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EDITORIAL

The influence of opinion leaders

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Key words
conflict of interest, drug industry, expert opinion

Aust Prescr 2012;35:74–5

Doctors and the general public believe that evidence should guide rational prescribing. In most Australian medical schools, students are taught evidence-based medicine to better equip them for critically appraising the evidence to guide their future management of patients. However, this is not always the mechanism by which doctors in practice seek solutions to clinical problems. A systematic review found that primary care physicians were more likely to seek answers to clinical questions from colleagues than from electronic resources.[1] Perhaps the most disappointing finding in this review was that the situation remained unchanged between 1992 and 2005, despite the digital revolution. It is very likely that most specialists also use colleagues as their main source of information to answer clinical problems.[2]

Doctors seek solutions from other doctors and due to the hierarchical relationship of this transfer of information, a relatively small number of doctors guide national and international prescribing patterns. These 'opinion leaders' have an influence far beyond their own prescribing patterns. The process and qualifications by which an individual becomes an opinion leader have never been defined and may be prone to manipulation by vested interests. This mechanism to disseminate information has risks as well as benefits.

Opinion leaders have several possible benefits. A small number of experts are very likely to achieve consensus in how to manage specific problems. This uniformity of approach allows patients to have relatively consistent treatment from primary care to specialist care, across ambulatory and inpatient settings.

Most doctors find it impossible to stay abreast of all the developments in their fields. Opinion leaders tend to have a very narrow focus within a subspecialty. This enables them to have a good working knowledge of the latest advances in their fields and facilitates the appraisal of the latest evidence and its influence on practice.

Opinion leaders are often involved in research. This gives them additional insights into the major advances within a specific field. They are frequent attendees and contributors at major international conferences and are aware of developments that may not even be published. A Cochrane systematic review has found that local opinion leaders (note – local rather than national) may successfully promote evidence-based practice.[3]

The major risk of opinion leaders seems to be related to the disproportionate influence that external agencies may bring to bear. Most concerns are about the influence of the pharmaceutical industry, but similar issues are apparent with companies manufacturing medical devices.

The pharmaceutical industry makes every attempt to contract opinion leaders, educate them about its products and seek their advice as to how to maximise sales. This is often through a mechanism such as drug-specific medical advisory boards. These contractual relationships are covert and unregulated, and the code of conduct of Medicines Australia is quite vague about these matters.[4] When does reimbursement for services rendered become coercion, and place an opinion leader under a sense of obligation?

Remuneration for an opinion leader may take multiple forms including payment for attendance at medical advisory board meetings, honoraria for giving lectures to specialists and general practitioners, and sponsorship to attend international meetings. Each component may seem relatively modest, but the totality can be significant. Opinion leaders would be unwise to foster relationships with only one company as major bias would result, and frequently enter into arrangements with multiple companies. Unfortunately, many opinion leaders pay scant attention to non-pharmacological strategies which typically do not provide the same incentives.

From the Editor

Although vaccination has been available since the 1950s, pertussis is still a problem in Australia. Philip Britton and Cheryl Jones explain the role of antibiotics in preventing further attacks.

Patients with asthma should know how to deal with acute attacks. Helen Reddel provides advice on how to write an asthma action plan for treating acute exacerbations.

Drug interactions may be acute or emerge over time. Ben Snyder, Thomas Polasek and Matt Doogue discuss how to look for likely interactions.

Loss of vision becomes more likely with ageing. Roland Bunting and Robyn Guymer tell us how the management of age-related macular degeneration has been improved by drugs aimed at vascular endothelial growth factor.

Detecting mutations of epidermal growth factor receptors is one indication for consulting a cytologist. Phillip Woodford and Rebecca Said give guidance on how cytology can help diagnosis.

The interests of pharmaceutical companies may coincide with the interests of patients. Novel drugs which dramatically improve the management of patients benefit all parties. The introduction of such drugs should rightly be facilitated by opinion leaders. However, a close relationship between industry and opinion leaders may have negative consequences. Examples include the creation of new diseases or the dramatising of relatively minor conditions. This medicalisation of ordinary life, for example male baldness, has been termed 'disease mongering'.[5]

The use of opinion leaders in such disease awareness campaigns is crucial. There is evidence that some opinion leaders have been successfully chosen and groomed by pharmaceutical companies. Individual doctors, who may not be well known or widely published, are chosen by a company because of their favourable views of a specific drug.[6] The promotion of these individuals as opinion leaders results in a distortion of the consensus process regarding the role of that drug.

A close relationship between companies and opinion leaders in research may also be problematic. The involvement of independent academics in research is one of the important safeguards in ensuring checks on companies. The inexplicable failure of a pharmaceutical company to report deaths in a large study of rofecoxib, and the subsequent defence of the drug's utility by some opinion leaders, raises questions regarding their independence.[7] Similarly, the involvement of opinion leaders does not seem helpful in convincing companies to publish the results of negative studies, particularly if there are other positive studies of the drug.

Most concerns are about the influence of the pharmaceutical industry

Pharmaceutical companies have a legitimate right to contract opinion leaders to help publicise their products and maximise their profits. Respected colleges[8] and medical associations have argued for greater transparency of the relationships between opinion leaders and companies. This would enable other health professionals to consider the putative financial gain when they weigh up the arguments of these opinion leaders. Such transparency has not been achieved, and how to monitor and deal with non-compliance with college and association guidelines remains a problem. Transparency would resolve many of the current tensions as to how opinion leaders are perceived. In the meantime, all opinions, including those contained in this editorial, should be treated with healthy scepticism. ◁

Conflict of interest: none declared

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Letters to the Editor

Management of polypharmacy: can we safely discontinue medications?

Editor, – The authors of the article on deprescribing (Aust Prescr 2011;34:182-5) remind us about the critical role all clinicians play in generating, and potentially mitigating, polypharmacy. There is a paucity of high quality evidence to guide when to discontinue medications, especially where the event to be avoided may not be experienced for years or decades.

