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Editorial

Setting a standard for electronic prescribing systems

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Key words: general practice.

(Aust Prescr 2011;34:2–4)

In Australia, electronic prescribing (e-prescribing) systems in general practice were first developed in the early 1990s by a few innovative general practitioners who wrote software for their own use. The uptake of e-prescribing systems was accelerated in 1999 because of Commonwealth government incentive payments of $10 000 to practices that acquired an email address and used e-prescribing software to write the majority of their prescriptions. Currently over 90% of general practitioners use one of the 20 or so commercial systems that are available to write prescriptions, order pathology and other tests, record medical progress notes or communicate with other healthcare providers.[1] Despite the widespread use of e-prescribing systems, there are no clear standards or guidelines for their development. This has led to a variety of systems with markedly different capabilities, particularly in terms of assisting general practitioners to prescribe safely and effectively.

Overseas studies have shown that e-prescribing systems can enhance the safety and quality of prescribing by ensuring complete and legible prescription orders, improving the detection of drug allergies and by reducing medication errors and adverse reactions.[2–5] However, these systems can also have unfavourable effects on workflow and communications, and can have unintended effects on prescribing. For example, they may introduce new types of errors[6–8] and high levels of unhelpful alerts, and impact on repeat prescribing.[9] General practitioners have also expressed concern about the comprehensiveness and accuracy of some of the information provided in their software.[10] In a comparative study of nine electronic prescribing and dispensing systems used in primary care in Australia in 2006, an expert panel found that most systems do not offer consistently useful and relevant information for general practitioners and pharmacists to make decisions about drug interactions.[11]

Recently, a number of organisations and researchers have identified desirable functionality and safety features for e-prescribing systems in various healthcare settings.[12–16] In Australia, the National Prescribing Service (NPS) has worked with general practitioners, professional organisations and the Medical Software Industry Association to identify the key features of e-prescribing systems which support patient safety and quality care.[17] Many of the safety and quality features identified for general practice apply equally to other settings such as hospitals or aged care.

For safety and quality, an ideal system needs suitable information resources, interoperability with other systems and clinical decision support. The goal of clinical decision support is 'to provide clinicians or patients with clinical knowledge and patient-related information, intelligently filtered and presented at appropriate times, to enhance patient care'.[18]

The ideal system should record clinical data such as diagnoses, medicines and allergies in a standard coded format. This helps to facilitate one system being able to 'talk to' another system and easily exchange patient data, for example with hospital systems or personal electronic health records when they become available. Information about recommended therapeutic options for the current diagnosis should be offered. The system ought to ensure that medicine selection processes are safe. In addition to drug interaction alerts, the system should provide warnings if a drug is contraindicated, the dosage regimen is potentially harmful, or if the drug is the subject of new safety advice from the Therapeutic Goods Administration. Warnings

In this issue…

Electronic systems can help health professionals find information quickly. Examples could be looking up the safety of analgesics for use during pregnancy, as discussed by Debra Kennedy, or the efficacy of non-surgical treatments for skin cancer, as reviewed by Stephen Shumack. However, James Reeve and Michelle Sweidan inform us that there are no standards for electronic prescribing systems.

Delirium is a common problem in older patients, but Gideon Caplan says that the diagnosis is often missed. The investigation of delirium may include tests of thyroid function and these are reviewed by Robin Mortimer.

A risk factor for delirium is dementia. As there are few drugs for dementia, people may try complementary medicines for cognitive impairment. While these products may not be very effective, Ken Harvey and Con Stough remind us that complementary medicines can have adverse effects and interactions.

need to be prioritised by clinical importance otherwise they may be ignored. Users should be able to see the reason for the alert.

Decision support and therapeutic information offered by the prescribing system must be underpinned by high quality, up-to-date evidence and guidelines. Independent, evidence-based drug information and clinical practice guidelines should be accessible from within the software. High quality patient resources, such as printable information leaflets and a suitably formatted current medicines list, are also important. The ideal system should have sophisticated reporting capabilities to enable clinicians to monitor clinical care and audit individual or practice performance. The system needs to be intuitive and easy to use in clinical practice.

How do current systems used by general practitioners in Australia rate? The NPS has evaluated seven commonly used systems against a predefined set of criteria (J Reeve, M Sweidan, unpublished, 2011). It found that features to support safety and quality were highly variable between systems and there were some significant gaps. Clinical decision support features were ranked the most important for safety and quality, but in five of the systems fewer than 50% of these features were fully implemented (for example, there were no alerts for harmful doses or new safety warnings). One of the main reasons for this is the lack of clinical information resources in a format which is suitable for decision support. When systems included decision support, it was often unclear where the information was derived from and whether it was up to date. Features relating to the medicine selection process and the recording and display of patient data were also rated as important. Another important safety issue identified was that most systems did not clearly differentiate between similar-named medicines during prescribing, increasing the risk of selecting the wrong drug from a list of products.

The findings of this evaluation highlight the need for guidance or standards to ensure that essential functionality and safety features are included in all e-prescribing systems. There is some related work currently in progress in Australia. The National e-Health Transition Authority (NEHTA) is developing standards in relation to drug and disease terminologies, messaging and unique identifiers – these are important foundations. The Australian Commission on Safety and Quality in Health Care, in conjunction with NEHTA, has developed guidelines for the safe implementation of Electronic Medication Management in hospitals. Recent progress has been made in the UK[14–16,19] and USA[18] on desirable functionality and design of systems to optimise usability and patient safety – much of this guidance will be applicable to the Australian setting.

Given the widespread use of electronic prescribing systems in day-to-day practice, coordinated activity to ensure these systems meet key quality and safety criteria is overdue. Clear guidance and standards are a prerequisite. Government, professional bodies and the software industry have a shared responsibility to develop and support processes to improve quality and safety in e-prescribing systems in Australia.

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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.

Managing cardiovascular disease in Aboriginal and Torres Strait Islander people

Editor, – I found the article about cardiovascular disease in Aboriginal and Torres Strait Islander people (Aust Prescr 2010;33:72-5) fascinating.

My interest is in the possible use of a polypill in this scenario. Trials of the polypill began in Australia early in 2010 and I am interested to know if Aboriginal and Torres Strait Islander people have been included in these trials. I am also curious to know which polypill combinations have been favoured in the studies, either the antiplatelet-ACE inhibitors-statin-thiazide diuretic or the antiplatelet-ACE inhibitors-statin-beta-blocker combination.

Is it not possible that the four-in-one combination would serve to improve adherence to cardiovascular treatment in indigenous communities and help to minimise screening and prevention requirements?

Claude Rigney
Pharmacist
Epping, NSW

Professor Jenny Reath and Associate Professor Ngiare Brown, authors of the article, comment:

The Australia-wide, National Health and Medical Research Council-funded polypill trial to which Mr Rigney refers does include a number of Aboriginal and Torres Strait Islander communities. As for participants in other sites, general practitioners in these communities are advised to choose a formulation relevant to the individual patient. For example, in a patient who has suffered a myocardial infarction, the beta blocker formulation would generally be preferred.

The hope is certainly that use of a polypill formulation will improve adherence and reduce costs.

Combination analgesics in adults

Editor, – Thank you to Dr Murnion for the excellent review of combination analgesics (Aust Prescr 2010;33:113-5). My understanding of the efficacy of codeine is that it is predominantly a prodrug and that the major analgesic effects derive through the actions of two of its major metabolites, codeine-6-glucuronide and morphine.

Under normal circumstances, most of the codeine is metabolised to codeine-6-glucuronide, with perhaps 10% appearing as morphine. The latter is produced through the action of cytochrome P450 2D6. It has been noted that a small proportion of the population have little CYP2D6 and receive less analgesia than expected. A similar effect is noted in those taking drugs such as fluoxetine which inhibit CYP2D6.

The converse is true for those hyper-metabolisers who have multiple copies of CYP2D6 or who take drugs such as dexamethasone which induce the enzyme.

Given the comments by Dr Murnion regarding the usefulness of paracetamol or a non-steroidal anti-inflammatory drug in conjunction with morphine, could she please comment on the possibility of better prescribing codeine (in combination or otherwise) based on the patient's CYP2D6 status.

Peter Bowron
Senior hospital scientist
Toxicology Unit – PaLMS
North Ryde, NSW

Dr Bridin Murnion, the author of the article, comments:

The analgesic efficacy of codeine resides predominantly in the morphine metabolite. Codeine-6-glucuronide is reported to have the low efficacy of the parent compound.[1]

Low efficacy of codeine in those with low activity of CYP2D6 (poor metabolisers) is recognised. In addition, of concern is

the potential for enhanced toxicity in ultra-rapid metabolisers, with reports of a neonatal death.[1]

Understanding of an individual's cytochrome P450 activity profile, and the impact of drugs on this, is of importance in development of new chemical entities and in optimising drug regimens in many therapeutic areas.[2]

Cytochrome phenotyping and genotyping for over-the-counter analgesics containing codeine requires further consideration, but may be of limited value given the likely cost of testing, limited efficacy of these preparations and significant public health concerns around opioid dependence and toxicity from co-ingested paracetamol or non-steroidal anti-inflammatory drugs.

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Hypertension, ACE inhibitors and angioedema

In the review about drug treatment of elevated blood pressure (Aust Prescr 2010;33:108-12), angioedema is not mentioned as a comorbid condition. I believe it would be helpful to do so.

Angioedema occurring with ACE inhibitors was first reported in 1980,[1] and may account for 40% of angioedema presentations to hospital.[2] Onset may be delayed.[3] Epidemiological studies have confirmed a significant excess exposure to ACE inhibitors in patients with angioedema with an estimated attributable risk of 80% (CI* 51–92).[3] An incidence of 0.68% over six months has been reported, so annual incidence may be greater than 1%.[4] Rates in people of African origin are even higher, at 1.62% over six months, so may be over 3% annually.[4] This is relevant in Australia, with recent immigration from Africa.

The importance of the relationship between ACE inhibitors and angioedema is underappreciated. In 2008 a patient reported a history of four episodes of angioedema, including admission to intensive care, followed by use of perindopril. He subsequently had further angioedema and the ACE inhibitor was stopped. In a recent audit of angioedema, four out of 25 patients on ACE inhibitors reported previous (sometimes multiple) episodes of angioedema.[5] In 2010 a 78-year-old woman on trandolapril was referred with her second episode of 'macroglossus of uncertain aetiology'. Unfortunately she developed airway obstruction and died nine days later.

There is a need for increased awareness of angioedema associated with ACE inhibitors, to reduce avoidable catastrophic outcomes. Including angioedema in tables of comorbid conditions to be considered when prescribing antihypertensives would assist with increasing awareness of this important association.

Genevieve Gabb
Consultant physician
Royal Adelaide Hospital

* CI confidence interval

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Tamsulosin-induced intraoperative floppy iris syndrome

Editor, – The medicinal mishap by Dr Fung and Professor McCluskey (Aust Prescr 2010;33:88-9) is perhaps timely due to the increasing use of medical treatments such as tamsulosin for benign prostatic hypertrophy. Intraoperative floppy iris syndrome is well recognised in the ophthalmic community where it has particular implications in cataract surgery.

This case emphasises the need for taking a complete drug history in patients. We specifically ask patients if they have used selective alpha$_1$ adrenergic antagonists, and put a stamp on the front of the history to ensure this is not overlooked if the patient requires cataract surgery in the future.

