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CONTENTS

Editorial

The professional pharmacist and the pharmacy business

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Key words: complementary medicines, drug therapy.

(Aust Prescr 2011;34:34–5)

According to current profession-specific standards, Australian pharmacists are expected to be competent in, among other things, the provision of primary and preventive health care.[1] They are often the first healthcare professionals contacted by patients, who they may treat or refer.

The other expected professional competencies are the preparation, review and dispensing of prescribed medicines, the ability to participate in research and educational activities, and the promotion of and contribution to optimal use of medicines. There are also three 'business' competencies which relate to professional and ethical behaviour, managing work issues and interpersonal relationships, and applying organisational skills in the practice of pharmacy.

It is implicit in the current competencies that a balance be struck between running a successful small business and providing professional services. The preparation and dispensing of pharmaceutical products largely achieves this balance because dispensing accounts for approximately 70% of the gross income of most community pharmacies. It is also responsible for most of the workload of community pharmacists, although this is expected to diminish with the progressive introduction of automated dispensing systems.

Professional services associated with the other expected professional competencies contribute to workload, but add little to the incomes of community pharmacies because these services are almost invariably provided free of charge. Any income is usually derived indirectly from the accompanying sales of products or medical devices. Retailing activities, including the sale of non-prescription medicines with or without professional advice, therefore account for approximately 30% of the gross income of community pharmacies.

Community pharmacies are undoubtedly a major retail outlet for complementary medicines. Selling these medicines is perceived by some as highlighting the conflict which can arise between running a small business and providing a professional service. The sale of products of doubtful efficacy could seem to favour small business requirements rather than professional practice.

Recent research has shown that consumers very often self-select complementary medicines.[2] The information which guides their selection comes mostly from friends, the internet, general practitioners and naturopaths. Nevertheless, the majority of consumers expect pharmacists to be knowledgeable about complementary medicines. A conflict is therefore almost certain to arise when pharmacists have to choose between recommending products for which there is good evidence of efficacy and just selling complementary medicines as retail products.

A possible resolution of this particularly evident area of conflict would be for pharmacists to expand their provision of primary health care so that they become more involved in the processes leading to product selection. Then, if consumers insist on complementary medicines, at least pharmacists should provide

In this issue…

Despite having more chronic disease than other Australians, Aboriginal and Torres Strait Islander people make less use of the Pharmaceutical Benefits Scheme. Noel Hayman tells us how their access to medicines can be improved.

Access to dental care can also be difficult in some areas. This can sometimes result in inappropriate treatment. Ricky Kumar, Paul Sambrook and Alastair Goss provide an example of why toothache should not be treated with antibiotics.

Inappropriate management of hyponatraemia can also have serious consequences. Gabriel Shannon advises us how to manage severe cases of hyponatraemia.

Just as certain drugs can cause hyponatraemia, others can cause cardiac adverse effects. Ingrid Hopper reviews some of the drugs which can result in heart failure, myocardial infarction and arrhythmia.

guidance and support about the selection process and about any significant health problems, directly or indirectly, which could result from the use of largely unproven remedies.

Expansion of the role of pharmacists in primary health care should be more than just assistance with the selection of complementary and over-the-counter medicines. Pharmacists should contribute in a more meaningful way as part of a team approach to health care so that referral to other members of the team, particularly general practitioners, is a key part of the process. Expansion of this 'triage' role is more likely to be limited by time and space constraints, and by perceived lack of adequate remuneration,[3] rather than by a need to develop a new role, because pharmacists are already providing millions of health-related consultations each year.[4]

In reality, payment for professional services other than the preparation and dispensing of pharmaceutical products will remain an unfulfilled goal until pharmacists unequivocally demonstrate they can contribute significantly to primary health care. At present they are 'off the radar' in this respect, largely because much of what is done is not recorded. In addition, there are few formal referrals of consumers to other healthcare providers, and there is seldom follow-up of the advice given by pharmacists.[5]

Community pharmacies are on the one hand small businesses and on the other are providers of a range of professional health services. While there is room for improvement, recognition and remuneration for their professional health services, the current arrangements have been successful in placing, at no cost to government, competent and respected healthcare professionals in the main streets of almost every suburb, town and city across Australia.

Nevertheless, the time has surely come for community pharmacists to decide once and for all if they are to embrace the changes necessary to improve substantially the 'non-prescription' services they offer. This would provide consumers with access to highly identifiable and accessible front-line healthcare professionals who are well equipped to decide if treatment or referral is necessary. Not to embrace the relatively straightforward changes which are necessary will mean that the tag given to community pharmacists by some commentators[6] as being the most over-qualified and underutilised of Australia's healthcare professionals will remain.

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Conflict of interest: none declared

Letters

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. Letters are usually published together with their responses or comments in the same issue. The Editorial Executive Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

Safe use of radiographic contrast media

Editor, – I would like to commend Kenneth Thomson and Dinesh Varma for their succinct discussion of the safety profile of iodinated radiographic contrast media (Aust Prescr 2010;33:19-22).

However a noticeable absence in the article is the discussion of oral contrast – particularly the increasing use of injectable iodinated radiographic contrast media as oral contrast (after dilution) for abdominal CT.

One of the issues related to iodinated media like iohexol or diatrizoate sodium is the alleged cumulative nephrotoxicity of these media when given orally in addition to the intravenous dose. This perception appears to be in error. From what I can tell, iohexol is poorly absorbed in the intact gastrointestinal tract and about 1% of the dose is excreted by the kidney. There is however a theoretical potential to cause renal dysfunction in a dehydrated patient as the hypertonic oral

iodinated media can cause excessive excretion of water into the gastrointestinal lumen, precipitating a body fluid loss into the third space.

I would appreciate it if the authors can comment on this as the use of oral iodinated media is becoming more common in Australia, replacing the cheaper but less palatable barium meal.

Shyan Goh
Locum orthopaedic registrar
Sydney, NSW

Dr Dinesh Varma, author of the article, comments:

We did not include oral contrast media mainly because the adverse effects and complications are extremely rare, as are the contraindications.

The most commonly used oral contrast media are barium sulfate-based agents or water soluble iodinated contrast agents. The use of injectable iodinated contrast media as oral contrast agent is extremely rare and if alternative contrast media are required for CT examinations, water is more commonly used as negative oral contrast media. Some centres have replaced positive oral contrast media with water in their CT abdomen protocols.

Some of the recognised adverse effects of iodine-based oral contrast agents are a mild laxative effect attributable to high osmolarity of diatrizoate meglumine and diatrizoate sodium. This can also result in dehydration with shift of fluid in the third space as you have mentioned. We also agree with your comments that renal impairment is usually a secondary effect of this phenomenon as these agents are sparingly absorbed from an intact gastrointestinal tract.

Other rare complications include aspiration, which may result in serious pulmonary complications. Anaphylactic reactions have also been reported.

Gentamicin: a great way to start

Editor, – The editorial by Robert Moulds and Melanie Jeyasingham (Aust Prescr 2010;33:134-5) states that 'For ongoing directed gentamicin therapy, other monitoring recommendations remain unchanged'.

Could the authors kindly clarify this statement, that is, what other recommendations remain unchanged, and unchanged compared to what?

Grace Abdini
Senior clinical pharmacist
Pharmacy department
Mount Druitt Hospital, NSW

Melanie Jeyasingham, an author of the article, comments:

Apart from plasma concentration monitoring, other monitoring recommendations for ongoing use of gentamicin remain unchanged from the previous recommendations in Therapeutic Guidelines: Antibiotic, version 13 (2006). This includes recommendations to monitor serum creatinine and calculate creatinine clearance two or three times each week, or more frequently if renal function is very unstable. Patients should be regularly asked about any hearing or balance problems and told to report immediately if they occur. For prolonged aminoglycoside courses (more than 5 days), formal vestibular function testing and high-frequency audiometric testing should be considered if available.

Bisphosphonates

Editor, – I read the letter by JF Walsh on bisphosphonates and osteonecrosis with interest (Aust Prescr 2010;33:167-70). Surely it is up to the treating clinician (for example the dental practitioner) to establish which medication a patient is on and assess their relative risks. Patients get overwhelmed with the list of potential side effects we inform them of. They quite rightly remember the common ones. A good drug history takes no time at all and dental practitioners should have this basic skill.

Andy Ryan
General practitioner
Seaford, SA

Collaboration between doctors and pharmacists in the community

Editor, – In her recent article (Aust Prescr 2010;33:191-3) Ms Rigby provides a timely, succinct analysis of the issues confronting the medical and pharmacy professions striving for better medication management in an era of increasingly complex health care. The necessity for a team approach in this environment is obvious. The challenge is defining relationships and boundaries for each of these health professionals and the patient. Trust is the touchstone upon which effective primary care operates. Any system promoting collaboration develops trust, not only with patients but between health professionals.

The Home Medicines Review system is challenged by administrative issues and poor reimbursement for quality reports. Current business rules restrict access. Where patients have no relationship with a pharmacy, the system breaks down, placing a barrier between general practitioner and accredited pharmacist. The referral process also takes no account of the skills and expertise of an accredited pharmacist (for example palliative care, geriatrics, de-prescribing, post-discharge and cultural issues).

In the face of an ageing population and overburdened hospitals discharging patients early, accredited pharmacists could develop expertise in areas where there are gaps in medication management. Allowing direct referral from general practitioners and giving consideration to co-location of pharmacists within a general practice will allow the growth

and development of this role for pharmacists. Any system is only as good as the people who participate in it. Trust and collaboration can only be achieved through patience, time and understanding while, above all, maintaining the interests of the patient.

Pradeep Jayasuriya
General practitioner
Cloverdale, WA

Deirdre Criddle
Consultant pharmacist
Dianella, WA

Debbie Rigby, author of the article, comments:

Thank you for your insightful comments and I agree that trust and confidence in pharmacists' clinical skills and knowledge is the key to collaborative patient-centred care. In July last year the Pharmacy Guild foreshadowed changes to the Home Medicines Review (HMR) model, including a direct referral model and post-discharge HMRs initiated by hospitals for high-risk patients. Direct referral to accredited pharmacists will provide greater flexibility to the HMR model and foster closer collaboration between general practitioners and pharmacists. This will be a welcome change to many general practitioners and accredited pharmacists. These proposed changes should not replace the existing HMR model which we know has produced many positive outcomes and satisfaction for patients. Ideally the direct referral model should always include the patient's preferred community pharmacy in the communication loop. This is especially important for hospital post-discharge medication reviews where medication reconciliation is a critical component.

For pharmacists to transition from the traditional role of dispenser to patient-centred practitioner, the culture of the pharmacy profession needs to move from a 'one size fits all' paradigm to allow role expansion for advanced practitioners in a collaborative environment.

Managing menopausal symptoms

Editor, – The article 'Managing menopausal symptoms' (Aust Prescr 2010;33:171-5) states that transdermal progesterone cream is minimally absorbed through the skin and there is no good evidence for its usefulness in relieving flushes, or in improving mood, libido or lipid profile.