Initiating any medication requires a framework to evaluate its continuing use and includes:

- explicitly categorising the level of prevention (primary, secondary or tertiary) that the new medication is addressing
- agreed, measurable and clinically relevant endpoints
- the time by which clinical benefits are likely to be experienced

◁

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 Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

LETTERS

- the time frame for expected toxicities
- the time period in which it is likely that a condition will manifest after a medication is stopped
- a plan to individually balance the net clinical benefit (observed clinical benefits vs harms).[1,2]

As a patient's overall clinical condition, prognosis and range of comorbid illnesses shift over time, their individual benefit:harm ratio will need to be updated continually for each long-term medication. Individually, the number needed to treat and the number needed to harm are not static nor linear over time, and the ratio between them will shift from the time each medication is introduced.[3]

With so much effort expended by industry establishing the short-term efficacy of medications that will be used in the long term, it is time for an expansion of comparative effectiveness research defining when long-term medications can be ceased safely and in which sub-populations this should occur.[4,5] To minimise iatrogenic morbidity and premature mortality, publicly funded studies to develop credible evidence are needed urgently to inform timely and confident discontinuation of appropriate medications.

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Danijela Gnjidic, David Le Couteur, Emily Banks and Andrew McLachlan, authors of the article, comment:

We thank David Currow and his colleagues for their comments. We agree strongly with them and would like to see randomised controlled trials of long-term use of medicines and outcomes of judicious cessation of medicines in older people.

Deprescribing in older adults has been found to be difficult. We recently reviewed methods of deprescribing to reduce polypharmacy and the impact on prescribing and outcomes in older adults.[1] While different interventions (for example pharmacy-based, physican-based and multidisciplinary-based interventions) can reduce medication exposure in older adults, the evidence for their clinical effectiveness and sustainability is limited and, where it is available, conflicting.

Moreover, time-limited trials of treatment may be suitable for safely discontinuing medications and guiding the deprescribing process in clinical practice.[2] Further research is needed to determine the most feasible and effective strategies for discontinuing medications, and to provide a better understanding of the clinical benefits of deprescribing.

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Critical appraisal: court in the Act

Editor, – The Therapeutic Goods Administration (TGA) wishes to ensure that readers of your recent editorial (Aust Prescr 2012;35:38-9) are not left with the misapprehension that they place themselves at legal risk by reporting concerns about a therapeutic good to the TGA. Your editorial failed to acknowledge that personal information relating to complaints made to the TGA is regarded as confidential and that neither the TGA, nor the Complaints Resolution Panel, publishes information that identifies a complainant. In the instance that you cite in your editorial, it was only after a third party published the complaint (and the identity of the complainant) on the internet that the company initiated legal action against Dr Harvey.

The TGA is particularly concerned to ensure that readers do not infer from your editorial that legal action taken by a company about the advertising of its product has implications for healthcare professionals who report suspected adverse events to the TGA.

Health professionals play an important role in ensuring the safe use of therapeutic goods by

reporting both adverse events and advertising breaches to the TGA. These reports are essential to the role of the TGA in safeguarding the health of all Australians who use therapeutic goods.

Your editorial further comments that the TGA's strategy of silence and secrecy gave the appearance we were doing nothing in respect of the alleged advertising breach. Although the TGA operates within a statutory framework and needs to ensure that proper procedures are followed when taking regulatory action, your editorial should have noted that a number of reforms announced by the Parliamentary Secretary for Health and Ageing in December 2011 are being implemented to address this concern.

Brian Richards
National Manager (acting)
Therapeutic Goods Administration
Canberra

Statins for primary prevention of cardiovascular disease

Editor, – Thank you for the article by Jane Smith 'Appropriate primary prevention of cardiovascular disease: does this mean more or less statin use?' (Aust Prescr 2011;34:169-72). In the very high risk category, when patients should be treated at any lipid level, there is no mention of family history.

The Pharmaceutical Benefits Scheme (PBS) and Therapeutic Guidelines recommendations are for patients with a family history of premature coronary heart disease (one or more first-degree relatives symptomatic before the age of 45 years, or two or more first-degree relatives symptomatic before the age of 55 years).

Is there any evidence for this and what would be the recommended dose?

Louise French
General practice registrar
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Associate Professor Jane Smith, author of the article, comments:

Dr French is correct to raise the issue regarding PBS recommendations about use of statins in this patient group.

The risk from 'family history of cardiovascular disease in first degree relatives under the age of 60 years' is validated to increase the relative risk of cardiovascular disease by 1.6–1.9.[1]

The risk from family history of cardiovascular disease has been shown to vary with the age and sex of the first degree relative. If both father and mother have had cardiovascular disease under the age of 50 and 60 years respectively, then the relative risk is increased by 6.9. However, if both father and mother had their cardiovascular disease over the age of 60 and 80 years then the relative risk is only increased by 1.3.[2]

Logically one could expect family history at a younger age to convey a higher risk, but I am unaware of a calculated value, other than relative risk, and I believe the recommendation to treat as high risk is based on expert opinion.

Such premature onset of cardiovascular disease suggests a genetic predisposition like familial hypercholesterolaemia, but this specific diagnosis is based on a number of criteria.

Risk calculators in the UK (QRISK2) and the New Zealand Heart Foundation adjust for family history. The Australian National Vascular Disease Prevention Alliance risk calculator and the Australian adjusted Framingham risk tables do not. The individual prescriber should accommodate this in their assessment.

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ARTICLE

Rational prescribing for asthma in adults – written asthma action plans

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Key words
beta agonists, corticosteroids

Aust Prescr 2012;35:78–81

SUMMARY

Written asthma action plans are an essential part of effective asthma management, but very few adult patients have them.

The key components of a written asthma action plan are how to recognise deteriorating asthma, what treatment to use and when to seek medical help. A section on the first aid to give in an emergency can also be included.

An action plan should be simple and personalised. Most plans advise patients to increase the dose and frequency of their inhaled treatments. Oral corticosteroids are advised for severe exacerbations.

Asthma action plans should be reviewed at least once a year.

Introduction

For the last 20 years, guidelines have recommended that all patients with asthma, regardless of severity, should have a personal asthma action plan giving instructions for how to recognise and respond to worsening asthma. The plan should be written, so the patient has a record of the instructions. It should describe the actions they should take, including changes in treatment and when to seek health care. Plans should be personalised for the patient's level of asthma control, their treatment, and their capability for appropriate self-management. Despite systematic reviews of randomised controlled trials supporting the benefits of written asthma action plans as part of self-management education,[1,2] only a small minority of people have one.[3] Although a lack of time contributes, uncertainty about therapeutic options is a significant barrier to provision of written asthma action plans by health professionals.[4,5]

Before writing an asthma action plan

Ask the patient about their usual triggers for worsening asthma, the words they use to describe it,[6] and the typical time frame. Patients with a history of sudden deterioration should be encouraged to seek medical care early. They should be referred for investigation of trigger factors and to assess if they have poor perception of airway obstruction. Also, ask what the patient usually does in response to worsening asthma, as this may alert you to problematic health beliefs or use of complementary therapies.

