients who are insulin dependent, taking oral medications or suffering from one of the many comorbid conditions associated with diabetes also need to be considered when prescribing exercise.

Hypoglycaemia

Exercise has an insulin-type effect which poses potential hazards for those who are insulin dependent or take oral hypoglycaemic medications. Exercise can cause hypoglycaemia if medication dosages or carbohydrate intake are not modified with increases in levels of physical activity.[3,4,6] Blood glucose levels will respond differently depending on the individual, exercise intensity and duration.[6] As a general rule though, extra carbohydrate should be ingested before exercise if the session is to last longer than 30 minutes or if pre-exercise blood glucose levels are less than 5.6 mmol/L.[3,6] As exercise-induced hypoglycaemia may occur many hours post exercise, regular blood glucose monitoring before, during and after exercise is recommended to establish blood glucose responses to exercise.[3,4,6] Alternatively, insulin dosage may be adjusted.[3,6] Referral to a diabetes educator to discuss these strategies is strongly recommended as is the carrying of emergency glucose supplies at all times during and after exercise to treat potential hypoglycaemia.

Box 2

Exercise programs for people with diabetes

Living longer, living stronger (Victoria, Western Australia)
Strength for life (South Australia)
Council on The Ageing www.cota.org.au
Phone 1800 182 324

Lift for Life
www.liftforlife.com.au
Phone 1300 733 143

Heartmoves
www.heartfoundation.org.au/Professional_Information/Lifestyle_Risk/Physical_Activity/Heartmoves.htm
Phone 1300 362 787

Diabetic retinopathy

The presence of diabetic retinopathy may also impact on exercise prescription. Exercise may have adverse effects on those with proliferative or severe non-proliferative retinopathy. Until the retinopathy has been stabilised, high intensity resistance and aerobic training should be avoided due to the risk of retinal haemorrhaging.[3,4,6] Nevertheless, patients with either of these conditions can still benefit from regular moderate exercise.

Peripheral neuropathy and vascular disease

Both peripheral neuropathy and vascular disease can increase the risk of injury and infection in the feet. Peripheral neuropathy can also affect balance, placing the patient at greater risk of falls. Some types of exercise such as treadmill walking should be avoided. Adequate footwear and regular screening for blisters is a must for these individuals, especially with weight-bearing activities.[3,4,6] Non-weight-bearing exercises such as cycling, and upper limb resistance training may minimise damage or infection.

Conclusion

Exercise can play a major role in prevention and management of diabetes. It can improve glycaemic control, reduce cardiovascular risk and improve quality of life. Both aerobic and resistance training modalities should form the cornerstone of any exercise program. Prescribed correctly and with adequate considerations of the barriers, motivators and medical concerns facing people with diabetes, exercise can be an extremely safe and effective treatment strategy.

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Further reading

Bowen K. Managing foot infections in patients with diabetes. Aust Prescr 2007;30:21-4.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 135)

7. High intensity exercise may cause haemorrhage in patients with diabetic retinopathy.
8. Patients with diabetes who have cardiovascular disease are precluded from undertaking an exercise program.

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.

Human papillomavirus vaccine

Cervarix (GlaxoSmithKline)

vial or syringe containing 0.5 mL liquid

Approved indication: prevention of human papillomavirus infection and associated genital disease

Australian Medicines Handbook section 20.1

This is the second vaccine to be registered in Australia against human papillomavirus infection. Like the first vaccine (see New drugs, Aust Prescr 2006;29:138–43), this product is not a live vaccine but is made up of virus-like particles derived from the major capsid (L1) protein. It is a bivalent vaccine, designed to protect against human papillomavirus types 16 and 18. These virus types are responsible for around 70% of invasive cervical cancers worldwide and are the most common oncogenic papillomavirus types isolated from Australian women.