Transdermal progesterone is poorly absorbed, which may explain the poor results obtained. However, if used transvaginally or rectally, absorption is much better.[1]

Progesterone does not relieve flushes. It is oestrogen which relieves flushes. However, it is an inhibitor of monoamine oxidase,[2,3] so it may well improve mood if absorbed in adequate quantities. It also remodels bone,[4] thus it is useful in counteracting osteoporosis. It has none of the adverse effects of synthetic progestogens, and I found it useful in patients with endometriosis who could not tolerate the synthetic progestins because of weight gain and irritability. Progesterone reversed these adverse effects.

The actions of the synthetic progestogens, apart from the effect on the uterine lining, are different from those of progesterone. Synthetic gestagens have been shown, in fact, to lower the body's production of progesterone.[5]

Iain Esslemont
General practitioner
Margaret River, WA

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Dr Terri Foran, author of the article, comments:

I would like to thank Dr Esslemont for his comments regarding the use of topical natural progesterone for the management of menopausal symptoms. I appreciate that many clinicians and their patients attest to its effectiveness in relieving a range of menopausal and premenstrual symptoms. I stand by my comments however that no large well-designed clinical trials have demonstrated these benefits to date. The small trials that do exist have used different doses, regimens and delivery systems and the results have been extremely variable. I must also admit to some personal concerns as to the quality assurance that governs the manufacturing processes of some of the constituents used in these products.

I am prepared to be convinced by good quality medical evidence that topical natural progesterone cream has a useful role to play in the treatment of menopausal symptoms. I would certainly encourage the manufacturers of these products to undertake such trials. Until that time however I feel it is difficult to recommend natural progesterone, whether transdermal, vaginal or rectal, as an effective therapy in menopausal women.

Improving Aboriginal and Torres Strait Islander people's access to the Pharmaceutical Benefits Scheme

***Noel Hayman**, Clinical director, Inala Indigenous Health Service, Inala, Queensland*

Summary

Despite having greater morbidity and mortality than other Australians, Aboriginal and Torres Strait Islander people underuse the Pharmaceutical Benefits Scheme. Increasing their access to medicines could improve their health. To improve access, there are some specific medicines on the Pharmaceutical Benefits Scheme for Aboriginal and Torres Strait Islander people. There is also the Indigenous Chronic Disease Package which will assist with the cost of medicines. Incentives are being provided for doctors to enrol their Aboriginal and Torres Strait Islander patients to obtain these benefits.

Key words: cost of drugs.

(Aust Prescr 2011;34:38–40)

Introduction

Aboriginal and Torres Strait Islander people suffer from the burden of chronic disease at a rate 2.5 times that of other Australians, with approximately one-third of the burden due to vascular diseases.[1] Cardiovascular disease, chronic kidney disease and diabetes are the main problems and share the common risk factors of smoking, high blood pressure, high cholesterol, physical inactivity, obesity and a low intake of fresh fruit and vegetables.[1] This increase in the burden of chronic disease should be reflected in an increase in the prescription of drugs for the treatment of heart disease, diabetes, chronic kidney disease, mental health and lung conditions. However, data from the Pharmaceutical Benefits Scheme (PBS) show that Aboriginal and Torres Strait Islander people access the PBS at a lower rate than other Australians.[2] Indigenous people also underuse primary healthcare consultations and specialist care.[2]

PBS drugs specifically for Aboriginal and Torres Strait Islander people

In 2005 a committee was established by the Commonwealth Department of Health and Ageing to provide advice on ways to improve the capacity of the PBS to meet the health needs of Aboriginal and Torres Strait Islander people. The Pharmaceutical Benefits Advisory Committee recommended that from 1 August 2006, 15 medications be listed on the PBS to treat common fungal skin conditions, chronic suppurative ear conditions and vitamin B_1 (thiamine) deficiency. Table 1 shows the current drugs available as authority prescriptions on the PBS specifically for Aboriginal and Torres Strait Islander people.[3]

The rationale for subsidising these drugs is the higher rate of disease seen in the Aboriginal and Torres Strait Islander population compared to the non-indigenous population. Indigenous people suffer higher rates of chronic suppurative otitis media (particularly children[4,5]), have higher rates of fungal infections,[6] are more likely to drink alcohol at harmful levels (thiamine prophylaxis),[7] have smoking rates 2–3 times higher than other Australians (nicotine replacement therapy)[8] and have higher rates of whipworm, strongyloidiasis and hookworm (albendazole).[9]

General practitioners working in Aboriginal and Torres Strait Islander Community Controlled Health Services are very much aware of this initiative and regularly prescribe these drugs for the benefit of their patients. However, many Aboriginal and Torres Strait Islander people access mainstream general practice where some doctors may be unaware of this important initiative for improving their access to these drugs.

Affordability of drugs

The price of medicines is a major barrier for Aboriginal and Torres Strait Islander people filling their prescriptions. Past Commonwealth inquiries have shown that despite them having higher morbidity than the non-indigenous population, government spending on the PBS was much lower for the indigenous population.[2,10] The Australian Institute of Health and Welfare report on Indigenous Health Expenditures in 2004–05 revealed that the average income per person for Aboriginal and Torres Strait Islander people was in the lowest 20–30% of all incomes in Australia. The Overcoming Indigenous Disadvantage Report 2007 found that indigenous people are more likely to live in larger households with more dependants and have lower incomes (gross median household income for indigenous adults was $340 per week compared to $618 for non-indigenous adults).[11] Low income is a real barrier to buying the large number of scripts often needed by Aboriginal and Torres Strait Islander people with chronic disease.

Table 1

Authority prescriptions specifically for Aboriginal and Torres Strait Islander people

Medication (Brand name)	Streamlined*
Mupirocin, nasal ointment 20 mg (as calcium) per g (2%) 3 g (Bactroban)	Yes
Nicotine, transdermal patch releasing approximately 15 mg per 16 hours (Nicorette patch)	No
Clotrimazole, cream 10 mg per g (1%) 20 g (Clonea)	Yes
Ketoconazole, cream 20 mg per g (2%) 30 g (Nizoral 2% cream)	Yes
Ketoconazole, shampoo 10 mg per g (1%) 100 mL (Nizoral 1%)	Yes
Ketoconazole, shampoo 20 mg per g (2%) 60 mL (Nizoral 2%)	Yes
Miconazole nitrate, cream 20 mg per g (2%) 15 g (Daktarin)	Yes
Miconazole nitrate, cream 20 mg per g (2%) 30 g (Daktarin)	Yes
Miconazole nitrate, cream 20 mg per g (2%) 70 g (Daktarin)	Yes
Miconazole nitrate, powder 20 mg per g (2%) 30 g (Daktarin)	Yes
Miconazole nitrate, lotion 20 mg per mL (2%) 30 g (Daktarin)	Yes
Miconazole, tincture 20 mg per mL (2%) 30 mL (Daktarin)	Yes
Nystatin, cream 100 000 units per g, 15 g (Mycostatin)	Yes
Terbinafine hydrochloride, cream 10 mg per g (1%) 15 g (Lamisil)	Yes
Thiamine hydrochloride, tablet 100 mg (Betamin)	Yes
Albendazole, tablet 200 mg (Zentel)	Yes
Ciprofloxacin, ear drops 3 mg per mL (0.3%) 5 mL (Ciloxan)	No
Terbinafine hydrochloride, tablets 25 mg (base) (GenRx Terbinafine, Sebifin 250, Tamsil, Terbihexal, Terbafine 250, Terbafine-DP, Zabel, Lamisil)	No

* Streamlined authority items do not require preapproval by Medicare Australia

Table correct as at March 2011. An up-to-date version of this list is available at www.pbs.gov.au.[3] Go to PBS Information, PBS Publications, then to the Factsheet 'Listings on the PBS for Aboriginal and Torres Strait Islander people'.

Indigenous Chronic Disease Package

To assist patients with chronic diseases, the Australian state and territory governments have invested $1.6 billion over four years commencing in July 2009. There is new funding for preventive health, expanding the Aboriginal and Torres Strait Islander health workforce and primary health care.[12] Part of the package aims to remove barriers which are reducing access to essential services such as the PBS.

General practices are given incentives to coordinate care for chronic disease. Accredited general practices registered under the scheme enrol and register their Aboriginal and Torres Strait Islander patients who have chronic disease, or risk factors for chronic disease, with Medicare Australia.[13] Eligible patients can then give their consent to be registered to receive their medicines at a reduced price.

The assistance scheme commenced on 1 July 2010. Eligible clients' prescriptions are processed in the usual manner except the prescriptions are endorsed with Close the Gap (CTG) by their doctor. This will enable patients who normally pay the full price of the prescription to pay only the concessional co-payment of $5.60. Patients who normally pay the concessional rate will receive their medicines free of charge. The package will facilitate many more Aboriginal and Torres Strait Islander people having access to PBS medicines, in metropolitan and regional areas across Australia. It is vital that all prescribing doctors are aware of this initiative so that all their Aboriginal and Torres Strait Islander patients with chronic disease will benefit.

What does this mean for your practice?

Aboriginal and Torres Strait Islander Community Controlled Health Services will have no barriers to identifying eligible

patients in their clinic population. In contrast, mainstream general practice may experience problems in identifying eligible Aboriginal and Torres Strait Islander people. General practitioners and practice staff should ask all patients whether they identify as being of Aboriginal and Torres Strait Islander origin by asking the National Standard Identification question 'Are you of Aboriginal or Torres Strait Islander origin?'.[14,15]

Once indigenous people are correctly identified and registered with Medicare Australia they are then eligible to access the co-payment assistance. Pharmacists will be reimbursed for the co-payment the patient no longer pays. General practices will be funded through the Practice Incentives Program Indigenous Health Incentive.[12]

Conclusion

Outcomes in chronic disease will be suboptimal if the patient does not have access to treatment. There are several initiatives which aim to improve the access of Aboriginal and Torres Strait Islander people to PBS medicines. The Indigenous Chronic Disease Package will reduce the cost of prescriptions for patients with chronic disease. This has the potential to help to close the gap in health between Aboriginal and Torres Strait Islander people and other Australians.

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Conflict of interest: none declared

Medicinal mishap

Mismanagement of dental infection

*Prepared by **Ricky Kumar**, Advanced trainee, **Paul Sambrook**, Director, and **Alastair Goss**, Professor and emeritus consultant, Oral and Maxillofacial Surgery, The Royal Adelaide Hospital*

Case

A 25-year-old man with schizophrenia presented as an emergency with severe pain and swelling of his left jaw and neck. He was febrile (38.9° C) and could only open his jaw 5 mm. Swallowing was difficult and he was dehydrated.

The patient had a history of toothache for three years. For the past two years he had experienced facial swellings. He had attended several medical clinics and received a range of antibiotics, mainly amoxycillin, but also erythromycin, tetracycline, metronidazole and amoxycillin with clavulanic acid. He had no recollection of ever being given a referral or being told that he must seek dental advice.