If asthma is not currently well controlled, write a temporary action plan. Update it once any change in maintenance management has been effective.

Action plan templates

Writing and reviewing action plans are required components of the Asthma Cycle of Care Service Incentive Payment available to Australian general practitioners. Preparing an action plan is simplified by using a template, which pre-prints some information and provides prompts for the personalised instructions. Clinicians should become familiar with a small number of action plan templates relevant to their practice population.

Tear-off action plan pads are available free of charge from the Department of Health and Ageing,* and new wallet-sized action plan cards were launched by the National Asthma Council in 2011. A range of action plan templates, some with translations, are available for free download from the National Asthma Council website,[7] including specific templates for children and for patients using the budesonide/eformoterol as maintenance and reliever regimen. Action plan templates are also available in some practice software packages.

What an action plan template should include

Check that your template includes prompts or spaces for:

- the patient's name
- current preventer and reliever drugs and doses
- the level of symptoms or peak flow at which they should move to the next step in the plan
- specific treatment changes for each step
- when to contact their general practitioner or a hospital

* National Mailing and Marketing, Department of Health and Ageing, phone (02) 6269 1000. Asthma Cycle of Care action plan pads (25 action plans per pad) are delivered free of charge within a few days after an order is placed.

- the doctor's name and phone number
- the date.

For most patients, symptom-based action points are sufficient.[2] Peak flow monitoring is only needed for patients with severe asthma, frequent exacerbations, or poor perception of airway obstruction.

Check that the patient can correctly use all inhaler devices included on their action plan.[8,9]

Prescribing options for worsening asthma

A wide variety of criteria have been proposed for defining mild or moderate exacerbations, but none has been validated.[10] Instead, the clinician should specify a level of symptoms and reliever use which is beyond the usual range of the patient's day-to-day variation. It is important to customise the plan to the patient's usual status, to avoid over- or underuse of the action plan. Night waking is an important (but late) indicator of worsening asthma.

Reliever medication

If asthma worsens, remind the patient to use their reliever inhaler, for example salbutamol, as often as needed. Although this may seem obvious, patients with well-controlled asthma often need a prompt to keep a reliever inhaler on hand.

Preventer medication

For patients taking conventional fixed-dose inhaled corticosteroids or inhaled corticosteroids with long-acting beta$_2$ agonists, current guidelines do not recommend doubling the dose of inhaled corticosteroid when asthma worsens. However, the evidence for not increasing the dose was from placebo-controlled studies in which the extra inhaled corticosteroids were not started until around five days after the patient's asthma began to worsen.[11] A recommendation to double preventer medication may be useful for some patients to remind them to take at least some, since poor adherence may have contributed to the deterioration.

Recently, there has been some evidence to support increasing inhaled corticosteroids to high doses for worsening asthma.[11] This can be done by quadrupling the usual dose of inhaled corticosteroid or, for those using a combination corticosteroid/long-acting beta$_2$ agonist inhaler, adding a high-dose corticosteroid inhaler (for example adding fluticasone 250 microgram inhaler or ciclesonide 160 microgram two puffs twice daily by spacer to the patient's usual preventer regimen). This approach may be helpful for patients who have major adverse effects with oral corticosteroids. It may be unsuitable if cost is a major issue, or for people such as singers who use their voice professionally, for whom a small risk of dysphonia may be unacceptable.

For patients using the combination of salmeterol with fluticasone, ensure that the action plan prescribes a dose that will provide the recommended dose of salmeterol (100 microgram/day). For example, if the usual dose is salmeterol/fluticasone 25/125 one puff twice daily, increase it to at least two puffs twice daily during exacerbations.

Patients prescribed the combination of budesonide with eformoterol as maintenance and reliever therapy should be reminded to use extra as-needed inhalations (100/6 or 200/6) as symptoms increase. The combined daily maximum for either formulation is 12 inhalations, but such high usage is uncommon.

Peak flow monitoring is only needed for patients with severe asthma, frequent exacerbations, or poor perception of airway obstruction

When asthma improves

Patients prescribed conventional fixed-dose inhaled corticosteroids or inhaled corticosteroids with long-acting beta$_2$ agonists should be prompted to continue any increased dose for two weeks and to contact the clinician if they do not improve within two weeks or are worsening. Patients using the budesonide/eformoterol combination inhaler as maintenance and reliever therapy should reduce their as-needed inhalations as symptoms improve.

Prescribing options when asthma is severe

There are no validated objective criteria for activating the severe section of an action plan. For each patient, the clinician should specify a level of symptoms or peak flow at which urgent action would be needed to prevent serious outcomes such as hospitalisation. Typical indicators for this step might be failure to improve after 2–3 days on the previous step, or rapid deterioration, or needing the reliever again within three hours. For patients using budesonide/eformoterol as maintenance and reliever therapy, addition of oral corticosteroids should be considered if the patient exceeds six reliever inhalations a day or is not improving over 2–3 days.

Reliever medication

Emphasise that for short periods the reliever can be used as often as needed, but that if it is needed more than four-hourly, medical review should be obtained. If the patient is using a metered dose inhaler, the reliever should be inhaled through a spacer (one puff at a time, shaking the inhaler between each puff) to improve effectiveness.[8,9] Stress that a nebuliser is not needed, as inhaler plus spacer is just as effective.[12]

Oral corticosteroids

For severe exacerbations, a short course of prednisolone, started by the patient following agreed criteria, is the recommended option. These criteria should state when the patients should also call their doctor or go to hospital.

Evidence for adults supports a daily dose of 50 mg (2 x 25 mg tablets) for a period of five days. Longer courses are not usually needed, so there is no need to taper the dose except if adverse effects are troublesome or treatment has been continued for more than two weeks.[5] It is important to discuss potential adverse effects such as irritability, depression, insomnia and weight gain, to emphasise that these resolve quickly, and to advise that the dose can be adjusted in future. Insomnia is reduced by taking prednisolone in the morning rather than twice daily.