Given that tamsulosin is prescribed by surgeons in another discipline it is important that urologists or other doctors prescribing this medication in older patients emphasise the risk it poses in cataract surgery. The potential for adverse effects from medical therapy needs to be considered in every patient. I have seen several patients on topical beta blockade for glaucoma develop such significant bradycardias that they have been considered for cardiac pacing before their drug history was properly checked. We need to be alert to the possibilities at all times to reduce the risk of harm to our patients.

Trevor Hodson
Consultant ophthalmologist
Mount Gambier, SA

Non-surgical treatments for skin cancer

***Stephen P Shumack**, Dermatologist, Royal North Shore Hospital, Sydney*

Summary

Skin cancers have traditionally been treated with surgical excision. This is the most effective treatment option, but over the last few decades non-surgical treatments have become available. These include cryotherapy, topical fluorouracil and imiquimod creams, and photodynamic therapy with methyl aminolevulinate hydrochloride. While they may sometimes have a superior cosmetic result, non-surgical treatments should not be used when the diagnosis is unclear or if follow-up is not assured.

Key words: fluorouracil cream, imiquimod cream, photodynamic therapy.

(Aust Prescr 2011;34:6–7)

Introduction

In Australia, the number of skin cancers treated each year exceeds the total number of other cancers treated. Non-melanoma skin cancers are the most common type and include basal and squamous cell carcinomas. Precancerous lesions (solar keratoses) are also extremely common. Other rarer forms of skin cancer such as melanoma and atypical fibroxanthoma are usually surgically removed.

Surgical excision is still the most commonly used and most effective treatment for skin cancers. For the treating practitioner, it provides histopathological confirmation of the diagnosis and evidence of margin control. However, because of the relatively benign nature of non-melanoma skin cancers, other non-surgical treatment options have been developed over the last few decades.

Non-melanoma skin cancers – the problem

Basal cell carcinomas

Statistically we know that almost 50% of Caucasian Australians will develop a basal cell carcinoma before the age of 70. Once a basal cell carcinoma has developed, it is likely that the same person will develop another within three years. They rarely metastasise but can be locally invasive.

Solar keratoses and squamous cell carcinomas

Solar keratoses are premalignant skin lesions that are very common in Caucasian Australians after the age of 45 years. They have a very small risk of transformation (approximately 1%) into squamous cell carcinomas.

Squamous cell carcinomas are potentially more serious than basal cell carcinomas as they can occasionally metastasise and even sometimes prove fatal.

Non-surgical treatments

Given the very large numbers of skin cancers seen in Australia and their relatively benign course, non-surgical treatments, which have minimal morbidity associated with the treatment and in many cases a superior cosmetic result, have been investigated. These non-surgical treatment options, however, are often not as effective as surgical excision and have lower cure rates. They are not generally indicated for treatment of recurrent skin cancers.

Cryotherapy

Liquid nitrogen cryotherapy is the primary treatment for solar keratoses in Australia. Most solar keratoses are treated with a short (2–5 seconds) freeze. This effectively removes about 70% of all solar keratoses treated.

Cryotherapy is most suited for low-risk primary tumours of basal cell carcinoma or Bowen's disease (squamous cell carcinoma *in situ*) on the trunk and limbs. It has lower cure rates on the face so is not recommended for treating facial skin cancers. Cryotherapy should only be used for well-defined skin cancers and is contraindicated for morphoeic basal cell carcinomas.

For basal cell carcinomas, the lesion is marked out with a 1 cm margin. The area is frozen and kept solid for 20–30 seconds, then allowed to thaw for approximately 3–5 minutes before being refrozen for 20–30 seconds. This produces a weeping wound which may take 1–2 months to heal. Because of the slow healing, this treatment should not be used below the knee, particularly in people with compromised circulation. An excellent scar is achieved with liquid nitrogen cryotherapy for basal cell carcinomas although it tends to be hypopigmented so it should not be used in those with pigmented skin.

Bowen's disease can be treated with cryotherapy as a single freeze of approximately 5–10 seconds. Again, healing times can be prolonged so care needs to be used on the lower leg or sites with poor healing. Smaller lesions (<1 cm diameter) are often best treated in this way.

Fluorouracil cream (5%)

This has been available for over 30 years. It is used twice a day for three weeks as a treatment for multiple solar keratoses, particularly on the head and scalp areas. The cream usually produces significant inflammation that will take 1–2 weeks to settle. This can be eased with cold compresses and medium potency steroid creams. The greater the inflammatory reaction,

the more efficacious the treatment.

There are also a small number of case reports indicating that 5% fluorouracil cream can be used quite effectively to treat Bowen's disease. This is usually used twice a day for 4–6 weeks with excellent cosmetic results. Significant inflammation tends to occur during the latter period of this treatment course.

As a general rule, fluorouracil cream should not be used as a treatment for basal cell carcinomas as there is little evidence of its efficacy.

Imiquimod cream (5%)

Topical imiquimod has been investigated as a treatment for solar keratoses and basal cell carcinomas over the last 15 years. Initially it was developed and marketed as a treatment for external genital warts. We know that imiquimod activates the local immune system through toll-like receptor 7. This activation causes an inflammatory reaction which clears cancerous and precancerous cells. There is evidence that imiquimod cream is effective as a treatment for solar keratoses.[1] In Australia, it is approved for three applications a week up to 16 weeks, or alternatively one or two cycles of four weeks of treatment. It produces varying degrees of inflammation but treatment frequency can be titrated to ensure low to moderate inflammation. If significant inflammation develops treatment should be stopped until it has almost subsided. Topical steroid creams should not be used to settle the inflammation as they have a theoretical risk of reducing efficacy.

Imiquimod cream is listed on the Pharmaceutical Benefits Scheme as a treatment for biopsy-proven superficial basal cell carcinomas where other treatment options are unsuitable. The treatment schedule is five times a week for six weeks. Efficacy rates of around 80% are less than with surgical excision but are still acceptable, particularly when considering the sometimes large defects and scars seen with surgical excision.

There have been a number of small case series looking at imiquimod as a treatment for Bowen's disease. This is not an approved indication in Australia, but nevertheless imiquimod does work relatively well in this condition when applied 3–5 times a week for up to six weeks.[2]

Photodynamic therapy

In Australia, photodynamic therapy with red light and methyl aminolevulinate hydrochloride has been approved as a treatment for Bowen's disease, solar keratoses and basal cell carcinoma. Efficacy rates are around 80–85%. The cream is left on for approximately three hours and then a special red light is applied. This can cause some degree of pain during the illumination process. Occasionally the patient needs rest periods or local anaesthetic to reduce the pain. Inflammation occurs after treatment which usually settles within a week or so. Treatment is repeated 1–4 weeks later to ensure high efficacy rates with superficial basal cell carcinoma, thin nodular basal cell carcinoma and Bowen's disease. This is currently not a subsidised treatment in Australia.

For solar keratoses, only a single treatment is usually required and 'field areas' are treated such as the scalp, temples or forehead.

Radiotherapy

This was the traditional non-surgical option for skin cancers and was used commonly until the late 1960s. Since then, the use of surgical excision as a treatment option has increased significantly. Radiotherapy provides an excellent alternative in many cases of non-melanoma skin cancer, particularly when surgery is relatively contraindicated. It is also useful as an adjunctive therapy to surgery in difficult or recurrent cases of skin cancer.

Newer treatments

There are a number of new topical treatments that have been investigated over the last few years. One of these promising products is ingenol mebutate, which was originally developed in Australia. Phase III studies have been undertaken for basal cell carcinoma and solar keratoses.

Conclusion

Given the relatively benign nature of basal cell carcinomas, Bowen's disease and solar keratoses, non-surgical treatment options have been investigated as an alternative to surgery. These have the advantage of often little treatment-associated morbidity for the patient, as well as often a superior cosmetic outcome. The disadvantage is that these treatments are usually not as effective as surgical excision, so regular follow-up (6–12 monthly) over a number of years is required to guard against recurrence at the treatment site.

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Further reading

Basal cell carcinoma, squamous cell carcinoma (and related lesions) – a guide to clinical management in Australia. Sydney: Cancer Council Australia and Australian Cancer Network; 2008.

Dr Shumack has been an investigator and speaker for 3M.

Self-test questions

The following statements are either true or false
(answers on page 31)

1. Cryotherapy is not recommended for treating skin cancers on the face.
2. Fluorouracil cream is an effective treatment for basal cell carcinomas.

Analgesics and pain relief in pregnancy and breastfeeding

***Debra Kennedy**, Director, MotherSafe, Royal Hospital for Women, and Conjoint Lecturer, School of Women's and Children's Health, University of New South Wales, Sydney*

Summary

Women should be reassured that pain can be treated during pregnancy and lactation and that they need not suffer unnecessarily. Overall, appropriate therapeutic doses of the commonly used analgesics including paracetamol, aspirin and opioids have not been associated with an increased incidence of birth defects. The use of non-steroidal anti-inflammatory drugs in the third trimester is not recommended. Untreated persistent pain can have adverse effects for the mother and her pregnancy and women with persistent pain should ideally have optimisation of their pain management before pregnancy.

Key words: codeine, non-steroidal anti-inflammatory drugs, opioids, paracetamol.

(Aust Prescr 2011;34:8–10)

Introduction

Pain during pregnancy may be due to acute conditions such as injury or infection, or secondary to underlying medical disorders such as rheumatoid arthritis. Pain related to pregnancy can also occur.

Inadequately managed persistent pain can result in depression and anxiety. These may impact on a woman's physical and psychological wellbeing and can potentially have an adverse effect on her pregnancy.

Women should not suffer unnecessarily from pain during pregnancy and lactation. If used appropriately, common analgesics such as paracetamol, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are relatively safe.

In counselling women about taking medicines during pregnancy it is always important to emphasise that all couples have a background risk of around 3% of having a baby with a major birth defect and that approximately 15% of all recognised pregnancies end in miscarriage, regardless of any drug exposures. Over 85% of women use some medication during pregnancy and analgesics are the most common preparations used, after vitamins, in all trimesters of pregnancy, with over 50% of women using analgesics during their pregnancy.[1]

The risks or otherwise of drug exposures need to be put into the context of this background risk. Women and their health professionals can then make informed decisions and weigh up the potential risks of treating versus not treating pain during pregnancy and breastfeeding.

Paracetamol

Paracetamol is the analgesic and antipyretic drug most widely used in Australia, particularly by pregnant women. Although it readily crosses the placenta in its unconjugated form, in therapeutic doses it does not appear to increase the risk of birth defects or other adverse pregnancy outcomes. Despite paracetamol's widespread use there are, somewhat surprisingly, no prospective controlled studies about its use in pregnancy.