Two weeks before presentation the patient developed trismus and difficulty in swallowing. He went to an emergency

department and was given oral analgesia and amoxycillin with clavulanic acid before being discharged without arranged follow-up. The patient briefly improved, but re-presented a few days later so he was admitted for intravenous amoxycillin and metronidazole. He improved and was discharged with advice to 'next time' go to a hospital with an oral and maxillofacial service.

On presentation, the clinical diagnosis was Ludwig's angina or a spreading neck infection from an acute dental cause. Direct endoscopic examination of the oropharynx showed an extension of the swelling into the lateral oropharynx, a deviation of the uvula and marked swelling with imminent supraglottic obstruction.

An orthopantomograph (Fig. 1) was taken with an oral and maxillofacial surgeon present and the patient was intubated before being placed in a CT scanner (Fig. 2). The left mandibular second molar and six other decayed teeth were removed. Copious amounts of pus were drained intra-orally and via a skin incision.

Microbiological swabs for culture and sensitivity were taken before starting empirical intravenous cefalotin and metronidazole. Culture and sensitivity showed that the bacteria were resistant to the penicillins and tetracyclines, but sensitive to the cephalosporins and metronidazole.

The patient was in intensive care for 48 hours and remained in hospital for a further three days. On review at six months he had fully recovered and had attended the local government dental clinic.

Comment

The principles of managing infection, such as, remove the cause, drain the pus and support the host, have been known since the time of Hippocrates. The advent of antibiotics changed the management of life-threatening infections. However, the inappropriate use of antibiotics and increasing resistance have seen the return of severe spreading infections from common causes.

The case reported is not exceptional, but represents the daily or weekly workload of specialist units at major metropolitan hospitals. In the past ten years we have treated over 1000 similar cases and have had three fatalities. One patient died of airway obstruction, another died of septicaemia caused by bacteria with multiple resistances to antibiotics and the third died from cerebral infection with a background of community-acquired methicillin-resistant *Staphylococcus aureus*. All these cases could have been prevented by timely dental intervention. Antibiotics may temporarily alleviate symptoms, but in the medium to long term the delay in treatment due to the use of antibiotics makes the condition worse.

Recommendation

Dental pain and swelling is a dental problem which should be treated by a dentist. If the patient presents to a doctor they should be referred to a dentist. Access to affordable and timely dental services is crucial.

A patient who presents with upper neck swelling, difficulty in swallowing and who cannot open their jaw 2 cm, no longer just has a dental problem but has an airway problem. Their airway should be secured before transfer to a hospital with the appropriate surgical, medical and anaesthetic facilities.

Do not simply prescribe antibiotics for dental infections.[1,2] Emphasise the need for dental treatment as soon as possible.

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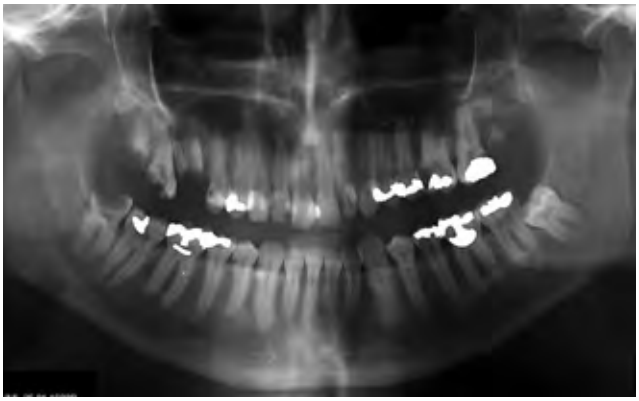
Fig. 1

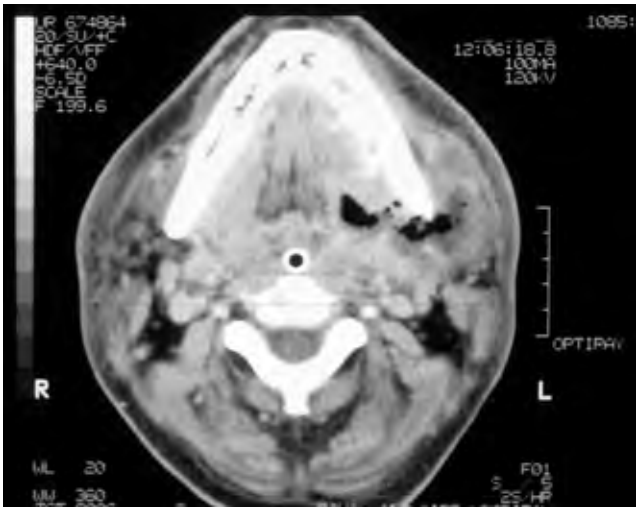
Orthopantomograph of dental abscess



There is obvious decay on the right side, but these teeth are draining into the mouth. The cause of the infection is the abscess on the left lower second molar which is not draining into the mouth, but is draining into the left submandibular triangle.

Fig. 2

CT scan of a submandibular abscess



There is marked generalised neck swelling. (The patient was intubated before being placed in the scanner.)

Severe hyponatraemia – recognition and management

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Summary

Hyponatraemia is the most common electrolyte disorder. In its severe form it has a high morbidity and mortality. The cause of the hyponatraemia must be identified by clinical assessment and investigations including serum and urinary sodium and osmolality. Determining if the patient is euvolaemic, hypovolaemic or hypervolaemic helps guide treatment. Most cases are caused by drugs, inappropriate secretion of antidiuretic hormone, and fluid retaining conditions such as heart failure. In addition to managing the underlying cause, severe hyponatraemia requires correction of the serum sodium. Treatment should be in an intensive care unit. Correcting the serum sodium too quickly risks causing cerebral demyelination which is frequently fatal.

Key words: antidiuretic hormone, osmotic demyelination syndrome, sodium.

(Aust Prescr 2011;34:42–5)

Introduction

Hyponatraemia is defined as a serum sodium under 135 mmol/L. It is the most common electrolyte abnormality and is often a marker of underlying disease. Severe hyponatraemia, defined as a serum sodium of less than 120 mmol/L, occurs in 2.5–6% of inpatients. Hyponatraemia is associated with increased morbidity and mortality (up to 60-fold) in hospitalised patients.[1,2] It is also associated with increased mortality in patients in intensive care, patients with hepatic cirrhosis, congestive heart failure and community-acquired pneumonia, and liver transplant patients who were hyponatraemic at the time of transplantation.[2,3] Severe hyponatraemia is also associated with prolonged hospitalisation and its treatment can cause adverse outcomes including death. Severe hyponatraemia is therefore a medical emergency, requiring intensive care.

Classification of hyponatraemia

There are several methods of classifying hyponatraemia, and classification based on the fluid status of the patient is the most easily understood. By far the commonest cause of hyponatraemia in clinical practice is dilutional hyponatraemia due to retention of water in excess of sodium. This requires a deficit in renal water excretion which is usually due to, or accompanied by, an inability to adequately suppress antidiuretic hormone.

Euvolaemic hyponatraemia

In euvolaemic hyponatraemia the extracellular fluid volume is normal. It is the most common form of hyponatraemia. Causes include:

- syndrome of inappropriate antidiuretic hormone (see Box 1)
- drugs (see Box 2)
- hypothyroidism
- hypocortisolaemia
- primary polydipsia
- exercise-associated hyponatraemia (due to excessive hypotonic fluid intake in the setting of increased antidiuretic hormone secretion).

Hypovolaemic hyponatraemia

In hypovolaemic hyponatraemia the extracellular fluid volume is reduced. Causes include excessive gastrointestinal losses and salt-losing nephropathies. Cerebral salt wasting is an occasional cause of hyponatraemia in neurosurgical patients or patients with subarachnoid haemorrhage.[4] Thiazide diuretics can cause hypovolaemic hyponatraemia, but are more commonly associated with euvolaemic hyponatraemia.

Hypervolaemic hyponatraemia

In situations of water and sodium retention, hyponatraemia will result if the water retention exceeds the sodium retention. Extracellular fluid is increased. Cardiac failure, cirrhosis of the liver, renal failure and nephrotic syndrome can cause hypervolaemic hyponatraemia.

Other categories of hyponatraemia

Hyponatraemia can also be classified by the serum osmolality. Isotonic hyponatraemia can be caused by absorption of irrigating fluid containing glycine, sorbitol or another isosmotic non-sodium compound during urological or gynaecological procedures. Hypertonic hyponatraemia can occur when an osmotically active compound such as glucose or mannitol

Box 1

Causes of syndrome of inappropriate antidiuretic hormone secretion *

Drugs

Tumours with ectopic hormone production

- small cell and other pulmonary carcinomas
- pancreatic and duodenal carcinoma
- head and neck malignancies
- mesothelioma
- lymphoma

Central nervous system disorders

- infections
- cerebral tumours
- stroke or intracerebral haemorrhage with raised intracranial pressure
- hydrocephalus
- Guillain-Barré syndrome
- multiple sclerosis

Pulmonary disease

- pneumonia and other infections
- acute respiratory failure with or without positive pressure ventilation
- asthma
- pneumothorax

Miscellaneous

- major thoracic or abdominal surgery
- transphenoidal pituitary surgery
- postoperative pain
- positive pressure ventilation
- HIV/AIDS
- extreme exercise
- hereditary

* Euvolaemic hyponatraemia with natriuresis and urine osmolality greater than plasma osmolality in patients with normal renal, thyroid and adrenal function

enters the intravascular space in sufficient concentration to pull water from the intracellular to the extracellular space. This causes a dilutional fall in serum sodium while at the same time raising the serum osmolality.

Clinical assessment

Acute severe hyponatraemia is an emergency which requires a planned and stepwise approach to assessment, investigation and treatment to minimise the harms of this condition and its treatment. The shorter the duration of hyponatraemia the more likely the patient is to be symptomatic and in need of active treatment. Symptoms such as nausea or headache, or the development of lethargy, confusion, coma or seizures, are indicative of acute, or acute on chronic, hyponatraemia and require immediate action.

Patient history

Is there a history of gastrointestinal or renal disease to suggest excessive solute loss, or a history of excessive fluid intake to suggest exercise-associated hyponatraemia or psychogenic polydipsia? Is there anything in the history (headache, symptoms suggestive of an occult malignancy) to suggest the syndrome of inappropriate antidiuretic hormone secretion? Does the patient have symptoms of hypothyroidism or of Addison's disease?

Medication history

What is the patient's medication history? Is the patient taking any drugs known to be associated with hyponatraemia (see Box 2)?

Examination

What is the patient's fluid status – is the patient dehydrated (hypovolaemic hyponatraemia), euvolaemic (euvolaemic hyponatraemia) or fluid overloaded (hypervolaemic hyponatraemia)? Is there evidence of congestive cardiac failure or stigmata of chronic liver disease to suggest hypervolaemic hyponatraemia? Are there any signs of thyroid disease or hypocortisolaemia? Are there any signs suggestive of malignancy as a cause of syndrome of inappropriate antidiuretic hormone secretion?