While underuse of prednisolone is a danger for patients who experience depression, irritability or increased weight, a tendency to overuse (and hence greater risk of osteoporosis and cataracts) may be seen in patients who experience euphoria. Patients with diabetes should be asked to check their blood glucose more often when taking oral steroids as they may need to adjust their treatment.

Preventer medication

Remind patients to keep taking their preventer medication during severe exacerbations. Explain that although they are also taking an oral corticosteroid, inhaled corticosteroids work by a different mechanism so both are needed.

When asthma improves

Additional inhaled therapy should be continued for at least a week after symptoms resolve. Arrange for a follow-up visit after any severe exacerbation, to identify the trigger and assess whether maintenance treatment needs to be modified. The action plan should also be reviewed (see Box).

Asthma emergencies

The final section of a written asthma action plan often provides information about asthma first aid. Ask the patient to show this section, about what to do in an emergency, to their friends and family. Asthma first aid training is available through asthma foundations and other organisations.† The basic principle for pressurised metered dose inhalers is '4 x 4 x 4' – that is, a single puff separately into a spacer followed by four breaths through the spacer, shaking the inhaler between each puff; this is repeated four times. After another four minutes the process is repeated again.

Terbutaline or budesonide/eformoterol, by dry powder inhaler, may also be used for first aid. Give an initial two inhalations then repeat after a few minutes.

If the patient obtains little or no improvement, is having difficulty speaking or their lips turn blue, call an ambulance and say someone is having a severe asthma attack. Keep giving reliever medication while waiting for the ambulance. Emphasise to patients that in an asthma emergency they should never try to drive themselves to hospital.

Reviewing a written asthma action plan

Action plans should be reviewed (see Box) whenever maintenance medications are changed, or at least yearly.

Conclusion

Evidence-based principles can be applied to any written asthma action plan template. Health professionals should become familiar with an action plan template for each of the two main asthma treatment regimens (preventer therapy with short-acting beta$_2$ agonist reliever, and budesonide/eformoterol maintenance and reliever therapy), and know how to complete each. An action plan can be used during consultations to help with patient self-management education, and to encourage shared decision-making about how worsening asthma will be managed. ≺

Box **Reviewing a written asthma plan**

Write any new drugs or doses into the 'usual management' section

Check that the criteria for worsening asthma are appropriate for the patient's usual status when well

Ask whether the patient's asthma has worsened since the last visit and what the trigger was

Ask if the action plan was used. If not, does the patient need another copy? Where will they keep it so they can find it in future? If the action plan was used, did the patient feel that it worked? Were they happy with the action points and the treatment changes? Did they have any adverse effects? Does anything need to be modified?

Emphasise that the action plan is personalised for each patient's needs

Write an updated prescription for oral corticosteroids and any other drugs needed for the action plan. These should be dispensed before travel or for patients with a history of sudden exacerbations.

† www.nationalasthma.org.au/emergency
www.asthmaaustralia.org.au/training

Associate Professor Reddel has served on advisory boards for AstraZeneca, GlaxoSmithKline and Novartis, and has provided consulting for Biota, GlaxoSmithKline and Novartis. She has received honoraria from AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline for educational presentations, is chairing a joint data monitoring committee for AstraZeneca, GlaxoSmithKline, Merck and Novartis, and has received research funding from AstraZeneca and GlaxoSmithKline. She contributed to the development of action plan templates for budesonide/eformoterol maintenance and reliever therapy, and a generic action plan template and an asthma first aid chart for the National Asthma Council.

Note: The April 2012 issue of *Australian Prescriber* featured an article on rational prescribing for ongoing management of asthma in adults, also by Dr Reddel.

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Q:

SELF-TEST QUESTIONS

True or false?

1. Action plans should advise against the use of spacers during exacerbations of asthma.
2. Patients with an exacerbation of asthma should not start oral corticosteroids before being examined by a doctor.

Answers on page 103

Dental note

Asthma action plans

Although asthma frequently presents in childhood, it can occur for the first time at any age. An asthma attack can occur during dental treatment so a plan for managing these attacks is always prudent.

Patients who regularly use inhalers should be advised to bring them to dental appointments so that they can self-medicate if necessary. Ideally patients would have a written asthma action plan to provide information about asthma first aid. Dentists should ask their patients to bring their written asthma action plan and discuss with them what to do in an asthma emergency. This discussion may further prompt the patient to undertake a written asthma action plan with their doctor.

The basic principle of management of acute asthma is giving repeated doses of an inhaled bronchodilator (the 4 x 4 x 4 rule). More detail is given in Therapeutic Guidelines: oral and dental.[1]

Michael McCullough
Chair
Therapeutics Committee
Australian Dental Association

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ARTICLE

Pertussis prophylaxis

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Cheryl A Jones
Professor[1,2]

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Key words
antibiotics, exposure, whooping cough

Aust Prescr 2012;35:82–4

SUMMARY

Pertussis has significantly increased in Australia, particularly in older children and adults. These patients do not always exhibit classical symptoms and are an important source of infection for young infants.

Antibiotic treatment, isolation of index cases and timely vaccination are important strategies to prevent transmission of pertussis.

Evidence of the efficacy of chemoprophylaxis for pertussis is limited. Assessing efficacy is often confounded by a delay in diagnosis of the index case.

Antibiotic prophylaxis after exposure to pertussis aims to limit transmission to non-immune contacts. It is recommended for high-risk groups such as unimmunised infants, women in late pregnancy and individuals who may be a source of infection.

Introduction

Pertussis, also known as whooping cough, is caused by the bacterium *Bordetella pertussis*. Humans are the only known host for this pathogen.

There has been a recent resurgence of pertussis notifications in Australia and developed countries unrelated to changes in immunisation rates, particularly in adolescents and adults. Suggested reasons for the increase include:

- increased diagnosis and reporting
- waning immunity after childhood vaccination
- underdiagnosis of infection because of atypical presentations, which has resulted in an adult reservoir of circulating *B. pertussis*.[1]

Clinical presentation

In its classical form, young children with pertussis present with a non-specific coryzal illness associated with a mild cough (catarrhal phase) after an incubation period of approximately one week. This is followed 1–2 weeks later by a spasmodic cough with an inspiratory whoop commonly associated with post-tussive vomiting (paroxysmal phase). This phase can last up to six weeks before symptoms gradually resolve over a number of weeks. Infants in the first months of life may present with apnoea alone. Older children, adolescents and adults may have mild or no cough, or a chronic non-productive cough. They only rarely present with a classical paroxysmal cough with a whoop. This group are now the most important source of infection in young infants.