The drug is not considered to be teratogenic although some retrospective studies including the US Collaborative Perinatal Project found an increased risk of any congenital abnormality and specifically an increase in congenital dislocation of the hip in exposed infants. A registry-based study from Denmark of 26 424 children who were exposed to paracetamol *in utero* during the first trimester found no increase in either the specific or the overall rate of birth defects compared with unexposed controls.[2]

Aspirin

Aspirin is used to treat mild pain and fever, and low-dose aspirin is also prescribed by some obstetricians (often with heparin) to reduce the risk of adverse outcomes in pregnant women with antiphospholipid syndrome and recurrent miscarriages.[3] Overall, aspirin is not associated with an increased risk of congenital malformations, although one meta-analysis suggested an association between first trimester aspirin use and increased risk of gastroschisis*.[4]

NSAIDs

NSAIDs including ibuprofen, naproxen, indomethacin and diclofenac are widely used to treat mild to moderate pain and fever. They are inhibitors of cyclo-oxygenase. In the fetus and newborn, cyclo-oxygenase is a potent dilator of the ductus arteriosus and pulmonary resistance vessels. Its inhibition could potentially cause premature closure of these vessels. These

* an abdominal wall defect resulting from rupture of the amniotic membrane during gut-loop herniation or, later, due to delayed umbilical ring closure

drugs have not been shown to increase the risk of structural birth defects or other adverse outcomes such as preterm delivery or low birth weight. However, a case-control and population-based observational cohort study from Scandinavia demonstrated an increased risk of spontaneous abortion with first trimester use of NSAIDs but with no evidence of other adverse pregnancy outcomes. Major flaws in this study, however, were that it was prescription-based and retrospective and did not control for the indications of use of NSAIDs (such as underlying fever or viral illness).[5]

A Californian study also showed an 80% increase in the risk of miscarriage associated with first trimester use of both aspirin and NSAIDs. This association was not seen with paracetamol.[6]

A suggested mechanism to explain the increased risk of miscarriage is interference with implantation as a result of effects on the prostaglandin pathway. Women who have used NSAIDs inadvertently during the first trimester should be reassured about the use, but other analgesics such as paracetamol should be recommended as preferable options for subsequent use.

Use of NSAIDs after 30 weeks gestation is contraindicated because of their potential to cause premature closure of the fetal ductus arteriosus and persistent pulmonary hypertension. High doses of NSAIDs in the third trimester may also reduce perfusion of the fetal kidneys and decrease fetal urine output. This is why NSAIDs are occasionally used as an intervention to try and reduce liquor volume and the chances of cord entanglement in cases of mono-amniotic twin pregnancy. Most of the cases of reduced output are reversible, but there have been reports of only partial resolution and even of death due to anuric renal failure.[7,8]

As with the older NSAIDs, the main concerns with the COX-2 inhibitors are effects on the ductus arteriosus as well as perfusion of the fetal/neonatal kidney and intestine. Topical NSAIDs generally result in negligible blood levels and would be considered to be relatively safe in pregnancy although absorption is increased by use over a large surface area or the application of heat.

Opioids

Opioids such as codeine, oxycodone, hydromorphone, hydrocodone and morphine, as well as drugs such as pethidine and tramadol, are used to treat moderate to severe pain. Codeine is also widely used in various over-the-counter preparations. Overall, opioid analgesics have not been associated with an increase in birth defects or other adverse outcomes such as miscarriage. There are also reassuring data on longer-term neurodevelopmental follow-up in exposed infants. The main concern about these drugs is that persistent use may lead to dependence and tolerance in the mother with resultant withdrawal (neonatal abstinence syndrome) in the neonate.

Women with persistent pain who may require high doses of opioids during pregnancy should seek advice about optimising their pain management before pregnancy. Sometimes alternative drugs including tricyclic antidepressants may help to control persistent pain and reduce opioid exposure. Tricyclic antidepressants have not been associated with an increased rate of birth defects or long-term neurodevelopmental effects.[9]

Breastfeeding

Paracetamol is considered to be safe for use during lactation. The estimated dose received via breast milk is 6% of the maternal dose. It should be remembered that paracetamol is widely used at doses far greater than this for children.

Use of NSAIDs after 30 weeks gestation is contraindicated

NSAIDs, such as ibuprofen and diclofenac, are considered to be compatible with breastfeeding. The infant doses relative to the maternal doses are 0.65% and 1% respectively, even in women taking high doses – for example diclofenac suppositories 75 mg.[10] The advantage of using these drugs, especially in the immediate postpartum period, is a reduced need for opioids and the potential risks associated with them.

Aspirin is generally not recommended for treatment of pain during breastfeeding mainly because there may be significant adverse effects in infants (the relative infant dose may be as high as 10%) and safer alternatives are available. There is also the theoretical concern that aspirin can cause Reye's syndrome in infants.[10]

Genetic polymorphisms and opioids

Cytochrome P450 2D6 catalyses the O-demethylation of codeine to morphine and genetic polymorphisms in the CYP2D6 gene can affect the metabolism of codeine. One of the polymorphisms may result in reduced efficacy of codeine which can be a potential clinical problem.

The case report of a breastfed neonate, who died following maternal codeine use postpartum, highlights the risks of opioid toxicity in patients with another polymorphism – duplication of the CYP2D6 gene.[11] This results in ultra-rapid metabolism of codeine and significantly increases the production of morphine. In adults this can lead to significant opioid toxicity despite small doses of drug, and thus breastfed infants of such patients are also at risk of serious toxicity. The incidence of this gene duplication varies in different populations, from approximately 1% in Denmark and Finland to 10% in Greece and Portugal and up to 30% in Ethiopia.

There are also other genetic polymorphisms involved in morphine metabolism that theoretically could reduce its clearance.

Caution needs to be exercised in terms of breastfeeding and minimising the risk of opioid toxicity in both mothers and babies. Short-term use is unlikely to pose a significant risk but longer-term or chronic use can be potentially dangerous, particularly

in those people who are ultra-rapid metabolisers due to the CYP2D6 duplication. Mothers and babies should be carefully observed and monitored for signs of opioid toxicity. In most cases the occurrence of central nervous system depression with opioids is consistent between mother and baby (although babies appear to be more sensitive to the effects of opioids) and so if a mother appears to have adverse effects of opioids there should be a low threshold for examining the baby and excluding toxicity.[12] If longer-term pain relief is required, then other drugs such as NSAIDs should be considered as first-line treatment.

Conclusion and recommendations

At MotherSafe we reassure women regarding inadvertent NSAID use, but recommend paracetamol as first-line treatment of fever and pain during pregnancy. Codeine or another opioid analgesic can be added to treat more severe pain. NSAID use is contraindicated in the third trimester and alternative analgesics should also be considered in the first trimester.

Women and their doctors should however be reassured that there are safe options to treat pain, both acute and chronic, during pregnancy and breastfeeding.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 31)

3. Paracetamol does not cross the placenta.
4. NSAIDs should be avoided during the third trimester.

Dental notes

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

Analgesics and pain relief in pregnancy and breastfeeding

Dentists often advise patients regarding pain management for dental pain and generally the recommendation for pregnant women to use paracetamol, as the first-line treatment of fever and pain, is reasonable. However, on occasions the dental pain experienced will warrant the short-term use of drugs which include therapeutic doses of codeine. The use of these drugs for short-term treatment (2–3 days) in women who are pregnant or breastfeeding should not pose any adverse risk.

It is probably prudent for dentists not to prescribe non-steroidal anti-inflammatory drugs for pain relief during pregnancy. If their patients are experiencing profound, persistent pain it would be advisable to liaise with the patient's medical practitioner for appropriate management. Importantly, accurate diagnosis and timely dental treatment will dramatically and effectively reduce the pain for these patients. This will diminish the requirement for systemic pain relief.

Book reviews

Pregnancy and breastfeeding: medicines guide

Melbourne: Pharmacy Department, Royal Women's Hospital; 2010.

346 pages. Price $93.50 incl postage, discount for bulk orders

***David M Pache**, Senior clinical pharmacist, Mater Pharmacy Services, and Conjoint lecturer, School of Pharmacy, University of Queensland*

The Royal Women's Hospital of Melbourne has updated information previously published as two volumes ('Drugs and pregnancy' and 'Drugs and breastfeeding') to create this new, combined resource. It includes over 900 drugs available in Australia. This book is not a pocket-sized reference, however the ring-bound format means that it is easily left open on the desk.

Following the introduction and guidelines for use, the general medicines information section provides broad, but somewhat limited, details on selected pharmacotherapeutic classes. Substances of dependence are included here, but drugs with therapeutic indications possess individual monographs (for example, compare amphetamine with dexamphetamine). Interestingly, the topic of smoking is covered under the entry of nicotine.

Future volumes would be enhanced by expansion and referencing to pertinent sources in the bibliography located at the back. The table covering complementary and alternative medicines, though not exhaustive, is useful. An expanded version covering more herbal remedies had been included in the previous 'Drugs and pregnancy' edition, but this time implications for lactating mothers have been addressed.

Drugs are listed alphabetically. Preferences for arranging drug names tend towards their full description. For example, valproate is found under sodium valproate, rather than its parent acid and pharmacologically-active component. Abbreviations have been used throughout, but these are clearly explained in the 'Guidelines for use'.

This is a straightforward, no-nonsense reference tool that provides clear, succinct clinical information and advice on medications in respect of their use for pregnant and lactating women. The simplicity of presentation improves accessibility across health disciplines. Purists might decry the absence of detailed critical evaluation of significant trials, but this book is intended for health professionals requiring advice for immediate action. A brief perusal of the bibliography indicates references mostly sourced from the last decade with a clear attempt to be as up to date as possible for certain more sensitive topics, such as epilepsy.

In summary, a very useful, easily accessible tool, produced by an experienced team for health professionals faced with ever-increasing demands on their time.

Therapeutic Guidelines: Palliative Care. Version 3.

Melbourne: Therapeutic Guidelines Limited; 2010.

361 pages. Price $39, students $30, plus postage. Also available in electronic formats as eTG complete.

***Philip Lee**, Senior staff specialist, Palliative medicine, Westmead Cancer Care Centre, Westmead Hospital, Sydney*

The third edition of Therapeutic Guidelines: Palliative Care has been prepared by an expert group of experienced palliative care clinicians. This book is an excellent source of concise information about common palliative care problems encountered by health workers who are involved in the care of patients with a life threatening and terminal illness. It is a useful guide for those currently working in the field of palliative care, those undertaking training and clinicians who may occasionally provide palliative care for a patient.

The first few chapters present an easy to read overview of palliative care principles, the holistic approach to providing palliative care and a description of the multidisciplinary team approach to modern palliative care. There are chapters, which cover the emotional, ethical, and communication challenges which face all those who care for patients at the end of life. This also includes a chapter on the emotional care of health professionals in a field in which burnout and stress are all too common. An excellent chapter 'Pertinent practical points' gives expansive answers to frequently asked questions.

The largest part of the book deals with clinical management of common problems and gives an excellent overview of frequently used drugs. These drugs can be challenging to clinicians who primarily work outside palliative care. There are a number of drugs used 'off-label' and some unregistered drugs, such as cyclizine and levomepromazine, are obtained through the Special Access Scheme of the Therapeutic Goods Administration.

The final chapters cover the most common symptoms that patients present with, including pain, fatigue, gastrointestinal, respiratory and psychiatric symptoms. The approach of assessing and managing each symptom is systematic and well described.

This book is an excellent, succinct source of reliable palliative care information. It is also available in an electronic version, which includes all the supporting references.