Box 2

Principal causes of drug-induced hyponatraemia

Diuretics: particularly thiazide diuretics, including combinations with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists

Antidepressants: tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, venlafaxine

Antipsychotics: phenothiazines, haloperidol

Antiepileptics: carbamazepine, oxcarbazepine, valproate, lamotrigine

Antidiabetics: chlorpropamide, tolbutamide

Antibiotics: ciprofloxacin, trimethoprim-sulfamethoxazole, rifabutin

Antiarrhythmics: amiodarone

Antihypertensives: angiotensin converting enzyme inhibitors (angiotensin receptor antagonists), amlodipine

Anticancer/chemotherapeutic drugs: vincristine/vinblastine, cisplatin/carboplatin, alkylating agents, methotrexate, levamisole

Proton pump inhibitors

Non-steroidal anti-inflammatory drugs

Oxytocin, antidiuretic hormone analogues

Amphetamines: MDMA (ecstasy)

Investigations

When investigating hyponatraemia, it is important to consider whether the sodium result is correct or if there has been a laboratory or sampling error. If investigations suggest a diagnosis of syndrome of inappropriate antidiuretic hormone secretion, further investigations to identify intracranial or intrathoracic pathology or occult malignancy at another site are required.

Renal function and electrolytes

A low sodium with normal renal function indicates dilutional hyponatraemia either euvolaemic or hypervolaemic, especially if serum urea is low. Impaired renal function, especially with an elevated serum urea, suggests hypovolaemia and hypovolaemic hyponatraemia. A high serum potassium suggests chronic renal disease or, if the urea and creatinine concentrations are only mildly elevated, hypocortisolaemia.

Osmolality

The serum and urine osmolality should be measured in all patients with hyponatraemia. Serum osmolality will be low in all cases of hyponatraemia except for the rare cases of isotonic or hypertonic hyponatraemia.

The appropriate physiological response to dilutional hyponatraemia is to maximise water excretion by passing maximally dilute urine. The maximal excretional capacity of the kidney is 10–15 L per day and maximally dilute urine has an osmolality of less than 100 mmol/kg. In a patient with dilutional hyponatraemia and normal renal function, urine osmolality greater than 100–150 mmol/kg indicates lack of appropriate suppression of antidiuretic hormone or an inability to maximally dilute the urine due to other mechanisms such as diuretic therapy. In euvolaemic hyponatraemia, with a urinary osmolality of greater than 200 mmol/kg, one of these two abnormalities must be present.

Urine sodium

The clinical assessment of hydration status is frequently inaccurate so urinary sodium is an important measurement as it assists in the differentiation of the hypovolaemic from the euvolaemic patient.

A urine sodium under 20 mmol/L indicates hypovolaemic hyponatraemia where the sodium loss is of extra-renal origin as the kidneys are reabsorbing sodium. Patients with hypervolaemic hyponatraemia due to cardiac failure, cirrhosis or nephrotic syndrome without renal failure may also have a low urinary sodium.

A urine sodium above 20 mmol/L indicates euvolaemic hyponatraemia of any cause. The urinary concentration of sodium is usually high because of the relatively low urine volume passed in these conditions. High urinary sodium concentrations can also be seen in hyponatraemia associated with renal salt wasting and renal failure, and in patients on diuretic therapy.

Endocrine tests

Thyroid function tests should be performed in all patients to exclude hypothyroidism as a cause of hyponatraemia. The possibility of hypopituitarism and Addison's disease should always be considered in the differential diagnosis of hyponatraemia. If there is a clinical suspicion, measure morning cortisol and adrenocorticotrophic hormone (ACTH), with or without a short ACTH stimulation test.

Treatment of hyponatraemia

In addition to correcting the serum sodium, the management of hyponatraemia must always include treatment of the underlying cause. This could be withdrawing the probable causative drug, treating postoperative pain, treating hormonal abnormalities and treating identifiable causes of the syndrome of inappropriate antidiuretic hormone secretion.

Severe or symptomatic hyponatraemia should be treated as a medical emergency. Failure to act makes progression to altered consciousness, seizures, and permanent brain damage or death probable. These patients must be managed in a hospital with onsite 24-hour pathology and appropriate medical and specialist staffing.

Euvolaemic hyponatraemia

While fluid restriction is the initial treatment of choice in asymptomatic patients, more active and urgent treatment is required in the symptomatic patient with severe euvolaemic hyponatraemia. It is the commonest type of severe hyponatraemia and prompt intervention to raise the serum sodium is indicated. Isotonic saline is contraindicated as it can be associated with a further fall in serum sodium. Hypertonic saline should only be used in symptomatic patients with very low serum sodium concentrations. The infusion aims to increase the serum sodium to a 'safe' level, usually considered to be greater than 120–125 mmol/L depending on the initial concentration. The rate of increase in serum sodium should be limited to prevent complications. There are a variety of formulae for predicting the increase in serum sodium expected from alterations to the rate and volume of hypertonic saline infusion. However, these formulae often result in over-correction, probably due to alterations in the clinical state not predicted at the time the calculation was performed, such as the commencement of a diuresis following the start of the saline infusion, placing the patient at risk of adverse effects.[5]

A recent review has suggested that immediate treatment should be the infusion of 100 mL of 3% sodium chloride over one hour.[5] If symptomatic hyponatraemia with fitting persists, a further 200 mL over the next two hours can be given. The aim

of treatment is to raise the serum sodium into a 'safe' range usually recognised as greater than 120 mmol/L, and to abolish the patient's symptoms. Once these goals have been achieved further hypertonic saline should not be given, although ongoing fluid restriction will usually be required. It may take 48–72 hours for the patient's symptoms to improve.

The maximum rate of increase in serum sodium should not exceed 10 mmol/L over 24 hours and 18 mmol/L over 48 hours to minimise the risk of osmotic demyelination.[5,6] In patients with liver disease a slower rate of correction is indicated in view of their greater risk of osmotic demyelination. Hypertonic saline can only be administered safely in a hospital with intensive care facilities associated with 24-hour onsite pathology, as the patients must be closely monitored and have their electrolytes checked every two hours. However, the initial infusion of hypertonic saline may need to be given before transfer to that higher level care in consultation with the accepting team.

Hypovolaemic hyponatraemia

The history and clinical examination will be supported by biochemistry consistent with hypovolaemia. The urine sodium will be below 20 mmol/L except in cases of renal salt wasting and renal failure. Treatment consists of volume expansion with isotonic saline. This is the only situation in which the use of isotonic saline is appropriate treatment for hyponatraemia.

Hypervolaemic hyponatraemia

Cardiac failure, hepatic cirrhosis or renal disease should be easily recognisable by history, clinical examination and the results of renal and liver function tests. The management is to treat the underlying disease process and will usually include fluid restriction and diuretic therapy.

Complications of treatment

The treatment of hyponatraemia has been a controversial topic largely due to the recognition of cerebral demyelination ('central pontine myelinolysis', 'osmotic demyelination') as a specific pathological entity associated with hyponatraemia and with the rate and extent of the correction of serum sodium in these patients.

Excessively rapid restoration of serum sodium, and 'overcorrection' of serum sodium above the normal range, have been associated with cerebral demyelination which is irreversible and frequently fatal, and may not be evident for several days after treatment has been completed. The patient recovering from hyponatraemia may deteriorate unexpectedly. Depending on the area of the brain affected, a variety of neurological or psychiatric symptoms may develop. When excessively rapid correction has been recognised, there are reports of lowering serum sodium by various means including the administration of desmopressin to try to avoid osmotic demyelination.[5,7-10]

Conclusion

Severe hyponatraemia is associated with increased morbidity and mortality. When it develops acutely or in hospital and is associated with symptoms, urgent treatment is required. This will usually include the administration of hypertonic (3%) saline in a hospital with 24-hour pathology and intensive care unit services.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 59)

1. Cerebral demyelination may develop several days after the correction of severe hyponatraemia.
2. In the management of severe hyponatraemia, the infusion of hypertonic saline should continue for 48 hours after the serum sodium returns to the normal range.

Australian Government
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Medicines Safety Update

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Medicines Safety Update is the drug safety bulletin of the Therapeutic Goods Administration (TGA). It is published in each issue of *Australian Prescriber*. You can also read it and sign up for free Medicines Safety Update email alerts on the TGA website at www.tga.gov.au/adr/msu.htm

In this issue:

Drug-induced hyponatraemia

Summary

Drugs are a common contributor to hyponatraemia. Diuretics, antidepressants, antiepileptics and antihypertensives appear commonly as suspected causes in reports to the TGA.

Hyponatraemia, defined as serum sodium less than 135 mmol/L, is often caused by drugs, with diuretics, antidepressants and antiepileptics some of the most commonly implicated medicines.[1] We present a summary of recent cases of hyponatraemia reported to the TGA. Management of severe hyponatraemia is discussed in this issue of *Australian Prescriber*.[2]

Between January 2009 and 2011, the TGA received 136 reports of hyponatraemia. Drugs well known to be associated with hyponatraemia appear in many reports (Table). Similar to reports of hyponatraemia received between May 2005 and Oct 2008,[3] drug combinations are suspected in many reports, with the combination of a diuretic with an ACE inhibitor or angiotensin receptor blocker appearing in 41 reports.

Just over half of the reports (76; 56%) described patients aged 70 or over and 64% (49) of these involved females. Older age is acknowledged to be a risk factor for hyponatraemia.

Commonly reported symptoms with hyponatraemia were confusion, dizziness, dehydration, nausea and vomiting, although a number of reports describe asymptomatic hyponatraemia detected on routine laboratory tests. One example is the case of a 91-year-old woman admitted to an emergency department for lower leg pain. Her serum sodium was found to be 124 mmol/L. One month earlier, when she started taking escitalopram, her serum sodium was 139 mmol/L. The reporting health professional considered escitalopram to have contributed to the hyponatraemia. Escitalopram was ceased and the woman was treated with fluid restriction and sodium replacement.

Other cases describe more severe, symptomatic hyponatraemia. Severe hyponatraemia is usually defined as serum sodium less than 120 mmol/L. In one case, a 71-year-old woman taking carbamazepine and indapamide experienced mental deterioration and was found to have serum sodium of 114 mmol/L. Both drugs were ceased and her symptoms resolved.

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Drugs implicated in reports of hyponatraemia to the TGA, January 2009–January 2011

Class / drug	Number of reports
Thiazide diuretics	47
Antihypertensives	
angiotensin receptor blocker	28
ACE inhibitor	23
Antidepressants	
selective serotonin reuptake inhibitor	22
serotonin–noradrenaline reuptake inhibitor	20
mirtazapine	7
Carbamazepine	13

Rotavirus vaccination and risk of intussusception: investigation of a possible safety signal

Summary

The TGA has released an analysis of rotavirus vaccine and the risk of intussusception. A detailed report of the analysis, and links to fact sheets for parents and immunisation providers, are available from the TGA website (www.tga.gov.au).