Mortality and morbidity

Mortality from pertussis is rare overall, but approaches 1% in infants under six months. However, morbidity from infection is common. It can include hospitalisation, superinfection, failure to thrive, cerebral hypoxia and encephalopathy in infants. Sleep disturbance, rib fracture and prolonged cough can occur in adults.

Transmission

B. pertussis is highly infectious and is spread by coughing or sneezing. Rates of transmission to susceptible contacts are up to 50% in the community and about 80% in susceptible household contacts.

Isolating infected cases until antibiotic treatment renders them non-infectious (five days) is the most important means of stopping pertussis circulating in the community.

Vaccination

Whole cell pertussis vaccines, introduced in the 1950s, significantly reduced pertussis in children. Acellular vaccines, introduced in Australia in 1999, have similar efficacy to whole cell vaccines with fewer adverse effects.

The current national immunisation schedule recommends primary immunisation with acellular pertussis vaccine (given in conjunction with diphtheria and tetanus immunisations – DTPa) at two, four and six months of age with booster doses at four and 15–17 years.[2] Waning immunity has been observed in older children and adults with this schedule. For this reason, booster vaccination is now also recommended for high-risk contact groups including adults planning a pregnancy, adult family members of newborns, and child and healthcare workers.

Australian guidelines[2] recommend a single dose of an acellular vaccine for contacts of pertussis older than eight years, and catch-up vaccination for unvaccinated or partially vaccinated (incomplete infant vaccination) contacts up to their eighth birthday.

Clinical trials are underway to evaluate neonatal pertussis vaccination and vaccination of pregnant mothers to limit pertussis transmission to newborns.

Management of the index case

Australian guidelines for the public health management of pertussis recommend antibiotic treatment of the index case with exclusion from childcare, school, work or other environments where high-risk contacts may be present, until they are non-infectious (that is, after five days of antibiotic treatment).[2] Treatment must be commenced in the first 21 days of illness to be effective. It does not shorten the duration of the illness, but does limit the duration of infectivity.

Guidelines for chemoprophylaxis

Chemoprophylaxis to prevent secondary transmission is not recommended in most situations because of the delayed presentation of the index case, and the cost and adverse effects of antibiotics. However, given the high risk of mortality and morbidity associated with infection of the newborn, particularly in the context of the rising incidence of pertussis in the community and the high transmission rate, chemoprophylaxis is recommended to limit transmission to those most at risk of the infection (that is, young infants). Data to support this recommendation are limited.

Australian guidelines recommend post-exposure chemoprophylaxis for contacts to whom transmission is most likely, and when there is significant risk of morbidity or mortality or risk of transmission to other high-risk groups.[2] These groups include:

- all household contacts of an index case when the household includes children less than two years who have received less than three doses of vaccine (including newborn infants)
- any woman in the last month of pregnancy
- all adults and children in a childcare arrangement with an index case, if the group contains children less than two years who have received less than three doses of vaccine
- healthcare workers in maternity and neonatal units
- infants in maternity and neonatal units where a healthcare worker was the infected case.

Therapy must be started within 21 days of exposure to the index case to be effective.

US guidelines for chemoprophylaxis[3,4] are broader than Australian guidelines and recommend prophylaxis for all household contacts and other close contacts, regardless of age and immunisation status. They also recommend prophylaxis for high-risk contacts after 21 days of illness in the index case.

UK guidelines[5] are similar to Australian guidelines, but extend 'vulnerable contact' definitions to include unimmunised and partially immunised infants or children up to 10 years of age, immunocompromised individuals and people with chronic illnesses (asthma, congenital heart disease).

Antibiotics

Macrolide antibiotics are the drugs of choice for prophylaxis. Trimethoprim-sulfamethoxazole is an alternative treatment. The duration of therapy is the same as a treatment course (Table 1). The age of the recipient, cost and availability are all important factors that determine the choice of the individual drug.

Azithromycin is the antibiotic of choice in infants under one month of age due to safety concerns about other macrolides in this age group, particularly the association between erythromycin, pyloric stenosis and cardiac arrhythmias.

Evidence

Published data on the efficacy of chemoprophylaxis for pertussis are limited. A Cochrane review of antibiotics for pertussis was updated in January 2011.[6] Two trials of antibiotic prophylaxis were included in the review. Both studies were prospective,

Table 1 **Recommended antibiotic for post-exposure prophylaxis for pertussis** [1]

Drug	Dose <1 month old	Dose 2–6 months old	Dose >6 months old	Adult dose
Azithromycin	10 mg/kg as a single dose for 5 days	10 mg/kg as a single dose for 5 days	10 mg/kg (max 500 mg) as a single dose for a day, then 5 mg/kg (max 250 mg) as a single dose for 2–5 days	500 mg day 1 250 mg days 2–5
Clarithromycin	Not recommended	7.5 mg/kg twice daily for 7 days	7.5 mg/kg twice daily (max 500 mg/dose) for 7 days	500 mg twice daily for 7 days
Erythromycin	Use if azithromycin unavailable Age <7 days: 10 mg/kg twice daily for 7 days Age 7–28 days: 10 mg/kg every 8 hours for 7 days	10 mg/kg every 6 hours for 7 days	10 mg/kg (max 250 mg/dose) every 6 hours (max 1 g/day) for 7 days	erythromycin: 250 mg every 6 hours for 7 days erythromycin ethylsuccinate: 400 mg every 6 hours for 7 days
Trimethoprim-sulfamethoxazole	Not recommended <2 months of age	4/20 mg/kg twice daily for 7 days	4/20 mg/kg (max 160/800 mg) twice daily for 7 days	160/800 mg twice daily for 7 days

randomised, controlled trials of erythromycin versus placebo for asymptomatic household contacts. In one of the trials, children less than six months old were excluded, and one of the trials had incomplete outcome data. Combined data demonstrated no statistically significant difference in *B. pertussis* culture positivity, whooping cough or paroxysmal cough in the treatment group compared to controls.