Thyroid function tests

***Robin H Mortimer**, Professor, Department of Endocrinology, Royal Brisbane and Women's Hospital, and the University of Queensland, Brisbane*

Summary

Thyroid disorders can be difficult to detect clinically, but thyroid function tests can assist in making a diagnosis. Measuring thyroid stimulating hormone is the first step. If it is abnormal, free thyroxine should be measured. A raised concentration of thyroid stimulating hormone with a low concentration of free thyroxine suggests hypothyroidism. A low concentration of thyroid stimulating hormone with a high concentration of free thyroxine suggests hyperthyroidism. Measuring thyroid autoantibodies may help establish the cause of the dysfunction. Different assays can give different results, and tests of thyroid function may be affected by drugs and intercurrent illness.

Key words: thyroxine, triiodothyronine, thyroid stimulating hormone.

(Aust Prescr 2011;34:12–15)

Introduction

The thyroid gland secretes thyroxine (T_4) and triiodothyronine (T_3). These hormones are essential for normal growth, development and metabolic function.

Altered thyroid function is common. For example, the prevalence of hypothyroidism may be up to nearly 10% of the general population.[1] As thyroid disorders may not present with classical clinical signs, it is essential to have accurate assays of thyroid function to assist in the diagnosis.

Thyroid physiology (Fig. 1)

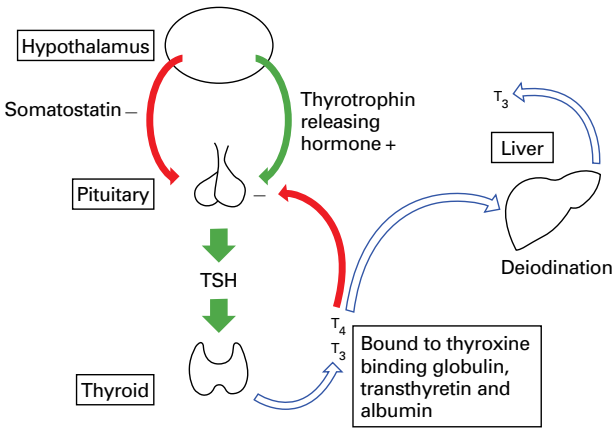
The thyroid gland actively transports diet-derived iodide from the blood by means of a cell membrane iodide pump called the sodium-iodide symporter. Iodide then combines with tyrosines in thyroglobulin, mediated by thyroperoxidase, to form T_4 (4 iodine atoms) or T_3 (3 iodine atoms). The uptake of iodide and the release of T_4 and T_3 are enhanced by thyroid stimulating hormone (TSH) which is secreted by the pituitary gland.

About 90% of thyroid hormone released is T_4 and 10% is T_3. In some hyperthyroid states the ratio of T_3 to T_4 is higher. Both hormones are co-secreted with thyroglobulin and circulate in blood bound to thyroid hormone binding proteins (thyroid binding globulin, transthyretin and albumin). A very small unbound ('free') fraction is available for uptake by cells. Much of the T_3 in the blood is generated by the liver after enzymatic removal of an iodine atom from T_4.

TSH secretion is mainly regulated by circulating T_4 (which is deiodinated to T_3 in the pituitary) and to a lesser extent by circulating T_3. There is a classical negative feedback loop between T_4 and TSH. This is log-linear (log TSH is inversely proportional to free T_4), which means that small changes in free T_4 cause large

Fig. 1

Pituitary-thyroid physiology



The hypothalamic hormones thyrotrophin releasing hormone and somatostatin stimulate or block secretion of thyroid stimulating hormone (TSH). TSH stimulates iodide uptake by the thyroid and synthesis of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). T_4 and T_3 circulate bound to the thyroid hormone binding proteins (thyroxine binding globulin, transthyretin and albumin). A very small free fraction of thyroid hormone is available for cellular action. T_4 is deiodinated in liver and other tissues to form the more biologically active T_3. T_4 is also deiodinated in the pituitary to T_3 which inhibits TSH secretion.

inverse changes in TSH concentrations. TSH secretion is also regulated by the hypothalamic hormones thyrotrophin releasing hormone (stimulating) and somatostatin (inhibiting).

Blood tests relevant to thyroid disease

TSH is the hormone which is usually tested. It is the only test funded by the Medicare Benefits Scheme to screen for thyroid disease when there is no history of thyroid problems.

Thyroid stimulating hormone

TSH is a sensitive marker of thyroid function because it is influenced by small changes in free T_4 concentrations. A low TSH usually indicates hyperthyroidism whereas raised TSH usually means hypothyroidism. Over the years the lowest concentration of TSH which can be detected by assays has progressively fallen, allowing better separation of normal and hyperthyroid states.

Thyroid hormone assays

Only very small fractions of thyroid hormones are not bound to protein. These free thyroid hormones are the physiologically important thyroid hormones in blood. Modern immunoassays that estimate free hormone concentrations are widely available.

Changes in serum albumin concentrations, abnormal binding proteins, free fatty acids and drugs such as heparin, frusemide and phenytoin may interfere with these assays. Most laboratories now use chemiluminescent methods that are more (but not completely) resistant to such interference. When results do not fit into a recognised pattern the laboratory should be consulted to identify such interferences.

Thyroid-related autoantibodies

If a person has altered thyroid function, testing for thyroid antibodies helps to determine if they have an autoimmune condition.

Thyroperoxidase autoantibodies

Thyroperoxidase antibodies are also known as thyroid microsomal antibodies. They are present in autoimmune thyroid disease, but there is debate about whether low levels are always pathological. Unfortunately, there are significant differences between laboratories when the same sera are studied, and lower detection limits are variable. Assay sensitivities and reference ranges can therefore vary quite widely.

Thyroperoxidase antibodies can cause hypothyroidism in at least two ways. Firstly they can block thyroperoxidase thereby inhibiting T_4 and T_3 synthesis and secondly through antibody-dependent cell cytotoxicity and thyroid inflammation. Low concentrations may not be associated with evidence of thyroid dysfunction, but the incidence of raised TSH increases as antibody levels rise. The prevalence of positive antibody levels and mild hypothyroidism increases with age.

The concentration of thyroperoxidase antibodies may fluctuate in patients with autoimmune thyroid disease. This has no clinical significance and repeated measurements are not recommended. Maternal thyroperoxidase antibodies cross the placenta, but their effects on fetal thyroid function are unclear.

Thyroglobulin autoantibodies

Thyroglobulin autoantibodies are also a marker of autoimmune thyroid disease, but are less common than thyroperoxidase antibodies. Thyroglobulin autoantibodies do not inhibit thyroperoxidase or mediate antibody-dependent cell cytotoxicity and are therefore markers rather than mediators of autoimmune thyroid disease. There are considerable variations in sensitivity and reference ranges between assays. Other autoimmune diseases can also increase the concentration of thyroglobulin autoantibodies.

TSH receptor autoantibodies

TSH receptor autoantibodies may stimulate or less commonly block the TSH receptor. Stimulating antibodies cause Graves' disease and probably also cause the associated ophthalmopathy. Blocking antibodies can cause hypothyroidism. The assay of TSH receptor autoantibodies done in clinical laboratories cannot distinguish between stimulating or blocking antibodies. This is not usually relevant as clinical hyperthyroidism would suggest that the dominant antibody is stimulatory.

Measuring TSH receptor autoantibodies can be useful if the cause of hyperthyroidism is not apparent. However, initial hopes that remission of Graves' could be predicted by falling autoantibody levels have not been supported by most studies.

Measurements of TSH receptor autoantibodies do have an important role in managing pregnant women with Graves' disease. High concentrations of maternal TSH receptor autoantibodies can predict fetal and neonatal hyperthyroidism. It is important to recognise that TSH receptor autoantibodies do not always fall after successful treatment, so pregnant women with a previous history of Graves' disease should be screened for TSH receptor autoantibodies.

Thyroglobulin

Thyroglobulin, a large glycoprotein, represents about 80% of the wet weight of the thyroid and is co-secreted with thyroid hormone. Concentrations are high in patients with raised TSH concentrations or nodular goitres, but it is not clinically useful to measure thyroglobulin in these situations.

Most papillary and follicular carcinomas synthesise and secrete thyroglobulin, but raised thyroglobulin levels are not a reliable indicator or screening test for thyroid malignancy. Thyroglobulin concentration becomes a useful marker of remaining or recurrent cancer in patients who have had a total thyroidectomy and remnant ablation with radioiodine for papillary and follicular carcinoma.

Unfortunately, up to 20% of patients with differentiated thyroid cancer have thyroglobulin autoantibodies that interfere with the thyroglobulin assay, leading to underestimation of thyroglobulin concentration. Thyroglobulin autoantibodies should therefore be measured, with a sensitive assay, on all thyroglobulin samples.

Reference ranges

As most commercial assays do not physically measure the analyte, results given are always an approximation of actual levels. Each assay, even for the same analyte, will therefore give slightly different results because of intrinsic variations in the reagents used and the effects of interfering illnesses and substances. Free T_3 levels are the most variable between assay methods.

Reference ranges are altered by ethnicity, age and iodine intake. In Australia these factors are probably not clinically significant. Different ranges also apply in pregnancy, neonates and very young children.

Reference ranges are defined as those into which 95% of a normal population fall. (Accordingly 2.5% of normals will have higher and 2.5% will have lower results than the reference range.) Each assay must therefore be interpreted in terms of its own reference range. The practical implications of this are that blood test results from different laboratories may not be directly comparable and their interpretation requires examination of the reference ranges.

Reference ranges change in pregnancy. In early pregnancy chorionic gonadotrophin is secreted by the placenta in large amounts. This is structurally similar to TSH (but is not measured by the TSH assay) and stimulates the maternal thyroid. This leads to increased maternal thyroid hormone secretion and a reduced maternal TSH. Occasionally women develop mild hyperthyroidism in the first trimester, especially if they have hyperemesis.

Detecting and confirming thyroid dysfunction (Table 1)

The inverse log-linear relationship between free T_4 and TSH means that TSH concentrations are sensitive indicators of thyroid dysfunction. A raised TSH suggests hypothyroidism[2] while a low TSH suggests hyperthyroidism. There are other causes of low TSH concentrations, notably hypothalamic-pituitary disease, but this is very uncommon in the general population. The finding of an abnormal TSH should lead to measurement of free T_4 levels.

Interpretation of thyroid function tests may be particularly difficult if the patient is systemically ill. Starvation or severe illness can be associated with dysregulation of TSH secretion and reduced deiodination of T_4 to T_3 (the 'sick euthyroid' syndrome). Low TSH and T_3 levels are typical and can cause diagnostic confusion.

Very occasionally a raised TSH with a normal free T_4 relates to interference in the TSH assay. Very rarely, thyroid hormone resistance or a pituitary TSH-secreting adenoma is associated with a mildly raised TSH in the presence of a raised free T_4.

Treatment with amiodarone is often associated with abnormal thyroid function tests. The most common finding is a raised TSH caused by inhibition of pituitary T_4 to T_3 conversion, but true hypothyroidism and hyperthyroidism can occur. Diagnosis and management may be complex and require expert advice.

Hyperthyroidism

A low TSH and raised free T_4 indicate hyperthyroidism and should lead to consideration of causation and treatment. The majority of younger patients will have Graves' disease, but older patients are more likely to have nodular thyroid disease.