The TGA, in collaboration with state health authorities, has undertaken an investigation of a possible association between the rotavirus vaccines Rotarix (GSK) and RotaTeq (Merck/CSL) and the occurrence of a rare form of bowel obstruction known as intussusception. Intussusception is a condition caused by the telescoping of one segment of the bowel into another. It is estimated to occur each year in around 80 per 100 000 children under 12 months of age, which represents approximately 200 cases per year in Australia. The peak incidence is in infants 5–10 months of age, with 80% of cases occurring before 24 months of age. It is much more common in males than females.

Intussusception was found to be an adverse effect of the first generation rotavirus vaccine (RotaShield, Wyeth) that was available in the US in 1998–99. RotaShield was estimated to cause intussusception in 10–20 of every 100 000 doses given to infants, and was voluntarily withdrawn in October 1999.[1,2] RotaShield was not used outside the US; however, as the historical incidence of intussusception is 2.5 to 3 times higher in infants in Australia than in the US, this would have translated to 25–60 cases of intussusception for every 100 000 doses of RotaShield if the vaccine had been used here.

Subsequently two new rotavirus vaccines, Rotarix and RotaTeq, were developed. Both were tested in large studies designed to explore the risk of intussusception. In each of these placebo-controlled preregistration studies, approximately 35 000 infants were given rotavirus vaccine, with no increased risk of intussusception observed.[3,4] However, as large preregistration safety studies may not always detect rare events, postmarketing studies have been undertaken in a number of countries.

In Australia, two postmarketing studies have been conducted to investigate whether the new rotavirus vaccines are associated with an increased risk of intussusception. The first study used two surveillance systems – the Paediatric Enhanced Disease Surveillance with active surveillance of intussusception cases in four tertiary centres, and the Australian Paediatric Surveillance Unit with national retrospective reporting of intussusception cases by paediatricians. This study, conducted in NSW, Victoria, WA and SA, found an apparent four-fold increased risk of intussusception in babies within one week of being given the first dose of either vaccine, compared with historical data on hospitalisations coded as intussusception, but no overall increase in overall rates of intussusception up to the age of 9 months. This is much lower than the risk found with the earlier RotaShield vaccine.

Following this, a large self-controlled case series study using data on all hospitalised cases coded as intussusception from NSW, Victoria and WA was commissioned by the TGA. This study found a statistically significant four-fold increase in the occurrence of intussusception in the first 1–7 days following the first dose of either Rotarix or RotaTeq compared with other time periods after vaccine receipt. This increase in risk translates to approximately two additional cases of intussusception occurring in every 100 000 first doses of vaccine, or six additional cases each year in children under 12 months of age in Australia. *These findings are preliminary, as the data are subject to confirmation.*

It is currently unclear whether this represents a true increase in overall risk of intussusception, or an early increase in risk in infants which is compensated for by a subsequent decrease in risk leading to a reduction in cases of intussusception in older children. Longer-term studies are required to clarify this.

Prior to the introduction of rotavirus vaccine, there were an estimated 10 000 hospitalisations annually in children under five years due to rotavirus gastroenteritis. Since the introduction of Rotarix and RotaTeq onto the National Immunisation Program, emergency department visits for acute gastroenteritis in young children have declined and hospitalisations for rotavirus gastroenteritis in the under-5-years age group have been reduced by over 70%.[5,6] Based on the established benefits of rotavirus vaccination and the rare occurrence of intussusception, both the World Health Organization and the Australian Technical Advisory Group on Immunisation have recommended the continued use of rotavirus vaccine for infants under the National Immunisation Program.

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Coversyl and Coumadin: new packaging to reduce potential for dispensing errors

Summary

Pharmacists are asked to be aware of the similar packaging for Coversyl and Coumadin and to take extra care to ensure that dispensing errors do not occur.

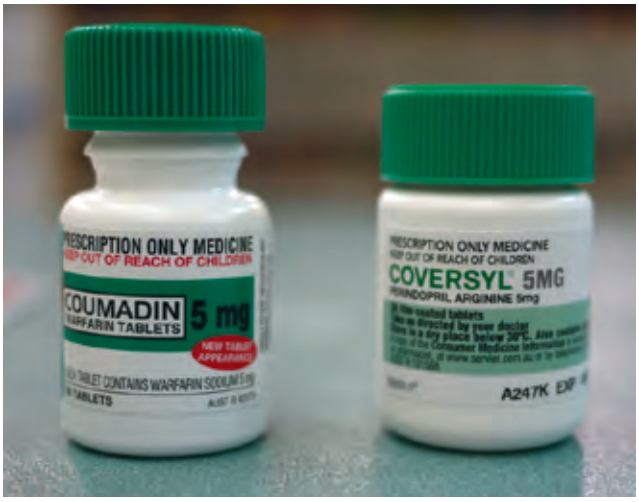
Coversyl (perindopril) and Coumadin (warfarin) 5 mg appear near each other in the pharmacy dispensary and both are packaged in white bottles with green caps and labels (see figure). The similarity arose when changes were made to the Coversyl packaging to comply with new requirements for a child-resistant closure.

In late November 2010, the TGA received two reports of dispensing errors associated with Coversyl and Coumadin. In one case a patient developed haematuria when Coumadin was dispensed instead of Coversyl. Despite several weeks of warfarin therapy, the patient's INR was 3. The patient made a full recovery and did not require warfarin reversal. In the other case a patient's INR dropped to 1.1 when Coversyl was dispensed in place of Coumadin. The patient did not experience any symptoms. Coversyl was ceased, anticoagulant therapy reintroduced and the patient made a full recovery.

The sponsor for Coversyl, Servier, has been working with the TGA to review and update the Coversyl packaging. New Coversyl packaging has been approved by the TGA and is expected to start appearing in pharmacies in April 2011. The updated packaging will include new labelling and white lids.

Packaging for Coversyl and Coumadin tablets

Coversyl packaging will soon change to reduce the similarity between the bottles



In the interim, Servier has worked with the Pharmacy Guild to publish an article advising pharmacists of the similarities between the Coversyl and Coumadin packaging. Alerts have also been issued by Pharmaceutical Defence Limited and the Australian Commission on Safety and Quality in Health Care.

Pharmacists should take care when dispensing not only Coversyl and Coumadin, but all drugs with similar trade names or packaging, ensuring appropriate checking and use of barcode scanners.

Medicines Safety Update is written by staff from the Office of Product Review. Editor: Ms Elspeth Kay. Principal Medical Advisor: Dr Megan Keaney. Contributors to this issue include Dr Katherine Gray and Dr Shaun Williams. For correspondence or further information about Medicines Safety Update, contact the TGA's Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114.

What to report? You do not need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. We particularly request reports of all suspected reactions to new medicines, all suspected medicines interactions, and suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website (www.tga.gov.au/adr/bluecard.pdf) and with the April, August and December issues of *Australian Prescriber*
- **online** on the TGA website (go to www.tga.gov.au and click on 'report a problem' on the left)
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

BRCA testing for familial breast cancer

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Summary

Mutations in the BRCA1 and BRCA2 genes are associated with hereditary breast and ovarian cancer. Genetic testing is available in specialised laboratories, but is expensive and presents a significant technical and interpretative challenge. Identification of a causative mutation carries lifelong health and psychosocial implications for the woman and her relatives. It also influences surveillance and treatment options. Testing should therefore only be considered with professional genetic counselling by specialists in familial cancer clinics.

Key words: genetic testing, mutations, ovarian cancer.

(Aust Prescr 2011;34:49–51)

Introduction

Breast cancer is the most common form of cancer among women in Australia. A woman has approximately a 1 in 10 chance of developing breast cancer at some point in her life. Most of these breast cancers are sporadic, reflecting the inevitable accumulation of errors in a person's DNA with age. However, 5–10% of affected women have a strong underlying and heritable predisposition to develop breast cancer.

Mutations in many different genes can cause a predisposition to develop breast cancer. For most women with familial breast cancer, the causative mutation is unknown and cannot be identified. However, the mutations most commonly identified in women with familial breast cancer are breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2). Together these mutations are found in approximately 20% of cases (that is, 1–2% of all breast cancers). Mutations in other genes, for example, TP53, CDH1, PTEN and STK11, are associated with rare genetic syndromes which can also predispose to breast cancer.

BRCA1 and BRCA2 genes

The BRCA1 gene is found on chromosome 17 and the BRCA2 gene is found on chromosome 13. They are tumour suppressor genes. The proteins encoded by these genes are part of a multi-protein complex which repairs damaged DNA. The complex normally repairs double-strand breaks in the DNA by homologous recombination. A cell which has lost BRCA1 or BRCA2 activity is unable to repair this damage and can rapidly accumulate mutations which eventually lead to cancer.[1]

A heritable mutation in either gene greatly increases the chance that a cell will become malignant. These mutations are inherited as autosomal dominants and there is a 50% chance that a child will inherit the abnormal gene from a carrier parent. The child will also inherit a normal copy of the gene from the other parent which will function, but the cell lacks a backup should this normal copy fail. With the inevitable accumulation of genetic errors with age, the normal copy may eventually become mutated (sometimes called the 'second hit') and the cell is left with no functioning BRCA gene. The resulting rapid accumulation of uncorrected errors in the cell's DNA usually leads to cancer.

For reasons that are not clear, the loss of BRCA1 or BRCA2 function increases the risk of some but not all cancers. Female carriers of a mutation in BRCA1 or BRCA2 are at high risk of developing breast cancer and ovarian cancer, while male carriers are at increased risk of breast and prostate cancer. In addition there is also a slightly increased risk of a wide range of other cancers, but the predominant cancer risk by far is that of breast and ovarian cancer.[1]

It is possible for someone to carry both a BRCA1 and BRCA2 mutation (double heterozygote) but this is very rare, accounting for less than 1% of all BRCA mutation carriers. For reasons that are not clear, double heterozygotes do not have a higher risk of cancer nor more severe disease compared to single mutation carriers.

Indications for BRCA testing

A family history of breast or ovarian cancer is the basis for making a clinical diagnosis of familial breast or ovarian cancer in a specific patient. The family history can also provide an indication of the risk of breast or ovarian cancer in an unaffected woman. Simple guidelines for assessing and interpreting a family history of breast and ovarian cancer are available from the National Breast and Ovarian Cancer Centre (www.nbocc.org.au).[2]

The clinical diagnosis of familial breast or ovarian cancer is not necessarily an appropriate indication for genetic testing for

mutations in the BRCA1 and BRCA2 genes, as the majority of women with familial breast cancer do not have an identifiable mutation in a known gene. Mutation analysis of the BRCA1 and BRCA2 genes is complex and expensive and is not justified in many women with familial breast or ovarian cancer. The current cost to the Australian healthcare system is $2–3000 per patient screened. There are a number of algorithms to estimate the likelihood of finding a BRCA1/BRCA2 mutation in a patient, but the positive predictive value of these algorithms is generally poor. The general consensus among familial cancer specialists in Australia is that a woman should be offered genetic testing for the BRCA1 and BRCA2 mutations if the estimated probability of finding a mutation is greater than 10%. The mutation search usually starts with testing the blood from an affected individual. Once a mutation has been identified, genetic testing of unaffected relatives (often called presymptomatic testing) may provide useful information regarding the risk of cancer and allow carriers to undertake specific cancer prevention and detection strategies before the development of disease.