The efficacy of macrolide antibiotics for the treatment of pertussis was included in the same review.[6] Eleven randomised or quasi-randomised controlled trials were included. All trials involved only children. The review concluded that 'antibiotic treatment is effective in eliminating *B. pertussis* from the nasopharynx and thus rendering participants non-infectious, but does not alter the clinical course of the illness'. In terms of microbiological eradication and relapse, there was no difference in the efficacy of short (7 days) versus long courses (10–14 days) of erythromycin (estolate or unspecified salt of erythromycin), or short courses of erythromycin estolate (7 days) versus short courses of azithromycin (3–5 days) or clarithromycin (7 days). There is no evidence for the use of roxithromycin in the management of pertussis.

Other antibiotics that demonstrate similar efficacy to the macrolides include trimethoprim-sulfamethoxazole, oxytetracycline and chloramphenicol. Oxytetracycline and chloramphenicol are not recommended because of their more significant adverse effect profile, particularly in children.

Observational studies of post-exposure prophylaxis describe high rates of efficacy for erythromycin in reducing culture-confirmed *B. pertussis* in contacts of pertussis cases. They also report the prevention of clinical symptoms in these contacts as well as decreases in secondary transmission (attack rates) in household contacts.[6] Other studies report control of pertussis outbreaks with chemoprophylaxis in conjunction with other control measures including case isolation and treatment of cases (based on clinical and microbiological criteria).

The efficacy of prophylaxis is said to be optimal if given within 2–3 weeks of exposure (symptoms in the household contact case), but data are limited.

Safety of chemoprophylaxis

Adverse effects from therapy are of particular importance in young infants. All recommended antibiotics suggested for prophylaxis are associated with gastrointestinal adverse effects. Infantile hypertrophic pyloric stenosis may occur in neonates given erythromycin as post-exposure prophylaxis.[7]

Both clarithromycin and erythromycin inhibit cytochrome P450 3A. This is an important consideration if there is co-administration of drugs metabolised by this pathway. Azithromycin does not inhibit the P450 enzyme system to the same degree, but it is an inhibitor of P-glycoprotein. It has a better tolerability profile than the other macrolides. Trimethoprim-sulfamethoxazole is not recommended for pregnant women, nursing mothers, or infants aged less than two months. It can be associated with a range of hypersensitivity reactions, some of which are severe.

Cost and availability of azithromycin

Azithromycin is not listed on the Pharmaceutical Benefits Scheme for pertussis treatment or prophylaxis so it is expensive for the patient relative to the other macrolides. Its availability in some parts of the community is limited.[8]

Conclusion

National and international guidelines recommend prophylaxis with macrolides after exposure to pertussis in targeted groups. The efficacy of prophylaxis is limited in published trials, but observational data are encouraging. Its effectiveness in many situations may be further confounded because of delay in diagnosis of the index case.

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. Adolescents and adults with pertussis usually present with the classical paroxysmal cough with an inspiratory whoop.

4. Clarithromycin is not recommended as prophylaxis for pertussis in newborns.

Answers on page 103

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ARTICLE

Drug interactions: principles and practice

SUMMARY

Drug interactions are an avoidable cause of patient harm. Harm may occur due to either increased drug effect causing toxicity or decreased drug effect leading to therapeutic failure.

Drug interactions should be considered both in the differential diagnosis of symptoms (for interactions that have already occurred) and when prescription changes are made (for potential interactions).

Software checkers for drug interactions are widely available, but have limited clinical utility.

Patient harm from drug interactions can be reduced by:

- using a personal formulary – using few drugs and knowing them well
- recognising drugs that are major perpetrators of interactions
- recognising narrow therapeutic index drugs as vulnerable to interactions
- applying clinical pharmacology principles.

Introduction

A drug interaction occurs when a patient's response to a drug is modified by food, nutritional supplements, formulation excipients, environmental factors, other drugs or disease. Interactions between drugs (drug–drug interactions) may be beneficial or harmful. Harmful drug–drug interactions are important as they cause 10–20% of the adverse drug reactions requiring hospitalisation and they can be avoided.[1] Elderly patients are especially vulnerable – with a strong relationship between increasing age, the number of drugs prescribed and the frequency of potential drug–drug interactions.[2] Knowing how drug–drug interactions occur and how to manage them is an important part of clinical practice.

Types of drug–drug interactions

Interactions between drugs may be categorised by the underlying mechanism (see Box):

- *Behavioural* drug–drug interactions occur when one drug alters the patient's behaviour to modify compliance with another drug. For example, a depressed patient taking an antidepressant may become more compliant with medication as symptoms improve.[3]
- *Pharmaceutic* drug–drug interactions occur when the formulation of one drug is altered by another before it is administered. For example, precipitation of sodium thiopentone and vecuronium within an intravenous giving set.
- *Pharmacokinetic* drug–drug interactions occur when one drug changes the systemic concentration of another drug, altering 'how much' and for 'how long' it is present at the site of action.
- *Pharmacodynamic* drug–drug interactions occur when interacting drugs have either additive effects, in which case the overall effect is increased, or opposing effects, in which case the overall effect is decreased or even 'cancelled out'.

Pharmacokinetic drug–drug interactions

Pharmacokinetics is 'what the body does to the drug'. These interactions occur when one drug (the perpetrator) alters the concentration of another drug (the object) with clinical consequences.

Altered bioavailability

This occurs when the amount of the object drug reaching the systemic circulation is affected by a perpetrator drug. For orally administered drugs this occurs when absorption or first-pass metabolism is altered. Drugs with low oral bioavailability are often affected while those with high bioavailability are seldom affected. For example, alendronate and dabigatran have low oral bioavailability. Alendronate co-administration with calcium decreases

Box **Mechanisms of drug interactions**

Behavioural: altered compliance

Pharmaceutic: outside the body

Pharmacokinetic: altered concentration

- **B**ioavailability: absorption or first-pass metabolism
- **C**learance: metabolism or excretion of active drug
- **D**istribution: cell membrane transport to the site of action

Pharmacodynamic: altered effect

- Mechanism: molecular signal (e.g. receptor)
- Mode: physiological effect

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Key words
drug interactions, patient harm, pharmacodynamics, pharmacokinetics, therapeutic index

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Pharmacokinetic drug–drug interactions can be managed by recognising drugs with a narrow therapeutic index and the major perpetrators of altered drug metabolism. Any change in prescription should take particular note of these two groups of drugs.

bioavailability and can result in no alendronate being absorbed. Conversely, dabigatran co-administration with verapamil increases bioavailability and can result in an increased risk of bleeding.