Table 1

Common results of thyroid function tests

Thyroid stimulating hormone	Free thyroxine	Free tri-iodothyronine	Thyroperoxidase and thyroglobulin autoantibodies	Comment
↔	↔	↔	↔	Normal
↑	↓	↓	↑	Primary hypothyroidism (Hashimoto's)
↑	↔	↔	↑	Subclinical hypothyroidism (Hashimoto's)
↓	↑	↑	↑	Hyperthyroidism (consider Graves', measure TSH receptor autoantibodies)
↓	↔	↔	↔	Subclinical hyperthyroidism (consider nodular thyroid disease)
↔↓	↓	↓	↔	Consider pituitary disease
↓	↔	↑	variable	T_3 toxicosis

↔ normal ↑ raised ↓ reduced

Transitory hyperthyroidism can be seen in patients with viral thyroiditis. Most have had a recent upper respiratory tract infection and present with neck tenderness and pain, which may be referred to the ear.

Some patients have a low TSH but normal free T_4. Measurement of free T_3 can then be helpful as some patients will have T_3 toxicosis caused by overproduction of T_3. If T_3 is not raised a repeat measurement of T_4 and TSH is warranted. This may show normal values, but a persistently low TSH with a normal free T_4 suggests autonomous thyroid function and a diagnosis of 'subclinical hyperthyroidism', which is usually associated with a nodular goitre (or, unusually, hypothalamic-pituitary disease). Subclinical hyperthyroidism in the elderly is associated with an increased risk of atrial fibrillation, stroke and osteoporosis.

Hypothyroidism

A raised TSH and a low free T_4 indicate primary hypothyroidism, almost always due to autoimmune thyroid disease but sometimes due to previous surgery or radioiodine administration. The incidence of raised TSH and thyroid antibody levels and hypothyroidism increases with age and is significantly more common in women.

It is not uncommon to find a raised TSH but normal free T_4. In most cases this suggests autoimmune thyroid disease. This subclinical hypothyroidism is more likely to progress to overt hypothyroidism when higher levels of TSH and thyroid autoantibodies are present.

Asymptomatic patients with a raised TSH and normal free T_4 require regular monitoring, especially if they are elderly or have high levels of antithyroperoxidase autoantibodies. Every six months is probably sufficient.

There is considerable debate about the normal upper limit of the TSH reference range. The high background prevalence of autoimmune thyroid disease as well as the age, iodine status, smoking prevalence and ethnicity of the 'normal' population has raised the 'normal' upper limit. In people without these factors the upper limit is probably 2.5 mIU/L. While mildly raised TSH levels rarely require treatment, a concentration above 4.0 mIU/L and the presence of thyroid antibodies is predictive of eventual hypothyroidism and indicates that these patients need to be followed up.[3]

Adjusting thyroxine treatment

Replacement thyroxine in hypothyroid patients should be adjusted to maintain TSH at about 2 mIU/L. It takes about six weeks for a change in thyroxine dose to achieve stable concentrations of free T_4. Changes to the dose of thyroxine, and tests of thyroid function, should not be done more frequently, unless clinically indicated. It is not uncommon for patients who are less than optimally compliant with recommended thyroxine treatment to take several tablets before a doctor's visit. This may be associated with a raised TSH, but normal free T_4.

Many patients with a history of differentiated thyroid cancer are advised to take suppressive doses of thyroxine. Guidelines[4] suggest that with persistent disease TSH should be kept below 0.1 mIU/L. Patients who presented with high-risk disease, but who are clinically free of disease, are advised to maintain TSH between 0.1 and 0.5 mIU/L for 5–10 years. Advice from commercial pathology laboratories that thyroxine doses be reduced in these patients should be resisted.

Adjusting treatment for hyperthyroidism

TSH may remain suppressed for weeks or even months after a patient starts antithyroid medications. It is useful to monitor free T_4 and free T_3 every 6–12 weeks to judge the adequacy of treatment. A rise in TSH indicates overtreatment. Patients with severe hyperthyroidism may need more frequent monitoring.

Conclusion

Thyroid dysfunction is common in the general population and TSH measurements provide a sensitive method for detection. An abnormal TSH requires further investigation, including at least measurement of free T_4. Interpretation of the results of thyroid function tests is facilitated by an understanding of thyroid hormone physiology, especially the normal inverse relationship between free T_4 and TSH concentrations. Variations in assay performance mean that it may be helpful to consistently use the same laboratory for an individual patient. An understanding of the effects of severe illness and medications on test results is also important.

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Conflict of interest: none declared

Managing delirium in older patients

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Summary

Delirium is an acute syndrome characterised by altered levels of consciousness, attention and cognitive function. It has many causes and frequently leads to, or occurs during, hospitalisation. Delirium requires urgent medical assessment. Unfortunately, the diagnosis is often missed. It is best treated by multidisciplinary intervention, addressing risk factors, treating underlying causes and minimising harm. Part of its management may be pharmacological, firstly ceasing drugs which may precipitate delirium – especially those with anticholinergic properties – and secondly, cautious use of antipsychotics for hyperactive symptoms.

Key words: aged, antipsychotic, dementia.

(Aust Prescr 2011;34:16–18)

Introduction

Delirium is an acute syndrome of altered level of consciousness, decreased attention and cognitive function, usually coming on over hours or days. It occurs most often in older people, associated with acute medical or surgical illness. It is commonly seen during hospitalisation – it affects up to a quarter of older hospitalised people on admission to hospital and a half can develop delirium during the admission.[1] Delirium may also develop at home, and is common in post-acute care, residential aged care and palliative care settings.

Symptoms

The symptoms of delirium usually fluctuate throughout the day and night, with disturbance of the sleep–wake cycle resulting in agitation at night and drowsiness during the day. The presentation varies, ranging from the floridly agitated, hyperalert, hyperactive patient to the drowsy, hypoalert patient sleeping quietly in their bed. Many patients have a mixture of symptoms including inattention, varying degrees of consciousness, hallucinations and delusions. Hypoalertness in patients is often mistaken for dementia, resulting in delayed or missed opportunities for therapeutic intervention.

Risk factors

Despite being so common, the pathophysiology of delirium is poorly understood. Susceptibility to this condition reflects a balance between the severity of the insult and the frailty of the central nervous system, so anyone can get delirium. It is not unusual in patients in intensive care or young people using recreational drugs.

Risk factors for delirium include dementia, older age, multiple comorbidities, psychoactive medication use, sleep deprivation, dehydration, immobility, pain, sensory impairment and hospitalisation. Delirium is closely linked to dementia – each is a risk factor for the other – and it is now recognised that delirium can cause irreversible decline in cognitive and physical function, as well as increased mortality and nursing home placement.

Frail older patients may present with delirium triggered by many medical or surgical problems (see box), often more than one at a time, so delirium presents a diagnostic challenge. Because it may be the only presenting symptom of a rapidly deteriorating patient, delirium is a medical emergency.

Preventing or reducing delirium

Multicomponent interventions have reduced aspects of delirium[2] such as delirium incidence, severity and duration, though not all three simultaneously. The Hospital Elder Life Program (HELP) (www.hospitalelderlifeprogram.org), administered by volunteers and ward staff, addresses six of the risk factors for delirium, namely cognitive impairment, sleep deprivation, immobility, dehydration and visual and hearing impairment. The program recommends the following:

- reorient and mobilise the patient
- reduce sensory deprivation
- ensure the patient is hydrated
- implement a non-pharmacologic sleep regimen
- limit catheters and restraints.

Box

MISTE – a mnemonic for possible causes of delirium

M	metabolic – hyponatraemia, hypoglycaemia, hypoxaemia
I	infective – urinary tract infection, pneumonia
S	structural – subarachnoid haemorrhage, urinary retention
T	toxic – drugs (e.g. digoxin, lithium) or poisons
E	environmental – being in hospital or the emergency department

Intensive orthogeriatric services, involving daily geriatrician review starting before surgery, reduce delirium in hip fracture patients.[3] An Australian study found that multidisciplinary geriatric rehabilitation in the home reduced the incidence of delirium compared to when it was given in hospital.[4] Haloperidol prophylaxis for hip surgery patients had no effect on delirium incidence, but did reduce the severity and duration,[5] whereas risperidone after cardiac surgery was found to reduce the incidence of delirium.[6]

Diagnosis and initial management

The crucial, and unfortunately, often missing step in delirium management is diagnosis. Given the large and increasing number of older patients in hospital, screening for delirium should become part of routine observations, at least for high-risk patients. However, some training of staff is required.

It is very useful, when unsure if a patient's poor cognitive status is new or pre-existing, to ask their family or carer whether they are usually like this.

Once delirium is identified, initial management aims to detect and treat underlying medical and surgical causes. The list of possible causes is long, and the simple mnemonic MISTE serves as an aide-memoire to categorise potential causes (see box). A comprehensive assessment including history, examination and appropriate investigations is required when delirium is detected, because many older patients have more than one diagnosis contributing to their delirium.

After delirium has developed, addressing the six HELP risk factors is useful. Managing a patient with hyperactive delirium can be a challenge on any ward. Restraints should be avoided, as they aggravate delirium, as well as increase injuries and falls. Where suitable, asking family to be present as much as possible, even organising a roster of relatives, generally helps to calm agitated patients. If this is not an option, ask an assistant-in-nursing to sit with the patient. A delirium room or ward where a calm, comfortable environment can be maintained is most beneficial for patients. Familiar objects or photographs from home also help.

It is important to prevent complications so, for example, agitated patients who keep climbing out of bed may be nursed on low-low beds or mattresses placed on the floor. It is preferable to allow an agitated patient to pace around a secure delirium ward than to sedate them as this can lead to hypostatic pneumonia or pressure sores.

Designing appropriate and safe facilities to manage patients with delirium should be a priority in building new hospitals. As patients may become delirious on any ward in the hospital it is useful to have a support person, such as a clinical nurse consultant, who can advise and train staff around the hospital.

Pharmacological management

Appropriate management of the underlying condition(s) and the drugs that the patient is taking, remains the mainstay of delirium treatment.

Stopping drugs that cause delirium

The importance of reducing or ceasing drugs that exacerbate delirium cannot be overemphasised. This highlights the importance of a thorough medication review. While anticholinergics and psychoactive medications (including antiepileptic and pain medications) are important, other drugs such as NSAIDs and sotalol may also contribute to the problem (see box). Even drugs that are used to treat delirium, particularly if given in excess, can prolong or worsen delirium. It is also important to enquire about over-the-counter and complementary medications, such as European mandrake or scopolia which have marked anticholinergic properties, as these may precipitate delirium.

Drug therapy for delirium

Drug therapy is reserved for patients who are at risk of harming themselves or others, for example by pulling out essential medical devices or lines. Drug treatment for delirium is an understudied area, with only a limited number of small trials to guide management. There are very few data comparing different drugs. The choice of drug is not guided by an understanding of the pathophysiology of delirium, which remains imprecise.

Antipsychotics

If drugs are needed, antipsychotics are generally accepted as first-line, except in delirium tremens. However, phenothiazine antipsychotic drugs such as chlorpromazine, which have prominent anticholinergic properties, should be avoided in older patients. Always remember the essential aphorism of geriatric pharmacology: start low and go slow. Suggested initial doses are haloperidol 0.5 mg, risperidone 0.5 mg or olanzapine 2.5 mg. Depending on the response additional doses can be given after 2–4 hours, otherwise daily. However for the more frequent dosing, the patient should be closely monitored for over-sedation.