Genetic testing of an unaffected person for a BRCA1 or BRCA2 mutation is generally not recommended unless a mutation has already been identified in a family member. If a mutation has not already been identified in a relative, it is impossible to interpret a normal result in an unaffected person. The normal result could mean that the person tested has not inherited the family's (unidentified) BRCA mutation, or that the person tested has inherited the family's non-BRCA mutation.

Genetic testing for a BRCA1 or BRCA2 mutation raises challenges in identifying which women should be tested, interpreting a complex test result, and managing the medical and psychological consequences of the result for both the patient and her relatives. For these reasons, the guidelines of the National Health and Medical Research Council recommend, and Australian laboratory standards require, that the testing is limited to specialists in familial cancer clinics. There are clinics across Australia and their services can be accessed by referral from medical practitioners.[3]

Mutation detection methodology

Analysis of the BRCA1 and BRCA2 genes is not simply 'two tests'. The BRCA1 and BRCA2 genes together consist of approximately 20 000 nucleotides. Analysis of each nucleotide in this length of DNA sequence presents a significant technical and interpretative challenge. There are approximately 10 laboratories in Australia which provide this service. DNA is extracted from a patient's blood sample and each exon of each gene is amplified by the polymerase chain reaction. Bidirectional sequencing is then performed on the products of the polymerase chain reaction. Any variation from the normal reference sequence must be assessed to determine if it is a benign variant, pathogenic mutation, or a variant of unknown clinical significance.

Direct sequencing does not detect large deletions or duplications which might involve many consecutive exons. Some laboratories can quantify the copy number of each exon relative to normal controls.

Interpretation of results

A normal person can have thousands of variations in their genetic code. In analysing the 20 000 nucleotides of the BRCA1 and BRCA2 genes, the laboratory will find many genetic variants. Some of these will be common variants that are well documented as being benign. The laboratory may also identify a variant which inactivates the gene and is documented as being pathogenic, that is, places a woman at high genetic risk of developing breast or ovarian cancer. There are international databases which catalogue variants and assist the laboratory in determining the significance of a particular variant. The laboratory may also identify one or more rare variants which are of unknown clinical significance.

The identification of a pathogenic variant carries significant implications for both the woman tested and members of her family. For this reason, the interpretation of a variant requires a high degree of scientific skill and accountability.

The failure to identify a pathogenic variant does not exclude the diagnosis of familial cancer. This is because the majority of women with familial breast or ovarian cancer do not have an identifiable mutation in the BRCA1 or BRCA2 genes.

The identification of a variant of unknown clinical significance is troubling for both the clinician and patient. However, such variants should not be the basis for clinical decision-making because, as more information is accumulated worldwide, many of them will turn out to be rare benign variants.

Once a pathogenic variant has been identified, other at-risk adult family members (male or female) can have a presymptomatic genetic test to determine their cancer risk. In this situation, the interpretation is much simpler. The relative has either inherited the pathogenic variant or not. This type of testing carries significant medical, psychological, ethical and social consequences. National clinical and laboratory standards require that such testing be accompanied by expert genetic counselling. For men, the principal reason for knowing their carrier status is to clarify the risk of their daughters inheriting the mutation.

Management

The main benefit of finding the familial BRCA mutation is the prevention or early detection of cancer in at-risk relatives. The care of someone carrying a BRCA1 or BRCA2 mutation must be individualised because the issues and options vary with the gene involved and the gender and age of the person.[4] Options include breast cancer surveillance, risk-reducing surgery and chemoprevention with drugs such as tamoxifen. Management involves the general practitioner and potentially multiple

specialists and genetic counsellors. At this time, BRCA mutation status usually makes little difference to the treatment of the cancer for the affected individual, but this may change with the availability of new drugs.

Genetic counselling

Genetic testing differs from most routine laboratory tests in that the detection of a mutation carries lifelong implications for the patient as well as relatives. The testing for BRCA1/BRCA2 mutations must always be accompanied by appropriate genetic counselling. This counselling should commence before any genetic testing and should be provided by a practitioner with professional genetic counselling training and experience.

Conclusion

BRCA1 and BRCA2 mutations are an important cause of familial breast and ovarian cancer. Genetic testing should take place in the context of appropriate pre-test and post-test genetic counselling, as provided by familial cancer clinics. The identification of pathogenic mutations has important implications for the clinical management of the patient and family members. However, a normal test result must be interpreted with caution. On one hand, the absence of an identified mutation in an affected woman does not exclude the clinical diagnosis of familial breast cancer. It is likely that the woman has a mutation in a different yet-to-be-identified gene. On the other hand, once a mutation has been identified in the family, a normal test result means that the person has not inherited the family's predisposition to develop cancer and does not require special cancer surveillance.

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Dr Suthers and Dr Lau are both employed by a public sector provider of BRCA genetic testing (SA Pathology). Dr Suthers also receives funding for research into familial breast cancer (National Health and Medical Research Council, Cancer Council SA and Australian Department of Health and Ageing).

Book review

Therapeutic Guidelines: Antibiotic Version 14 (2010)

***Penny Abbott**, General practitioner, Aboriginal Medical Service Western Sydney, and Senior fellow, Department of General Practice, University of Western Sydney*

This book has become the most essential desktop clinical tool of this well regarded series. It aims to guide antimicrobial use within both hospital and community settings. It is reassuring with the release of this new edition to know that you are consulting the updated version when you are seeking prescribing advice.

The accessibility of the information is strengthened by the ongoing presentation of concise, evidence-based prescribing advice in a systematic format. This makes the information easily usable within consultations.

Beyond providing immediate advice in unfamiliar prescribing situations, this book usefully discusses some common clinical problems, rewarding a read outside the consultation room. This includes expanded guidance on the management of patients who report penicillin hypersensitivity, and the treatment and prophylaxis of influenza. New recommendations for gentamicin as empirical therapy are another major change in this version.

The book also provides useful summaries of the latest management guidelines of important and diverse conditions, such as when to recommend symptomatic treatment of otitis media rather than antibiotic treatment, and the procedures requiring antibiotics for the prevention of endocarditis.

A change in structure in this edition has led to the removal of some sections which overlapped with other Therapeutic Guidelines editions. Some readers may be disappointed to find that some common gastroenterological, dermatological or respiratory conditions requiring antimicrobial management are no longer included in this book, with the reader being directed to other books in the series.

I recommend this book to busy clinicians, which is just about all of us! It is an essential guide to prescribing antimicrobials, although the electronic version, as part of the complete set, may be necessary to get a more complete coverage of the clinical scenarios the reader will face.

Cardiac effects of non-cardiac drugs

***Ingrid Hopper**, Clinical pharmacology fellow, Alfred Health, Melbourne*

Summary

Drugs prescribed for non-cardiac conditions can have unexpected and serious cardiac effects. These may occur while taking the drug or can be delayed for years. Often these adverse effects are not recognised until the postmarketing phase of drug development. An underlying cardiac abnormality can be a predisposing factor. Drugs with cardiac adverse effects include clozapine, rosiglitazone, non-steroidal anti-inflammatory drugs, tumour necrosis factor inhibitors, cancer chemotherapy and drugs for Parkinson's disease.

Key words: arrhythmia, heart failure, myocardial infarction.

(Aust Prescr 2011;34:52–4)

Introduction

Many drugs have unexpected cardiovascular effects. Health professionals should be aware of the potential for non-cardiac drugs to have effects on the heart when prescribing to patients with or without cardiac disease or cardiac risk factors. Data on the cardiac effects of non-cardiac drugs can be difficult to interpret. Adverse effects may become apparent late in the development of the drug, such as during review of the safety data or in the postmarketing phase. Trials may not have specified cardiovascular outcomes as an end point and the incidence of cardiac events can be low, so evidence is often derived from *post hoc* analyses or meta-analyses.

Myocardial infarction

Patients and physicians may be unaware that even some over-the-counter medicines may increase the risk of myocardial infarction.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used analgesics. Clinical trials of COX-2 inhibitors showed a slight increase in the rate of serious thrombotic vascular events, mostly myocardial infarction, compared with placebo.[1,2] Rofecoxib has been withdrawn from the market. Studies with celecoxib are conflicting but an increased risk of myocardial infarction probably exists with sustained use of high doses, especially in patients who already have a high cardiovascular risk.[3]

The cardiovascular problems observed with COX-2 inhibitors prompted further study of the older non-selective NSAIDs. Various observational studies and meta-analyses found that diclofenac, and possibly ibuprofen, were associated with an increased risk of myocardial infarction.[4,5] This relationship is dose-dependent, with higher doses resulting in more events. Evidence of the adverse effect of NSAIDs in patients with cardiovascular disease is scant, but a higher cardiovascular risk may potentiate the drugs' cardiotoxicity. NSAIDs, including COX-2 inhibitors, should therefore be used for the shortest time possible at the lowest effective dose.

Thiazolidinediones

The 'glitazones' are used as add-on treatment for patients with type 2 diabetes. Rosiglitazone was associated with increased rates of myocardial infarction, but not cardiovascular mortality, in a recently updated meta-analysis of 56 randomised controlled trials involving 35 531 patients.[6] The US Food and Drug Administration estimated that during 1999–2006 an excess 41 000 to 205 000 major cardiovascular events were potentially attributable to rosiglitazone.[6] Rosiglitazone has been removed from the European market and access is restricted in Australia and the US. Pioglitazone appears to be a safer alternative.

Antiretrovirals

Highly active antiretroviral therapy has been associated with significant improvements in long-term prognosis in HIV infection. However, it can result in adverse metabolic changes which increase the risk of diabetes and cardiovascular disease, including increases in cholesterol and triglycerides, insulin resistance and abdominal adiposity. The use of protease inhibitors in particular has been associated with an increase in myocardial infarction.[7] The relative contribution of the medications, lifestyle and the effect of HIV itself on cardiovascular disease is difficult to elucidate.

'Triptans'

The $5HT_1$ agonists used in migraine cause vasoconstriction of the cerebral vessels. $5HT_1$ receptors also exist in lower numbers and to a lesser extent in coronary arteries. There are rare reports of myocardial infarction, as well as other cardiovascular events, usually in patients with unrecognised cardiovascular disease, although some have occurred in patients with no cardiovascular disease and were thought to be due to vasospasm.[8] Cardiac risk stratification should therefore be undertaken before patients are prescribed these drugs.

Heart failure

Heart failure occurs as a complication of a variety of drugs. Patients with identifiable cardiac risk factors such as previous myocardial infarction, hypertension and advanced age are

at greater risk. Other risk factors relate to any underlying cardiovascular disease.

Non-steroidal anti-inflammatory drugs

NSAIDs do not appear to cause new occurrence of heart failure, however their use is strongly correlated with relapse of heart failure.[9] Patients known to have heart failure should therefore avoid NSAIDs. The risks are dose-dependent. Diclofenac appears to be associated with the greatest risk, but heart failure has been observed with all NSAIDs including COX-2 inhibitors.