Altered clearance

This occurs when the metabolism or excretion of the object drug is affected by a perpetrator drug. Object drugs with a narrow therapeutic index (see Table 1) are particularly vulnerable, as modest changes in concentration may be clinically important. Perpetrator drugs known to strongly affect drug metabolism (Table 2) are more likely to cause large concentration changes and hence clinical consequences.[4] Recognising these potential perpetrators of pharmacokinetic drug–drug interactions is important.

Metabolism

Changes in drug metabolism are the most important causes of unexpected drug interactions. These occur by changing drug clearance or oral bioavailability. There are several enzyme families involved in drug metabolism, and the cytochrome P450 (CYP) enzyme family is the most important (Table 2).

Inhibition of a cytochrome P450 enzyme increases the concentration of some drugs by decreasing their metabolism. For example, clarithromycin is a strong inhibitor of CYP3A-catalysed simvastatin metabolism, thus increasing the risk of myopathy.[5] Drug inhibition of cytochrome P450 enzymes is also used therapeutically. For example, ritonavir, a strong inhibitor of CYP3A, reduces metabolism of other protease inhibitors thus increasing their effectiveness in treating HIV (so called 'ritonavir-boosted' regimens).[6]

Induction of a cytochrome P450 enzyme decreases the concentration of some drugs by increasing their metabolism. For example, carbamazepine is a strong inducer of CYP3A that increases the metabolism of the combined oral contraceptive, thus increasing the risk of unwanted pregnancy.[7]

Table 1 **Examples of drug classes containing several narrow therapeutic index (object) drugs**

Drug class	Example
Antiarrhythmics	amiodarone
Anticoagulants	warfarin
Antiepileptics	phenytoin
Antineoplastics	sunitinib
Aminoglycoside antibiotics	gentamicin
Immunosuppressants	tacrolimus

The therapeutic index is often easier to recognise than define, as the vulnerability of the patient affects the dose–response relationship. A clinical question which is useful to identify a narrow therapeutic index drug is: would doubling or halving the dose of this drug have a major effect on this patient?

Prodrugs

Some drugs rely on cytochrome P450 enzymes for conversion to their active form. As this is usually dependent on a single enzyme pathway, prodrugs are particularly vulnerable to changes in metabolism. Inhibition of conversion from prodrug to active drug may lead to inadequate concentrations of the active drug and therapeutic failure. For example, tamoxifen is metabolised by CYP2D6 to its active form endoxifen, and concomitant therapy with the strong CYP2D6 inhibitor paroxetine has been associated with increased mortality in breast cancer.[8]

Excretion

Some drugs are excreted from the body unchanged in the active form, usually in the urine or via the biliary tract in the faeces. Changes in renal drug clearance may occur due to effects on renal tubular function or urine pH. For example, probenecid reduces the renal clearance of anionic drugs such as methotrexate and penicillin.

Altered distribution

This occurs when the concentration of drug at the site of action is changed without necessarily altering its circulating concentration. This is particularly an issue for drugs with intracellular or central nervous system targets. Some drugs cause significant changes in the cell membrane transport of other drugs. For example, verapamil inhibits efflux transporters (e.g. P-glycoprotein) increasing the concentrations of substrates such as digoxin and cyclosporin. Probenecid inhibits anion transporters (e.g. OAT-1) increasing the concentrations of substrates such as methotrexate and penicillins. Drug interactions involving transport are less well understood than drug interactions involving metabolism.

Pharmacodynamic drug–drug interactions

Pharmacodynamics is 'what the drug does to the body'. These interactions occur between drugs with additive or opposing effects. The brain is the organ most commonly compromised by pharmacodynamic interactions.

Pharmacodynamic interactions between drugs with additive effects may be intentional, for example when combining antihypertensives, or unintentional, for example serotonin syndrome caused by adding tramadol to a selective serotonin reuptake inhibitor (SSRI). Conversely, combining drugs with opposing effects can result in loss of drug effect, for example reduced bronchodilation by a $beta_2$ agonist prescribed with a non-selective beta blocker.[9]

Considering drug effects by organ is a useful way to recognise pharmacodynamic interactions. Ask yourself – might any of these drugs affect the same organ (for example the brain)? This approach allows you to consider interactions between drugs with different modes of action, for example an anticholinergic and a benzodiazepine.[10]

How to avoid unwanted drug–drug interactions in clinical practice

Ensure you have a full drug history including over-the-counter and herbal products. Pharmacodynamic drug–drug interactions can be anticipated based on knowledge of the clinical effects of the drugs involved. The better your pharmacological knowledge, the easier it is! Prescribe few drugs and know them well.

Pharmacokinetic drug–drug interactions are more difficult to anticipate since they are not predictable from the clinical effects of the drugs involved. Recognition of drugs that have a narrow therapeutic index (Table 1) and the major perpetrators of pharmacokinetic interactions (Table 2) will help identify most of these.

We use five 'rules' to manage potential drug–drug interactions in clinical practice:

1. Any *interactions* between existing drugs in a given patient have already occurred. Hence they are part of differential diagnosis.
2. Knowledge of the pharmacological effects of drugs and of patient physiology together allows recognition of potential pharmacodynamic drug–drug interactions.
3. Drugs with a narrow therapeutic index are particularly susceptible to pharmacokinetic drug–drug interactions (Table 1).
4. A small number of drugs are important 'perpetrators' of pharmacokinetic drug–drug interactions (Table 2).
5. Starting or stopping a drug is a prescribing decision that may cause a drug interaction.

Monitoring patients for drug toxicity or loss of efficacy is part of routine care. Checking for changes in symptoms, biomarkers of effect, or drug concentrations soon after prescription changes helps identify drug interactions early and can reduce harm.

Prescribe few drugs and know them well

Clinical resources for drug–drug interactions

A number of resources are available to help clinicians with drug–drug interactions:

- individual drug monographs in formularies, such as the Australian Medicines Handbook, are a useful starting point for learning about new drugs
- tables listing the major perpetrators of pharmacokinetic drug–drug interactions are available in the Australian Medicines Handbook or online (www.pkis.org)
- prescribing and dispensing software mostly generates alerts from tables of information about drug pairs. The time involved and the amount of irrelevant information retrieved may cause 'alert fatigue' and limit their clinical utility.[11]
- drug information services have access to reference information such as Stockley's Drug Interactions and Micromedex.