Efficacy

A number of small trials have shown that typical (particularly haloperidol) and atypical antipsychotics improve hyperactive symptoms, such as agitation, restlessness, thought and perceptual disturbance, and shorten the duration of delirium. Hypoactive symptoms such as drowsiness and sedation may be exacerbated. There is no clear evidence that atypical antipsychotics are more effective than typical antipsychotics, but they appear to have fewer extrapyramidal adverse effects.

Adverse effects

Extrapyramidal effects include akathisia (motor restlessness and muscular tension especially in the legs) and parkinsonism. These may occur in over half of older patients on antipsychotics, with the risk increasing with higher doses and longer duration of treatment.

Antipsychotics may prolong the QT_c interval. Neuroleptic malignant syndrome, a rare but potentially fatal disorder, is also more common with typical antipsychotics. It develops over 1–3 days, and symptoms include fever, extrapyramidal dysfunction with tremor and marked rigidity, autonomic disturbance including tachycardia and hypo- or hypertension, elevated creatine kinase and white cell count, and myoglobinuria. If suspected, antipsychotics should be ceased immediately and supportive measures instituted, including intravenous fluids.

Other adverse effects of antipsychotic drugs that affect older people during short-term treatment are sedation, orthostatic hypotension, epileptic seizures, weight gain and disturbed glucose and lipid metabolism. Sedation may, at times, be a desired effect but at other times it is an adverse effect, prolonging the delirium and increasing the risk of falls and fractures.

Evidence has emerged of an increased risk of stroke in older patients with dementia taking atypical antipsychotics, however the risk is thought to be similar with typical drugs.

Other drugs

Benzodiazepines are the treatment of choice for delirium tremens and delirium associated with benzodiazepine withdrawal. They can also be used in patients with neuroleptic malignant syndrome, Parkinson's disease or Lewy body dementia. However, the atypical antipsychotics may be used with caution in the latter two conditions.

Although anticholinergic drugs can contribute to the development of delirium, and ceasing them often helps improve delirium, there is no randomised evidence that the cholinergic drugs used to treat dementia (donepezil, galantamine or rivastigmine) have a role in the treatment of delirium.

Conclusion

Delirium is a common emergency, with high mortality rates, affecting older patients. Timely diagnosis, investigation, multicomponent intervention and judicious use of medications to treat and protect the patient can improve the chances of a good outcome. It is imperative that any hospital caring for significant numbers of older patients maintains a coordinated, multifaceted response to delirium.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false

(answers on page 31)

5. Dehydration is a risk factor for delirium in older people.
6. Benzodiazepines are recommended for the treatment of delirium tremens.

Caution with complementaries for cognitive impairment

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Summary

As the Australian population ages the burden of dementia is increasing. Conventional drug treatment only provides modest benefits for patients, so patients and their carers often turn to complementary medicines. Early trials showed promise for some compounds but larger better conducted studies have usually failed to confirm these benefits. However, there have been few large-scale interventions using complementary medicines for cognition. Health professionals should always ask patients (and their carers) if complementary medicines are being taken because adverse effects and interactions with conventional drugs can occur.

Key words: dementia, *Ginkgo biloba*, vitamin E.

(Aust Prescr 2011;34:19–21)

Introduction

In Australia around 200 000 people currently have dementia, including up to half of all patients in residential aged-care facilities. Given the projected rise of Australia's aged population, these numbers are likely to double in the next 20 years.[1]

Conventional drug treatment only provides modest benefits to patients with dementia and does not modify the underlying pathological progression. Patients and their carers may turn to complementary medicines, but this course of action is not without risk. Research by the National Prescribing Service (NPS) has shown that almost half the consumers surveyed had not discussed their use of complementary medicines with their doctors. Similarly, only half the general practitioners surveyed had asked their patients if they took these medicines. In addition, many general practitioners and pharmacists were unaware of the adverse effects of commonly used complementary medicines and their potential interactions with conventional medicines.[2]

Quality and safety

One of the main concerns with herbal products is variation in their active components, not all of which are known or standardised by regulation. A specific herbal product that has been shown to be efficacious in clinical trials may be materially different from another sold under the same name by another company. Patients (and carers) should ask whether the specific brand of complementary medicine they are considering buying has been clinically trialled. They should also check for an Aust L (listed) or Aust R (registered) number on the pack.[3]

A listed product only meets the standards of the Australian Therapeutic Goods Administration (TGA) for good manufacturing practice, while a registered product has clinical evidence which has been assessed to show that the product is efficacious.[3] Most complementary medicines are listed products and the TGA does not usually check the claims made for these products.

Perhaps the most important issue surrounding the use of herbal medicines is patient safety. While listed products are regarded by the TGA as 'relatively low risk', their safety has usually not been systematically studied in the same manner as it is for registered pharmaceutical products. There are few large-scale trials and they rarely assess safety as well as efficacy. It is difficult to make confident predictions about safety and most information comes from single case studies. Until systematic evidence emerges from carefully controlled studies, physicians should adopt cautious strategies in treating and advising patients who take complementary medicines, particularly if there are known herb–drug interactions.

Ginkgo biloba

There are 122 products whose name contains *Ginkgo biloba* listed on the Australian Register of Therapeutic Goods (ARTG). It is one of the commonest herbal medicines taken to prevent or treat cognitive impairment. Claims include, 'helps to improve blood flow to the brain' and 'improves memory and cognitive function'. There is some evidence that taking ginkgo leaf extract orally modestly improves symptoms of Alzheimer's, vascular, or mixed dementias, but this comes from poor quality studies.[4]

A study, funded by the US National Center for Complementary and Alternative Medicine, of the well-characterised ginkgo product EGb-761 found it ineffective in lowering the overall incidence of dementia and Alzheimer's disease in the elderly. Further analysis also found ginkgo to be ineffective in slowing cognitive decline. This trial recruited more than 3000 volunteers aged 75 and over who took 240 mg of ginkgo daily, and followed them for around six years.[5,6] Some smaller studies for

memory enhancement have had promising results, but a trial sponsored by the US National Institute on Aging of more than 200 healthy adults over age 60 found that ginkgo taken for six weeks did not improve memory.[7]

A recent press release reports that the IPSEN GuidAge study, involving 2854 participants aged 70 years or older complaining of memory problems, showed a statistically significant decrease in progression to Alzheimer's disease. The study authors conclude that the difference between their results and those of the earlier US study is due to differences in compliance.[8] At this stage the results should be treated with caution as they have not yet appeared in a peer-reviewed publication.

Adverse effects of ginkgo can include headache, nausea, gastrointestinal upset, diarrhoea, dizziness, or allergic skin reactions. Severe allergic reactions have occasionally been reported. There are case reports suggesting that ginkgo can increase the risk of bleeding.[9] It is therefore recommended that patients be cautioned if they take aspirin, warfarin or other antiplatelet or anticoagulant drugs, have bleeding disorders, or are expecting to have surgical or dental procedures.[4]

Vitamin E

A variety of antioxidants and free radical scavengers including vitamin E have been promoted for use in Alzheimer's disease. A recent Cochrane review concluded there is no evidence of efficacy of vitamin E in the prevention or treatment of Alzheimer's disease.[10] While oral vitamin E seldom causes immediate adverse effects, another Cochrane review suggested that vitamin E supplementation may increase mortality.[11]

Brahmi and Gotu Kola

There are 32 products on the ARTG whose names include *Bacopa monnieri* (Brahmi) or *Centella asiatica* (Gotu Kola) often combined together, with or without *Ginkgo biloba*. Claims include, 'traditional Asian and Ayurvedic herbs in a triple action synergistic formula to help improve memory retention, learning, concentration, alertness'. There is increasing evidence that standardised extracts of Brahmi, administered for at least three months, improve some aspects of cognition in healthy people but these observations need to be replicated in larger trials. A recent comprehensive review of the effect of bacopa extract on cognition in healthy people reported that of the seven known chronic trials in this area all showed significant cognitive improvements (Stough, unpublished, 2011).

There are no published randomised controlled trials of these herbs in dementia, either alone or in combination. A recent open-label study, in which five patients with Alzheimer's disease were given 300 mg of bacopa extract for six months,[12] found that four improved their Mini Mental State Examination scores and three improved on the Alzheimer's Disease Assessment Scale–cognitive subscale. Clearly, larger randomised double-blind trials are required.

While adverse effects appear uncommon, there have been three cases of hepatotoxicity associated with Gotu Kola.[13] There are some reports of changes in bowel function with bacopa extract.[12]

Acetyl-L-carnitine

There are 26 products containing acetyl-L-carnitine listed on the ARTG. They make claims such as, 'helps maintain healthy cognitive function and memory during ageing' and 'may provide protective effects against age related processes and neurodegeneration'. Acetyl-L-carnitine is structurally related to acetylcholine and it was thought it might act as an analogue of acetylcholine in patients with Alzheimer's disease. While some trials have reported positive results, a 2003 Cochrane review concluded there was 'no evidence of benefit of acetyl-L-carnitine for dementia'.[14] Orally, acetyl-L-carnitine is generally well tolerated although it may cause nausea, vomiting, gastrointestinal upset and agitation. One of its metabolites can cause the urine, breath and sweat to have a fishy odour. Acetyl-L-carnitine should be used cautiously if the patient is taking warfarin.[15]

Other products

There are other products promoted for cognitive enhancement on internet sites that are not listed or registered on the ARTG. These include drugs such as vinpocetine and huperzine A sourced from overseas. Patients should be warned that products obtained from these sites are likely to be sub-standard, adulterated and dangerous. There are also homeopathic formulations of dehydroepiandrosterone (DHEA) available from Australian pharmacies, health food shops and internet sites. This product is promoted for 'slowing down the ageing process'. Complaints that these preparations are neither efficacious nor in accord with homeopathic tradition have been upheld by the Complaints Resolution Panel;[16] however, similar claims continue to be made.[17]

Conclusion

Complementary medicines should always be included in a medication history of a patient with dementia. A non-judgemental discussion of risks and benefits should be informed by reputable sources of independent information. Possible adverse events should be reported. Patients and their carers should be told never to purchase medicines that lack an Aust L or Aust R number as the quality and safety of these products cannot be assured.

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Dr Harvey has provided advice to sponsors and industry associations involved with complementary medicines. Professor Stough has been the recipient of research grants from Flordis Medicines studying bacopa and cognition.

Valediction

John Tiller

Professor John Tiller retired as the chairman of the Editorial Executive Committee of *Australian Prescriber* at the end of 2010. This concluded a long association with the journal, beginning in 1992 when he stood in for a colleague on sabbatical leave for a year. Professor Tiller joined the Committee as a full member in 1995 and became the chairman in 2005.

Although Professor Tiller's primary interest is psychiatry, he has contributed greatly to the discussion of other therapeutic topics. His sense of humour has helped the Editorial Executive Committee through its considerable workload. Tiller's travel tales have been particularly entertaining.

Perhaps because of his extensive involvement in research, Professor Tiller is a firm believer in the importance of independent information about therapeutics. He has been a strong supporter and advocate for *Australian Prescriber* and has represented the journal well. The Editorial Executive Committee has appreciated this enthusiasm and looks forward to Professor Tiller's continuing support.

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Medicines Safety Update No. 1; 2011

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:

Clozapine and severe constipation

Summary

If left untreated, clozapine-induced constipation can lead to serious, potentially fatal complications including intestinal obstruction, ischaemia and perforation.

While myocarditis and blood dyscrasias are well-known serious adverse effects of clozapine, constipation associated with clozapine can also lead to serious complications if not detected and managed promptly.