Thiazolidinediones

The glitazones are thought to cause fluid retention by increasing sodium reabsorption in the distal nephron. This causes peripheral oedema and can worsen existing heart failure or cause new onset heart failure. Randomised controlled trials have clearly shown increased rates of hospitalisation for heart failure, but not increased mortality. However, these trials have generally excluded patients with symptoms of New York Heart Association (NYHA) class III and IV heart failure.[6] These drugs are therefore contraindicated in heart failure.

Cancer chemotherapy

The risk of cardiac complications associated with cancer treatment can be as great as the risk of recurrence of the cancer, particularly if there has been chest wall irradiation.[10] Anthracyclines (doxorubicin and daunorubicin), used in haematological and solid organ tumours, cause significant cardiac toxicity. Heart failure, typically a dilated or restrictive cardiomyopathy, develops within one month to a year after treatment, although it can occur after a decade or more. The incidence is directly related to the cumulative dose. At the recommended maximum lifetime dose of doxorubicin (550 mg/m^2), heart failure is observed in 7% of patients and increases rapidly above this maximum, although it can also occur with smaller doses. The patient's cardiac function should be monitored for life. Cyclophosphamide has also been shown to cause heart failure.

Trastuzumab is a recombinant IgG monoclonal antibody used in the treatment of human epidermal growth receptor-2 (HER-2) positive breast cancers. When used as monotherapy, trastuzumab is associated with a 3–7% increase in cardiac events, of which 2–4% are NYHA class III/IV heart failure. This incidence increases to as high as 27% when used in combination with anthracyclines. There is no clear relation to dose, and heart failure is often reversible, with re-initiation of therapy well tolerated.

Tyrosine kinase inhibitors, such as sunitinib, are small molecules which inhibit tumour growth and angiogenesis in metastatic renal cell carcinoma and certain gastrointestinal tumours. Heart failure and asymptomatic reduction in left ventricular ejection fraction has been observed in 10–15% of patients. Most cases improved when the drug was stopped.

Tumour necrosis factor inhibitors

The biological therapies that inhibit tumour necrosis factor are used to treat immune mediated inflammatory disease. These drugs were initially trialled for the treatment of heart failure, but in fact worsened the condition, and also caused heart failure in patients without any predisposing factors. Symptoms are mostly reversible when therapy is stopped, but deaths have occurred.[11]

Complementary therapies

Use of complementary therapies is common, especially in patients with chronic diseases, including heart failure. Evidence regarding their cardiac effects is scant and mostly anecdotal.[12] Herbal therapies have the potential to interact with drugs with narrow therapeutic index, including digoxin and warfarin. They can also reduce or potentiate pharmacological effects of cardiovascular medications.[13] Liquorice can cause fluid retention and precipitate heart failure, as well as hypertension.

Myocarditis

Inflammation of the myocardium can be caused by the direct effect of drugs or through an immune mechanism.

Clozapine

Myocarditis has been observed to occur at a rate of 0.7–1.2% in users of the antipsychotic, clozapine. This is 10 000 times the background rate in the general population.[14] Clozapine-induced myocarditis occurs in the first eight weeks of therapy. It is an unpredictable idiosyncratic reaction, unrelated to dose. Symptoms range from the mild to cardiogenic shock and death. Monitoring of troponin is recommended when starting clozapine. Echocardiography is used to assist in diagnosis, assess severity and follow recovery. Clozapine-induced myocarditis is mostly reversible with early recognition, so withdrawal of the drug is the mainstay of treatment along with supportive therapy.

Cardiomyopathy with longer term dysfunction of cardiac myocytes is also seen with clozapine therapy at a rate of 0.1%. It can occur at any time during therapy but usually after the first eight weeks. It is not clear whether this is due to direct cardiotoxic effects of the drug, or evolution of unrecognised myocarditis.

Valvular heart disease

The drugs which have been shown to cause valvular heart disease include ergot alkaloids used in migraine prophylaxis and the now withdrawn appetite suppressant fenfluramine.[15] The ergot-derived dopamine agonists cabergoline and pergolide, used in Parkinson's disease, have been associated with fibrotic reactions in the heart valves with consequent valvular regurgitation. Rates of clinically important regurgitation in the order of 25% have been found when these drugs are used for more than a year in Parkinson's disease.[16] The severity of the regurgitation is related to dose and duration of therapy. Regression of the valvular lesion has generally been observed after treatment stops.

Arrhythmia

Many drugs can prolong the QT interval on the ECG.[17] This can cause life-threatening ventricular tachycardias including torsades de pointes. It is the leading cardiac reason for which drugs are withdrawn from the market, and as a consequence measurement of the QT interval has become an important part of drug development.

Prolongation of the QT interval has been associated with tricyclic antidepressants, antipsychotics, stimulant drugs such as amphetamines, as well as erythromycin and other macrolides, especially in the presence of drugs which affect metabolism such as verapamil, diltiazem and ketoconazole.[18]

It is difficult to identify which drugs may cause atrial fibrillation because of its high background rate in the community. High-dose corticosteroids have been observed to cause this arrhythmia. Bisphosphonates are associated with a small increased risk, as is the cholinesterase inhibitor donepezil used in Alzheimer's disease.[19]

Bradycardia can be caused by cholinergic drugs such as neostigmine and clonidine. Sinus tachycardia can be caused by adrenergic agonists, such as beta agonists, and antidepressants including duloxetine and venlafaxine.

Conclusion

Various non-cardiac drugs can have off-target effects on the heart that may not be expected based on knowledge of the pharmacology. A thorough medication history should be sought from all patients, including drugs taken in the recent and distant past. The use of certain drugs, in particular anthracyclines, mandates lifelong cardiac follow-up, and both patients and prescribers should understand this. The cardiac risk profile and relevant comorbidities should be considered before prescribing non-cardiac drugs which have a potential for cardiac adverse effects.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 59)

3. Non-steroidal anti-inflammatory drugs should not be used if a patient has a history of heart failure.
4. The $5HT_1$ agonists used to treat migraine may cause coronary vasodilation.

Dental notes

*Prepared by **Michael McCullough**, Chair, Therapeutics Committee, Australian Dental Association*

Cardiac effects of non-cardiac drugs

Dentists have traditionally been concerned about the potential risk of cardiac effects from the vasoconstrictor, either adrenaline or octapresin, in dental local anaesthetics. However, the evidence shows that there is minimal effect from either of these drugs in appropriate dosage. There is a much greater effect from endogenous production of adrenaline if the dental procedure is painful.

Non-steroidal anti-inflammatory drugs are widely used for dental pain and dentists should be aware of the potential cardiac adverse effects, particularly with long-term use of these drugs. The concept of using these very effective drugs for the shortest time possible at the lowest effective dose is an excellent guiding principle for all patients. Concurrent use of other analgesics, as well as correct diagnosis and timely and effective provision of dental treatment, can go a long way in diminishing the long-term adverse effects of these drugs.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and 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.

Canakinumab

Ilaris (Novartis)

vials containing 150 mg lyophilised powder for reconstitution

Approved indication: cryopyrin-associated periodic syndromes

Australian Medicines Handbook section 15.2.2

Cryopyrin-associated periodic syndromes are a group of rare but often severe inflammatory disorders including familial cold autoinflammatory syndrome or familial cold urticaria, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease. These disorders are associated with mutations in the gene that encodes cryopyrin, a protein involved in the regulation of interleukin-1β. The defect results in over-production of interleukin-1β and leads to inflammation that can affect the skin, eyes, bones, joints and meninges. Patients may also experience severe fatigue, fever, myalgia, chronic anaemia and learning difficulties.

Currently there are no approved treatments for cryopyrin-associated periodic syndromes in Australia, but colchicine, corticosteroids and sometimes anakinra (Aust Prescr 2004;27:160-1) have been used in these patients. Canakinumab is a human monoclonal antibody that specifically binds to interleukin-1β, neutralising its activity. After subcutaneous administration, peak serum concentrations are reached after 7 days in adults and between 2 and 7 days in children. The average terminal half-life is 26 days in adults and between 22.9 and 25.7 days in children.

In an early study, four patients responded to one intravenous dose of canakinumab 10 mg/kg – urticarial rashes disappeared within 24 hours and patients experienced a complete response by one week. The median time until re-dosing after disease flare was approximately 26 weeks.[1]

In a larger 48-week trial, 34 of 35 patients (aged 4–75 years) responded to a single open-label subcutaneous dose of canakinumab 150 mg (or 2 mg/kg for those under 40 kg) within a month. After 8 weeks, patients who had responded were randomised to receive either canakinumab or placebo (at 8-week intervals) for a further 24 weeks. The 15 patients given canakinumab stayed in remission, whereas 13 of the 16 patients given placebo relapsed. Disease activity seemed to correlate with C-reactive protein and serum amyloid A concentrations – both were elevated in the placebo group but normalised in the canakinumab group. After 32 weeks, 6 of the 15 patients in the canakinumab group said their symptoms had completely gone compared to none of the patients in the placebo group. In a third phase of the trial, 31 patients were given open-label canakinumab (at least 2 doses over 16 weeks). Of the 29 who completed treatment, 28 people were in remission.[2]

As canakinumab suppresses the immune system, infections are a risk. The most frequently reported adverse reactions with canakinumab were upper respiratory tract infections and pharyngitis (up to 33.3%). Also, there were more suspected infections with canakinumab than with placebo (10 patients vs 4 patients).[2] Two patients given canakinumab had serious adverse events – one had urinary tract infection requiring hospitalisation and the other developed vertigo with acute closed-angle glaucoma. Both patients discontinued treatment.[2]

Because of the risk of infections, patients should be tested for latent and active tuberculosis before starting treatment and caution is urged in patients with a history of recurring infections. Canakinumab should not be started or continued in patients with active infection requiring medical treatment. Concomitant use of tumour necrosis factor inhibitors or live vaccines is not

recommended with canakinumab. Patients should complete all appropriate vaccinations before starting treatment.

As cytochrome P450 enzymes can be suppressed by cytokines such as interleukin 1β, canakinumab may reverse this and affect the metabolism of some drugs. Dose adjustment for drugs with a narrow therapeutic index may be necessary.

Due to lack of clinical data, canakinumab is not recommended during pregnancy and lactation or in children under 4 years of age. So far antibodies to canakinumab have not been detected in recipients of the drug.

Canakinumab is the first interleukin-1 blocker to be approved for cryopyrin-associated periodic syndromes in Australia. A subcutaneous injection every eight weeks appeared to be effective in reducing inflammatory symptoms, although the pivotal trial was very small. Prescribers need to be vigilant for infections in patients receiving canakinumab.

T manufacturer provided the product information

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Eltrombopag olamine

Revolade (GlaxoSmithKline)

25 mg and 50 mg tablets

Approved indication: idiopathic thrombocytopenic purpura

Australian Medicines Handbook Appendix A

Chronic idiopathic thrombocytopenic purpura is an immune condition caused by autoantibodies which bind to platelets. This leads to increased destruction of platelets, putting patients at risk of bleeding. The condition tends to have episodes of relapse and remission. If it cannot be controlled by corticosteroids, immunoglobulins or splenectomy, a drug such as romiplostim can be given to stimulate platelet production.