The bivalent vaccine has been compared to placebo in a randomised trial of 1113 North American and Brazilian women aged 15–25 years. These women were negative for type 16 or 18 DNA (by the polymerase chain reaction) and seronegative for virus types 16 and 18 at screening. Three doses of the vaccine or placebo were given, at 0, 1 and 6 months. Cervical and cervicovaginal specimens (taken at 3 or 6 month intervals) were analysed for human papillomavirus DNA and abnormal cytology for up to 27 months after the first injection.[1]

After 27 months, there were four cases of persistent infection with type 16 or 18 human papillomavirus in the vaccinated group (560 women) compared to 31 cases in the placebo group (553 women). Two women in the vaccine group had cytological abnormalities associated with virus type 16 or 18 compared to 27 women in the placebo group.[1] These abnormalities included atypical squamous cells of undetermined significance and low- and high-grade squamous intraepithelial lesions.

A follow-up study continued to monitor the women. Some of them were followed in total for approximately 48 months. These women had received all three doses of the vaccine or placebo and their treatment allocation was still double blind. In the follow-up phase, 10 out of 340 women had persistent human papillomavirus type 16 or 18 infection (for 10 months or longer) in the placebo group compared with none of the 357 women in the vaccine group.[2]

During the combined initial and follow-up phases of the trial, there were four cases of abnormal cytology or histology associated with type 16 or 18 virus in the vaccine group and 83 cases in the placebo group. There were no cases of cervical intraepithelial neoplasia in the vaccine group.[2]

There seemed to be some cross-protection of the vaccine against infection with other human papillomavirus types, particularly types 45 and 31. This corresponded to fewer cases of cytological and histological abnormalities in the vaccine group compared to the placebo group.[2]

There were no vaccine-related serious adverse events reported. However, there were more injection-site symptoms (pain, swelling, redness) in the vaccine group compared to the placebo group.[1,2]

The vaccine should be given intramuscularly in the deltoid region at 0, 1 and 6 months. The second dose can be delayed for up to 2.5 months after the first dose if necessary. The need for booster doses is currently unknown.

This bivalent vaccine appears to be effective in providing long-term protection against human papillomavirus types 16

and 18 infections and the precancerous lesions associated with them. The previously approved vaccine is quadrivalent and contains antigens from virus types 6, 11, 16 and 18. As human papillomavirus types 6 and 11 cause genital warts, the quadrivalent vaccine is indicated for males and females whereas the bivalent vaccine is only indicated for females, but for a wider age range (10–45 years).

T manufacturer provided only the product information

References

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2. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367:1247-55.

Insulin glulisine

Apidra SoloStar (sanofi-aventis)

100 IU/mL in 3 mL cartridges for use in reusable insulin injection device

Approved indication: diabetes mellitus

Australian Medicines Handbook section 10.1.1

Insulin analogues are genetically engineered to try and improve the control of blood glucose in patients with diabetes.[1] Insulin glulisine differs from human insulin by only two amino acids. This difference results in a more rapid and short-acting effect on blood glucose.

Patients can inject insulin glulisine in the 15 minutes before, or immediately after, a meal. The analogue reaches a higher maximum concentration faster than a subcutaneous injection of regular human insulin (55 vs 82 minutes) in type 1 diabetes. In type 2 diabetes, the median time to maximum concentration is 89 minutes with insulin glulisine and 94 minutes with insulin. Insulin glulisine is also eliminated more rapidly with a half-life of 42 minutes compared with 86 minutes for regular insulin. Although the maximum concentration of insulin glulisine is approximately twice that of regular insulin, one unit of insulin glulisine has the same glucose-lowering effect as one unit of regular insulin.

Insulin glulisine needs to be used with a longer-acting insulin to provide the patient's basal requirements. It should not be mixed with other insulins (except NPH insulins) before injection.

A comparative study, in patients with type 1 diabetes using insulin glargine for their basal requirements, found that the efficacy of insulin glulisine was similar to that of insulin lispro (another quickly absorbed analogue). In patients with type 2 diabetes using NPH insulin, injecting insulin glulisine 15 minutes or less before meals had a similar effect on glycaemic control to injecting regular insulin 30–45 minutes before meals.