A 2008 review of cases that had been published or reported to Australian or New Zealand pharmacovigilance programs described 102 cases of serious clozapine-induced gastrointestinal adverse effects, 28 (27.5%) of which resulted in death.[1] The main presenting symptoms were abdominal pain, abdominal distension and vomiting.[1]

To December 2010, the TGA had received 66 reports of serious gastrointestinal adverse events associated with clozapine, such as intestinal obstruction, paralytic ileus, intestinal ischaemia, intestinal perforation and gastrointestinal necrosis. Thirteen (19.5%) cases had a fatal outcome, although the gastrointestinal adverse event was not necessarily the cause of death in each case.

Constipation associated with clozapine, and with other typical and atypical antipsychotics, is largely due to peripheral anticholinergic effects. Concomitant administration of medicines with anticholinergic activity such as benztropine, tricyclic antidepressants and antipsychotics can contribute to constipation. In a review of 38 French cases of ischaemic colitis and gastrointestinal necrosis associated with treatment with antipsychotics (mostly typical antipsychotics or clozapine), 25 (66%) cases involved treatment with at least one other drug with anticholinergic activity. Fourteen (37%) of the cases reviewed had a fatal outcome; three of these were in patients on clozapine, two of whom were receiving clozapine monotherapy.[2]

Health professionals should counsel patients about the risk of constipation with clozapine and question patients about their bowel movements. Initiate treatment promptly if constipation is suspected or reported. An overview of management of constipation in adults was published in the August 2010 issue of *Australian Prescriber*.[3]

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Drug interaction between tamoxifen and antidepressants

Summary

A recent study has suggested a higher death rate amongst women taking tamoxifen for breast cancer who were also using the selective serotonin reuptake inhibitor paroxetine. This is thought to be a result of reduced conversion by cytochrome P450 2D6 of tamoxifen to a major active metabolite. Other studies have not found an association between CYP2D6 inhibitors and poorer outcomes in women taking tamoxifen. Until more conclusive data are available, it may be prudent to avoid, where possible, prescribing antidepressants that inhibit CYP2D6 to women with breast cancer being treated with tamoxifen.

Antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) are commonly used in women with breast cancer to treat major depressive disorder and, off-label, for hot flushes. It is estimated that up to 25% of women with breast cancer suffer from major depressive disorder during the course of their treatment and recovery.[1]

Tamoxifen is metabolised to one of its major active metabolites, endoxifen, by CYP2D6. Reduced plasma endoxifen levels have been reported with some SSRIs,[2] particularly those that are potent CYP2D6 inhibitors, which could result in reduced efficacy of tamoxifen. A recent observational study found an association between use of tamoxifen concurrently with paroxetine (an irreversible CYP2D6 inhibitor) and breast cancer mortality[3] but other studies have not found an association between CYP2D6 inhibitors and breast cancer recurrence or death in women taking tamoxifen.[4-6]

Although evidence from epidemiological studies is conflicting, the mechanism of the effect is biologically plausible, and so caution is warranted when prescribing antidepressants that moderately or strongly inhibit CYP2D6 to women taking tamoxifen (see box). Antidepressants with little or no inhibitory effect on CYP2D6 may be suitable alternatives. It should be noted that some other medicines inhibit CYP2D6, with examples of potent inhibitors including quinidine and cinacalcet.

Box

Antidepressant CYP2D6 inhibitors[7,8] *

Potent inhibitors

Bupropion†

Fluoxetine

Paroxetine

Moderate inhibitors

Duloxetine

Sertraline (mild inhibitor at doses < 100 mg/day)

* The information provided is a guide only. The precision in categorising the strength of CYP2D6 inhibition is limited for some antidepressants.

† Not registered in Australia for the treatment of depression

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Methysergide and retroperitoneal fibrosis

Summary

Retroperitoneal fibrosis is a well recognised adverse effect associated with long-term uninterrupted use of methysergide. To reduce the risk of this adverse effect, withdraw methysergide for 3 to 4 weeks at least every 6 months. Reduce the dose gradually during the last 2 to 3 weeks of each course to avoid rebound headache.

Methysergide (Deseril) is an ergot alkaloid derivative indicated for prophylaxis of migraine, cluster headaches and other vascular headaches. It is considered the most potent of the prophylactic drugs for migraine and may be effective when first- and second-line therapies fail.[1]

The most well-known serious adverse effect of methysergide is retroperitoneal fibrosis, which is usually associated with uninterrupted use for longer than six months, although cases have been reported with continuous use for less than six months.[2] Pleuro-pulmonary fibrosis and fibrotic changes of the pericardium and cardiac valves have also been associated with methysergide in a small number of patients.[3] Intermittent use of methysergide is recommended to reduce the risk of fibrotic complications.

The TGA has recently received two reports of retroperitoneal fibrosis where methysergide was suspected, bringing the total number of reports received, to December 2010, to 22. A 37-year-old woman who received methysergide uninterrupted for 16 months developed acute renal failure and required bilateral ureteric stents. In the second report, a 43-year-old woman who received methysergide uninterrupted for 30 months developed acute renal failure and required bilateral nephrostomy.

Methysergide should be withdrawn for 3 to 4 weeks after every six months or less of continuous use.[2] The withdrawal should be gradual, over 2 to 3 weeks, to avoid rebound exacerbation of migraine. Symptoms and signs such as general malaise, backache, girdle or flank pain, dysuria, oliguria, increased blood nitrogen or vascular insufficiency of the lower limb should raise the suspicion of retroperitoneal fibrosis.[2]

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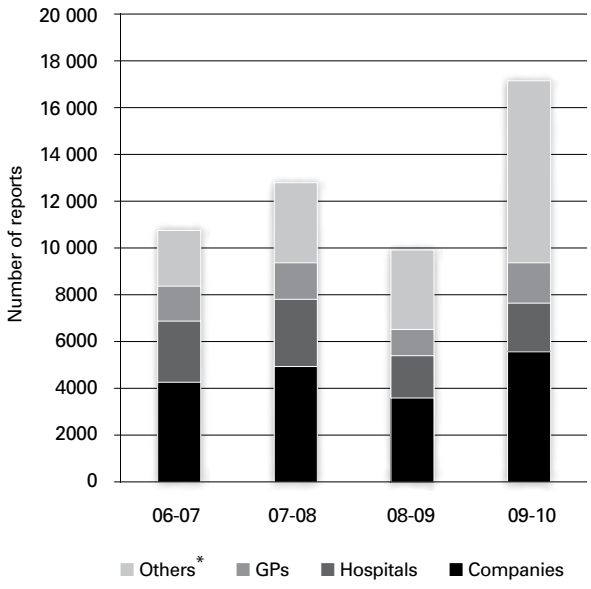
Thank you for your reports

The TGA received over 17 000 adverse reaction reports in 2009–10, which was an increase of more than 7000 reports from 2008–09. The increase in report numbers was largely attributable to the H1N1 influenza vaccination program, which used a variety of strategies to encourage consumers and health professionals to report adverse events, facilitating close monitoring of the vaccine's safety (see *Medicines Safety Update* Issue 4, August 2010). General practitioners contributed 1720 reports and pharmacists 790 reports.

The TGA thanks all those who have reported suspected adverse reactions – your reports are essential to early detection and investigation of potential safety signals. Please continue to report adverse events that might be related to a medicine or vaccine, particularly those that are serious or associated with new medicines or possible interactions (see 'What to report?' on page 25). There is no need to be certain that a drug caused the reaction – a suspicion is reason enough to report, and contributes valuable information to our medicines safety monitoring activities. Similarly, please report adverse effects that you consider to be known as these reports can contribute to a greater understanding of a medicine's safety profile.



* Includes state and territory health departments, members of the public, specialists and pharmacists

Suspected adverse reactions to vaccines: a reminder to report

Adverse events following immunisation (AEFIs) are notifiable conditions by healthcare providers in the Australian Capital Territory, New South Wales, Northern Territory, Queensland, South Australia, Victoria and Western Australia, and must be reported directly to the relevant health authority. In Tasmania, immunisation providers should report directly to the TGA. State and territory health authorities forward AEFI reports to the TGA.

Healthcare providers should report AEFIs promptly, and encourage consumers to report suspected adverse effects to their doctor, immunisation provider, state health authority or directly to the TGA (see 'What to report?' below). For health authority contact details and further information about the adverse effects of vaccines, see the Australian Immunisation Handbook (www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/handbook-home).

Medicines Safety Update is written by staff from the Office of Product Review, Therapeutic Goods Administration. Contributors to this issue include Dr Kevin Dodd, Dr Jennifer Elijah, Dr Katherine Gray and Dr Shaun Williams.

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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

Suspected reactions causing

- death
- admission to hospital or prolongation of hospitalisation
- increased investigations or treatment
- birth defects

Reports may be submitted:

- **using the 'blue card'** available from the TGA website (www.tga.gov.au/adr/bluecard.pdf) and in 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

New drugs: T-score for transparency

Access to information about drugs is essential for the quality use of medicines. Pharmaceutical companies and regulatory agencies, such as the Therapeutic Goods Administration (TGA), hold large quantities of information about individual drugs, but do not always share this information. To encourage transparency, *Australian Prescriber* rates companies' willingness to provide clinical information about new drugs. Table 1 shows how the companies have performed between January 2009 and December 2010.

The TGA is now publishing Australian Public Assessment Reports (AusPARs) for prescription medicines. While the Editorial Executive Committee welcomes this move to greater transparency, it will still ask companies to provide the clinical evaluations for their new products. While there are similarities, the AusPAR may not include all the details found in the regulator's clinical evaluation.

For 2011, the T-score has been revised to include the AusPAR.

The revised T-scores will be as follows:

T T T	manufacturer provided complete clinical evaluation
T T	manufacturer provided additional useful information
T	manufacturer provided the AusPAR and/or the product information
~~T~~	manufacturer declined to supply data
X	manufacturer did not respond to request for data

Table 1

Pharmaceutical company responses to requests for clinical evaluation data for drugs marketed Jan 2009 – Dec 2010

Company	Drug
T T T manufacturer provided clinical evaluation	
Amgen	denosumab
Ferring	degarelix
Pfizer	anidulafungin eletriptan
PharmaLink	cilostazol
Phebra	caffeine citrate
Roche	methoxy polyethylene glycol-epoetin beta tocilizumab
Sanofi Pasteur	H5N1 influenza vaccine
Shire	icatibant
Wyeth	methylnaltrexone
T T manufacturer provided additional useful information	
Abbott	omega-3-acid ethyl esters
Celgene	azacitidine
Commercial Eyes	melatonin
CSL	H1N1 influenza vaccine Japanese encephalitis vaccine
Eli Lilly	prasugrel

Table continued...