Like romiplostim, eltrombopag increases platelet production by interacting with the thrombopoietin receptor. Whereas romiplostim is a peptide which has to be injected, eltrombopag is a small non-peptide molecule which can be given orally. It should not be taken within four hours of antacids, dairy products or mineral supplements as these reduce absorption. Higher concentrations are reached in East Asian patients so a lower starting dose (25 mg) is recommended. Most of the dose is metabolised and most of the metabolites are excreted in the faeces. The elimination half-life in patients is 26–35 hours.

Eltrombopag increases the concentrations of rosuvastatin and may interact with other HMGCoA reductase inhibitors.

A dose-ranging study randomised 118 patients to take a daily dose of eltrombopag 30 mg, 50 mg or 75 mg or placebo for up to six weeks. These patients had platelet counts below 30 x 10^9/L despite treatment. The trial end point was a platelet count of at least 50 x 10^9/L. This was reached by 28% of the patients given eltrombopag 30 mg, 70% of those given 50 mg and 81% of those given 75 mg. Only 11% of the placebo group reached the end point. The significant advantage of the 50 mg and 75 mg doses led to the trial being stopped.[1]

A starting dose of eltrombopag 50 mg was used in a subsequent phase III trial in patients who remained thrombocytopenic despite having had at least one previous therapy. The dose was increased to 75 mg if patients did not achieve a platelet count of 50 x 10^9/L after three weeks. Compared to the 38 patients randomised to placebo, there was a significantly greater response in the 76 patients randomised to eltrombopag. The target platelet count was achieved at six weeks by 59% of the eltrombopag group, but by only 16% of the placebo group.[2]

To assess the efficacy of longer-term treatment, 135 patients with platelet counts below 30 x 10^9/L were randomised to receive eltrombopag 50 mg for six months. The dose could be adjusted to 25 mg or 75 mg as needed. Another 62 patients were randomised to take a daily placebo. After six months of treatment 79% of the eltrombopag group, but only 28% of the placebo group, had achieved a platelet count of 50–400 x 10^9/L on at least one occasion. The response to eltrombopag tended to be maintained. Significantly more of the patients taking eltrombopag were able to reduce their other treatments.[3]

Diarrhoea, nausea and vomiting were common adverse events in the clinical trials. Eltrombopag is potentially hepatotoxic. A study of patients with liver disease had to be stopped because of adverse events such as portal vein thrombosis. Liver function should be tested before treatment, then every two weeks until the dose is stable and then monthly.

Cataracts were reported in animal studies of eltrombopag. An eye examination is therefore recommended for patients before and during treatment.

A potential hazard of a rapid rise in platelet count is thrombosis. In clinical trials, thromboembolic events occurred in 3.8% of patients.

Eltrombopag may increase the risk of bone marrow fibrosis. This is one possible cause for a loss of response to treatment.

The effect of eltrombopag wears off quickly. Within two weeks the patients' platelet counts will fall back to baseline levels or below. There may be an increased risk of bleeding at this time.

Although treatment with eltrombopag reduces bleeding it does not completely prevent it. During the six month study 19%

of the patients taking eltrombopag and 31% of those taking placebo had bleeding as an adverse effect of treatment. This bleeding was serious in less than 1% of the eltrombopag group and 7% of the placebo group.[3]

Apart from oral administration, it is not known if eltrombopag has advantages over romiplostim. Until more is known about the long-term effects of stimulating the thrombopoietin receptor, the drug will be reserved for adult patients with an unsatisfactory response to other treatments.

T manufacturer provided the AusPAR

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Sapropterin dihydrochloride

Kuvan (Merck Serono)

100 mg soluble tablets

Approved indication: hyperphenylalaninaemia

Australian Medicines Handbook Appendix A

The amino acid phenylalanine is normally metabolised by phenylalanine hydroxylase to form tyrosine. This metabolism involves a co-enzyme called tetrahydrobiopterin (BH4). Inborn errors of metabolism or a deficiency of BH4 result in the accumulation of phenylalanine which leads to intellectual disability. There are many possible mutations. Phenylketonuria is the most common of the hyperphenylalaninaemias.

Patients with phenylketonuria have to follow a diet low in phenylalanine. The diet can be difficult to adhere to, so there has been research into other approaches. Supplementing BH4 may help to offset the abnormal metabolism. In a study of 31 patients with mild hyperphenylalaninaemia/phenylketonuria, giving BH4, after a loading dose of phenylalanine, reduced the concentration of phenylalanine in the blood.[1]

Sapropterin is a synthetic form of BH4. Although its bioavailability is probably low, it can be given by mouth. Taking the daily dose with food improves absorption.

An open-label trial of sapropterin treated 485 patients with phenylketonuria for eight days. The concentrations of phenylalanine in the blood fell by at least 30% in 96 of the patients.[2] A group of these responders was later enrolled in a double-blind trial.

In the double-blind trial the 89 patients were randomised to take sapropterin or a placebo for six weeks. Both groups had similar blood concentrations of phenylalanine in the two weeks before drug treatment began. These concentrations then fell by at least 30% in 44% of the sapropterin group, but in only 9% of the placebo group. The mean change from the baseline concentration was a fall of 235.9 micromol/L in the treatment group and a rise of 2.9 micromol/L in the control group.[3]

Although the trial included a few children, another study looked specifically at children who were 4–12 years old. In the first part of the trial the children were given an eight-day course of sapropterin. Those who experienced at least a 30% reduction in phenylalanine concentrations, to below 300 micromol/L, were eligible for the next part of the study. Following a washout period of at least one week, 46 responders were randomised to take sapropterin or a placebo for 10 weeks. After three weeks there was a significant difference in the blood concentrations of phenylalanine in the treatment and control groups. The mean concentrations fell in the 33 children who took sapropterin, but were unchanged with placebo. From the third week of the study, depending on the blood concentrations, supplements of phenylalanine were added to the children's diet. The amount could be increased or decreased every two weeks. At the end of the study the children given sapropterin had been able to tolerate significantly more supplements than the placebo group.[4]

The placebo-controlled trials were short and few differences emerged in adverse events. The events which were more frequent with sapropterin than with placebo included rhinorrhoea, pharyngolaryngeal pain, diarrhoea and headache. Nobody withdrew from the trials because of adverse reactions.[3,4] There were no studies of drug interactions, but sapropterin could interact with drugs such as methotrexate, which inhibit folate metabolism, and nitric oxide-mediated vasodilators such as sildenafil. There may be neurological adverse effects if the patient takes sapropterin and levodopa.

Only a minority of patients with phenylketonuria or BH4 deficiency will have a significant response to treatment with sapropterin. The only way to identify these patients is with a therapeutic trial. If there is no change in the blood concentration of phenylalanine after one month, treatment should be stopped. Sapropterin will not be effective enough to allow many patients to ease their dietary restrictions. A low phenylalanine diet should therefore continue during treatment with regular monitoring of blood concentrations.

T T manufacturer provided additional useful information

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Zonisamide

Zonegran (Sci Gen)

25 mg, 50 mg and 100 mg capsules

Approved indication: partial seizures

Australian Medicines Handbook section 16.1.3

Many adults with refractory epilepsy have partial seizures which may or may not become generalised. When monotherapy fails, it can be difficult to decide which adjunctive treatment will help the patient. Zonisamide adds to the list of drugs such as gabapentin, lamotrigine, tiagabine and topiramate, which can be used as add-on therapy. While it is a new drug in Australia, zonisamide has been available for many years in Japan.

Zonisamide is a sulfonamide, but its mechanism of action in epilepsy is uncertain. It may stabilise neuronal membranes by blocking sodium and calcium channels. Zonisamide is also a weak inhibitor of carbonic anhydrase.

The capsules are well absorbed and food does not affect bioavailability. Zonisamide has a long half-life so it takes up to 14 days for its concentration to reach a steady state. The dose should therefore not be increased at intervals of less than one week. Treatment begins with twice-daily doses, but patients can switch to once daily after the dose has been titrated to an effective level. Most of the dose is excreted in the urine as unchanged drug and metabolites, so clearance falls with declining renal function. Doses may therefore need to be titrated more slowly in patients with renal or hepatic impairment. The metabolism of zonisamide includes cytochrome P450 3A4 so there is a potential for interactions with other drugs acting on this enzyme system. Clearance is increased by phenytoin, sodium valproate and carbamazepine. Zonisamide may possibly interact with carbonic anhydrase inhibitors such as topiramate.

A study in the USA compared zonisamide with placebo in 203 patients with refractory partial seizures. Different regimens were used to titrate the dose, but all patients randomised to take zonisamide were on 400 mg daily from the eighth week of the study. Patients continued their usual antiepileptic drugs.

In the month before randomisation the median frequency of partial seizures was 13 in the placebo group and 11–13 in the zonisamide groups. During weeks 8–12 of the study, the median frequency of all seizures was reduced by 9% in the placebo group and by 40.5% in the zonisamide group.[1]

Another American study randomised 152 patients to add zonisamide or a placebo to their usual treatment for 12 weeks. The dose of zonisamide was titrated over four weeks to 400–600 mg daily. The baseline median frequency of seizures was approximately nine per month, but there was a 25.5% reduction after patients took zonisamide. In the placebo group there was a 6.6% increase in seizure frequency.[2]

In a European study 347 patients added a placebo or one of three doses of zonisamide to their usual therapy. The fixed-dose phase of the trial lasted for 18 weeks. During this phase, seizure frequency reduced by 17.4% in the placebo group and by 38.5% in patients taking zonisamide 300 mg daily. The efficacy of zonisamide 100 mg was not statistically different from placebo. While the median reduction in seizure frequency with zonisamide 500 mg was 46.1%, the response probably does not greatly increase above a daily dose of 400 mg.[3]

Frequent adverse effects with zonisamide include somnolence, dizziness and anorexia. Some patients lost weight during the trials.[1,3] Adverse neurological events include ataxia, nystagmus, agitation and altered cognitive function. Driving skills may be impaired.

Zonisamide can cause rashes, including Stevens-Johnson syndrome. The product information states that it is contraindicated if the patient has an allergy to sulfonamides.

Prescribers may need to consider monitoring renal function as zonisamide has been associated with increases in urea and creatinine concentrations. Patients should be advised to maintain their hydration in warmer weather as oligohydrosis and hyperthermia have been reported (mainly in children). Early development of the drug in the USA was halted because 3.5% of patients developed kidney stones.[1]

Zonisamide is teratogenic in animals and is not approved for use in children.

Although zonisamide reduces seizure frequency more than placebo, few patients will become free of seizures. Depending on the dose, a greater than 50% reduction in the frequency of all seizures is achieved by 30–53% of patients.

T T T manufacturer provided clinical evaluation

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The T-score (T) is explained in 'New drugs: T-score for transparency' in this issue, Aust Prescr 2011;34:26–7.

* 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.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/pmeds/auspar.htm)

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