Insulin glulisine has the same adverse reactions as other insulin preparations, but long-term experience is more limited. It has not been approved for use in children less than 12 years, but the reasons are not clear.

T manufacturer provided only the product information

Reference * †

1. Phillips P. Insulins in 2002. Aust Prescr 2002;25:29-31.

Lapatinib

Tykerb (GlaxoSmithKline)

250 mg tablets

Approved indication: breast cancer

Australian Medicines Handbook section 14.3.9

Lapatinib is a new drug for use in combination chemotherapy with capecitabine for patients with metastatic breast cancer. It is indicated for patients with tumours overexpressing HER2 (human epidermal growth factor receptor type 2) that have progressed after treatment with an anthracycline, a taxane and trastuzumab. Lapatinib causes growth arrest or cell death of tumour cells by reversibly inhibiting the intracellular tyrosine kinase domain of HER1 (human epidermal growth factor receptor type 1) and HER2.

Following oral administration of lapatinib, peak plasma concentrations are reached after approximately four hours. It is extensively metabolised, primarily by CYP3A4 and CYP3A5, then eliminated in the faeces.

Concomitant use of drugs that inhibit or induce CYP3A4, such as ketoconazole or carbamazepine, affects lapatinib's pharmacokinetics so dose adjustment of lapatinib with these drugs may be needed. The systemic exposure of lapatinib is increased in patients with moderate to severe hepatic impairment. As the bioavailability of lapatinib is increased with food, it should be taken at least one hour before or after eating.

Preliminary studies have indicated that lapatinib has biological and clinical activity against various solid tumours (including breast, ovarian and lung) that overexpress HER1 and HER2.[1,2] An interim analysis of the efficacy and safety of lapatinib in combination with capecitabine has been further evaluated in an open label phase III trial. In the study, 324 women with progressive HER2 positive locally advanced or metastatic breast cancer who had already tried other treatments (including an anthracycline, a taxane and trastuzumab) were randomised (in a 1:1 ratio) to receive either a lapatinib plus capecitabine combination or capecitabine alone. Lapatinib was given as a 1250 mg continuous daily dose and capecitabine was given as 2000 mg (when in combination) or 2500 mg (as monotherapy) per square metre of body surface in two divided doses for 14 days of a 21-day cycle.[3]

Clinical data were collected for 20 months after the enrolment of the first patient. During this period, data from 274 of the 324 enrolled women were collected for evaluation.

Overall survival rates were similar in both groups, with 36 deaths in the lapatinib plus capecitabine group and 35 in the capecitabine group. The overall response rate was 22% in the combination group and 14% in the monotherapy group. Patients on combination therapy had a longer median time to disease progression or death compared to those taking capecitabine alone (8.4 months vs 4.4 months).[3]

Diarrhoea was more common in women taking lapatinib plus capecitabine compared to those taking capecitabine alone (60% vs 39%). Dyspepsia and rash were also more common in the combination treatment group. Hand-foot syndrome, nausea and vomiting occurred to a similar degree in both groups. There were five fatal adverse events in the study – two women on combination treatment and three women on monotherapy. The death of a patient with diarrhoea, vomiting and small-bowel obstruction in the monotherapy group was deemed to be related to the study drug.[3]

Lapatinib has been associated with decreases in left ventricular ejection fraction, and asymptomatic cardiac events were detected in 2% of patients taking combination therapy in the trial.[3] Patients should therefore be evaluated before starting therapy and at 8–12 week intervals during treatment to ensure that cardiac function does not decline.

Although lapatinib in combination with capecitabine prolongs the time to disease progression in women with metastatic breast cancer, it does not actually improve overall survival rates compared to capecitabine on its own.

T manufacturer provided only the product information

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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 Medicines Agency (www.emea.eu).

Answers to self-test questions

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

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Postal: The Editor
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DEAKIN ACT 2600
AUSTRALIA

Email: info@australianprescriber.com

Website: www.australianprescriber.com

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Australian Prescriber
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DEAKIN ACT 2600
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