...Table continued

Company	Drug
Genzyme	plerixafor
GlaxoSmithKline	pneumococcal polysaccharide conjugate vaccine
Merck Sharp & Dohme	rizatriptan
Orphan	nitisinone
Sanofi-Aventis	alfuzosin
Servier	agomelatine
UCB Pharma	certolizumab pegol
Wyeth	desvenlafaxine succinate
T manufacturer provided only the product information	
Actelion	miglustat
Baxter Healthcare	vaccinia smallpox vaccine
Bayer Schering	rivaroxaban
CSL	nebivolol
GlaxoSmithKline	dutasteride pazopanib
Hospira	clofarabine
Janssen-Cilag	doripenem
Merck Sharp & Dohme	etoricoxib sugammadex
Novartis	valsartan, amlodipine/valsartan, valsartan/hydrochlorothiazide daptomycin
Phebra	arsenic trioxide
Sanofi Pasteur	influenza seasonal vaccine
UCB Pharma	lacosamide
T manufacturer declined to supply data	
Boehringer Ingelheim	dabigatran etexilate
CSL	H5N1 influenza vaccine
CSL Bioplasma	human C1 esterase inhibitor
Ipsen	triptorelin embonate
Janssen-Cilag	etravirine ustekinumab
Merck Sharp & Dohme	golimumab
Novartis	indacaterol vildagliptin
X manufacturer did not respond to request for data	
Alexion Pharmaceuticals	eculizumab
GlaxoSmithKline	ambrisentan H5N1 influenza vaccine

Your questions to the PBAC

Enoxaparin for haemodialysis – authority indications

Patients on haemodialysis are able to receive double the normal quantity of enoxaparin (Clexane) solution for injection per prescription – that is, 20 ampoules and 3 repeats versus the usual 10 ampoules. However, the restricted benefit listing for haemodialysis only covers the 20, 40 and 60 mg strengths. Clinicians are unable to prescribe double the quantity for the 80 and 100 mg strength for patients on haemodialysis. This seems a strange restriction. The recommended dose for haemodialysis is 1 mg/kg body weight for dialysis – so this restricts additional supply of medication to patients weighing 60 kg or less. It also creates additional cost for those patients above 60 kg, who choose to perform haemodialysis at home and have to purchase their own medication. Could this be reviewed?

Margaret Morris
Nurse practitioner – renal care, and anaemia co-ordinator
Dialysis Unit
St Vincent's Hospital
Melbourne

PBAC response:

At its December 2002 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended a differential listing for the 40 mg and 60 mg enoxaparin injections for patients undergoing long-term haemodialysis, whereby a maximum quantity of 20 and three repeats would be available. This recommendation was made following a request from a specialist physician who had asked that these two strengths be made available under a differential listing for haemodialysis patients with an increased quantity.

In December 2003, the PBAC further recommended the inclusion of the 20 mg injection under the haemodialysis listing, with a maximum quantity of 20 ampoules and three repeats. The PBAC did not extend the recommendation to the higher strengths (80 mg and 100 mg enoxaparin injections) as it held concerns about the risk of bleeding if they were made available. However, taking into account that the recommended dosage of enoxaparin is 1 mg/kg for haemodialysis patients and that more patients may receive treatment in the home than previously, this matter will be reviewed by the PBAC at its March 2011 meeting after seeking expert advice.

Do you have a question for the PBAC?

Australian Prescriber readers are invited to write in with their questions about decisions of the Pharmaceutical Benefits Advisory Committee (PBAC). The journal publishes selected questions from readers, together with answers from the PBAC. Questions may address issues such as regulatory decisions, pharmaceutical benefits listings and withdrawals.

This exclusive arrangement helps *Australian Prescriber* readers understand how the contents of the Schedule of Pharmaceutical Benefits (www.pbs.gov.au) are determined.

Letters and responses are reviewed by our Editorial Executive Committee and may be edited before publication. It may not be possible to reply to all individual questions.

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.

Corifollitropin alfa

Elonva (Schering-Plough)

prefilled syringes containing 100 microgram and 150 microgram/0.5 mL

Approved indication: ovarian stimulation

Australian Medicines Handbook section 10.5

Follicle stimulating hormone is used in the management of infertility. Two recombinant forms are available, follitropin alfa and follitropin beta. Women preparing for *in vitro* fertilisation need daily injections to stimulate follicular development. To reduce the number of injections, the hormone has been genetically engineered to form corifollitropin which has a more prolonged effect on the ovaries.

Corifollitropin combines follicle stimulating hormone with part of the human chorionic gonadotropin molecule. This extends the time to peak serum concentration and approximately doubles the half-life. A single injection can therefore sustain the growth of multiple follicles for a week. Corifollitropin is distributed and metabolised like follicle stimulating hormone with most of the dose being excreted in the urine. The appropriate dose is determined by the patient's weight.

In a placebo-controlled dose-ranging study of 55 women with anovulatory infertility, the follicular response increased with the dose of corifollitropin. Although a single subcutaneous dose induced a follicular response in 28 of the women, only eight ovulated.[1]

An open-label study compared different doses of corifollitropin alfa with daily injections of recombinant follicle stimulating hormone. The 99 women who were randomised were preparing for *in vitro* fertilisation or intracytoplasmatic sperm injection. More oocytes were retrieved from the women given corifollitropin than from the ovaries of women given recombinant follicle stimulating hormone. However, there was no significant difference in the number of good quality embryos produced.[2]

Corifollitropin and recombinant follicle stimulating hormone were then compared in a double-blind trial involving 1506 women weighing 60–90 kg. The women either had daily injections of follicle stimulating hormone or one injection of corifollitropin followed, after a week, by daily follicle stimulating hormone. Significantly more oocytes were retrieved from the women who had corifollitropin in the first week of treatment.[3]

Similar results were found in a trial of 396 women weighing 60 kg or less.[4]

In the trial of women of normal weight, 2.1% of those given corifollitropin discontinued treatment because of serious adverse effects compared with 0.4% of the group given recombinant follicle stimulating hormone. Ovarian hyperstimulation syndrome affected 7% of the corifollitropin group and 6.3% of the control group. Other adverse events also occurred with similar frequencies in each group.[3] Common adverse effects include pelvic pain, headache, breast symptoms and nausea.

Although, statistically, significantly more oocytes were retrieved from women given corifollitropin rather than recombinant follicle stimulating hormone, the difference between treatments was only 1.2 oocytes. Embryo quality was similar and there was no significant difference in the pregnancy rate. Pregnancies lasting at least 10 weeks occurred in 38.9% of the corifollitropin group and 38.1% of the control group, with multiple pregnancies in 28.2% and 23.1%.[3]

T T manufacturer provided additional useful information

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1. Balen AH, Mulders AG, Fauser BC, Schoot BC, Renier MA, Devroey P, et al. Pharmacodynamics of a single low dose of long-acting recombinant follicle-stimulating hormone (FSH-carboxy terminal peptide, corifollitropin alfa) in women with World Health Organization group II anovulatory infertility. J Clin Endocrinol Metab 2004;89:6297-304.
2. Devroey P, Fauser BC, Platteau P, Beckers NG, Dhont M, Mannaerts BM. Induction of multiple follicular development by a single dose of long-acting recombinant follicle-stimulating hormone (FSH-CTP, corifollitropin alfa) for controlled ovarian stimulation before *in vitro* fertilization. J Clin Endocrinol Metab 2004;89:2062-70.
3. Devroey P, Boostanfar R, Koper NP, Mannaerts BM, Ijzerman-Boon PC, Fauser BC; ENGAGE Investigators. A double-blind, non-inferiority RCT comparing corifollitropin alfa and recombinant FSH during the first seven days of ovarian stimulation using a GnRH antagonist protocol. Hum Reprod 2009;24:3063-72.
4. The corifollitropin alfa Ensure study group. Corifollitropin alfa for ovarian stimulation in IVF: a randomized trial in lower-body-weight women. Reprod Biomed Online 2010;21:66-76.

Meningococcal A, C, W_{135} and Y conjugate vaccine

Menveo (CSL)

vials containing powder for reconstitution

Approved indication: prevention of meningococcal disease

Australian Medicines Handbook section 20.1

Meningococcal disease is caused by the Gram-negative bacterium *Neisseria meningitidis*. The most prevalent disease-causing serogroups are A, B, C, W_{135} and Y. Asymptomatic carriage of meningococci in the upper respiratory tract is relatively common, but occasionally the bacteria invade and cause septicaemia and meningitis. Infection can be rapid and fatal and mainly affects children under two years. However, there is also a peak of incidence in adolescents associated with increased carriage rates.

Currently in Australia there are two types of meningococcal vaccine – meningococcal C conjugate vaccines and polysaccharide vaccines. The conjugate vaccines consist of serogroup C polysaccharide conjugated to a carrier protein. These vaccines are immunogenic in babies and are given from two months of age. However, they only protect against serogroup C disease. The polysaccharide vaccines contain serogroups A, C, W_{135} and Y, but because they are not conjugated to protein they may only protect for a short duration, do not induce immunological memory and are relatively ineffective in young children.

This new vaccine is a quadrivalent conjugate vaccine containing oligosaccharides from serogroups A, C, W_{135} and Y individually attached to *Corynebacterium diphtheriae* CRM_{197} protein. In a clinical trial of people aged 11 and over, one intramuscular dose of the vaccine was immunogenic and seemed to be non-inferior to a similar conjugate vaccine (Menactra).[1] In another trial of 11–17 year olds, the vaccine seemed to be comparable to a quadrivalent polysaccharide vaccine (Menomune).[2] Adverse events were generally mild and included injection-site reactions, headache, nausea and malaise.

Based on immunological data, this vaccine should protect against meningococcal infections caused by serogroups A, C, W_{135} and Y. However, it is important to remember that it will not prevent serogroup B disease. The vaccine is currently only indicated for people aged 11 years or older. The US Food and Drug Administration has requested additional safety data in infants before considering approval in this age group.

[T] [T] manufacturer provided additional useful information

References *†A

1. Reisinger KS, Baxter R, Block SL, Shah J, Bedell L, Dull PM. Quadrivalent meningococcal vaccination of adults: phase III comparison of an investigational conjugate vaccine, MenACWY-CRM, with the licensed vaccine, Menactra. Clin Vaccine Immunol 2009;16:1810-15.
2. Jackson LA, Jacobson RM, Reisinger KS, Anemona A, Danzig LE, Dull PM. A randomized trial to determine the tolerability and immunogenicity of a quadrivalent meningococcal glycoconjugate vaccine in healthy adolescents. Pediatr Infect Dis 2009;28:86-91.

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)

Correction

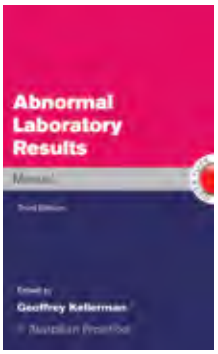
Vaccinia smallpox vaccine (Aust Prescr 2009;32:169-70)

[T] the manufacturer provided only the product information, not the clinical evaluation

New education program

NPS's latest education program for health professionals will be launched this month, focussing on managing lipids. It encourages greater use of risk assessment calculators to identify patients at risk of cardiovascular events, and early commencement of appropriate therapies. Resources have been developed to support conversations with patients about their cardiovascular health and provide information they can take home. For more information go to www.nps.org.au/health_professionals

Abnormal Laboratory Results – new edition coming soon



This comprehensive collection of *Australian Prescriber* articles examines the dilemmas of abnormal test results and outlines how to approach them. Each test is analysed and interpreted in a structured, logical way and assessed in terms of its abnormal and normal reference range. The results are then presented in a variety of clinical contexts so an accurate prognosis and recommendations on management can be made. Like the second edition, the third edition to be published in June 2011 has been edited by Professor Geoffrey Kellerman and is an excellent guide for medical students, hospital clinicians and general practitioners.

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