Pharmacodynamic drug–drug interactions can be managed based on anticipating known drug effects and monitoring the patient for those effects. They are often intentional. Unintentional harmful interactions are particularly common with multiple drugs acting on the central nervous system.

Conclusion

Most potential drug interactions can be recognised by applying principles of clinical pharmacology and good clinical care. Increased vigilance by clinicians at the time of changing drugs improves the chance of identifying unwanted drug interactions before they

Table 2 **Important perpetrators of cytochrome P450 drug–drug interactions** [4]

Enzymes	Inhibitors*	Inducers
CYP1A2	**ciprofloxacin, fluvoxamine,** ethinyloestradiol, interferon alfa-2b	phenytoin, rifampicin
CYP2C9	fluconazole	carbamazepine, rifampicin
CYP2C19	**fluconazole, fluvoxamine, ticlopidine,** fluoxetine, clarithromycin, voriconazole, moclobemide	lopinavir/ritonavir, rifampicin, St John's wort
CYP2D6	**bupropion, fluoxetine, paroxetine, perhexiline,** cinacalcet, doxepin, duloxetine, flecainide, moclobemide, quinine, terbinafine	
CYP3A	**macrolides e.g. erythromycin, clarithromycin** **azole antifungals e.g. voriconazole, itraconazole, ketoconazole,** fluconazole, posaconazole **protease inhibitors e.g. indinavir, ritonavir, saquinavir,** atazanavir, fosamprenavir non-dihydropyridine calcium channel blockers e.g. diltiazem, verapamil **grapefruit juice**, aprepitant, cimetidine, ciprofloxacin, cyclosporin, fluvoxamine, imatinib	carbamazepine, modafinil, phenytoin, phenobarbitone, rifabutin, rifampicin, St John's wort

* bold font indicates very strong inhibitors

cause significant harm. Knowing a few drugs well and making judicious use of available information is more effective for managing drug interactions than relying solely on electronic decision support. ◀

Conflict of interest: Dr Polasek has consulted for Genelex Corporation on the GeneMedRX Drug Interaction Checker. Dr Snyder, Dr Doogue: none declared.

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SELF-TEST QUESTIONS

True or false?

5. Drugs with high oral bioavailability are often affected by pharmacokinetic drug interactions.

6. Fluvoxamine is a strong inhibitor of cytochrome P450 2C19.

Answers on page 103

Drug interactions

Fatal rhabdomyolysis following voriconazole and simvastatin

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Case

An 85-year-old woman presented with an acute onset of generalised weakness and functional decline. The patient had a history of insulin-requiring diabetes, hypercholesterolaemia, hypertension, glaucoma and chronic kidney disease. She also had longstanding fungal keratitis (>60 days) which had been unsuccessfully treated with topical therapy.

The patient's chronic conditions were managed with multiple medications, including simvastatin 20 mg daily. She had started oral voriconazole, 200 mg twice a day, 32 days before her admission.

The patient was observed in hospital for a few weeks. She was examined by two ophthalmology senior house officers and an infectious diseases physician before a general physician made the diagnosis of rhabdomyolysis.

Blood tests showed a creatine kinase of 23 200 U/L (normal range 34–145), aspartate transaminase 1030 U/L (<31), alanine transaminase 393 U/L (<34) and creatinine 255 micromol/L (<110). Sodium, potassium, prothrombin time and full blood count were normal.

The rhabdomyolysis was suspected to be the result of a drug interaction between simvastatin and voriconazole.[1] Both drugs were ceased on day 20 of the patient's admission and her blood tests improved. Unfortunately, the woman's clinical symptoms did not resolve and she died of respiratory failure secondary to respiratory muscle weakness 10 days after the concurrent therapy was stopped.

Comment

Simvastatin is a substrate of cytochrome P450 3A4[2] and voriconazole is a known inhibitor of this enzyme.[2] However, their interaction is not documented specifically in key reference sources such as the Australian Medicines Handbook or in the product information, although class interactions are detailed.[2] It is listed as an interaction in dispensing software.[3]

Throughout the admission, the patient's medication was reviewed by three different clinical pharmacists.

They conducted a thorough medication history, reconciled this with her current medication chart and signed for pharmaceutical review without noticing the interaction.

A contributing factor to the interaction being overlooked was that there were multiple medication charts in use. As the woman was on simvastatin from home, it was not individually dispensed for her or entered on her previous discharge prescription. Simvastatin and voriconazole were therefore on different charts and the hospital pharmacy was only asked to supply voriconazole. Dispensing software would therefore not detect an interaction. A pharmacist could have independently identified the interaction on review of all charts, if they had been presented together.

The patient was on a low dose of simvastatin. As the risk of myopathy is linked to higher doses,[2] the clinicians may not have considered that there was a risk of a significant interaction. However, the woman was elderly with impaired renal function and multiple comorbidities, so she was at increased risk of adverse effects. Assessment of her drugs in relation to her condition did not result in any preventive actions such as reducing the dose of simvastatin, ceasing it altogether or ensuring monitoring for any signs of myopathy or altered blood test results.

Voriconazole requires multiple approvals for use in our hospital. The pharmacists stated that they focused primarily on the processes of approval and medication reconciliation. They did not consider whether the drug choice was appropriate or whether the patient's therapy needed reviewing in light of the new medicine. They described medication reconciliation as 'matching up' the patient's previous and current medications. The lack of a focus on anticipating, mitigating or preventing drug–drug, drug–patient and drug–disease processes resulted in none of the pharmacists identifying the potential drug interaction.

Conclusion

The interaction between voriconazole and simvastatin is not adequately described in commonly available references. The clinical significance of this interaction may be increased when individual patient factors are taken into account. Clinicians should be vigilant for this interaction and the need to consider individual risk factors when reviewing patients. A focus on tasks and processes in hospitals runs the risk of removing the patient as the focus of care. ≺

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ARTICLE

Treatment of age-related macular degeneration

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anti-vascular endothelial growth factor, bevacizumab, choroidal neovascularisation, ranibizumab

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SUMMARY

Age-related macular degeneration is a common cause of visual loss. There may be choroidal neovascularisation or geographic atrophy.

Evidence is accumulating for the importance of avoidable risk factors in age-related macular degeneration, such as smoking and obesity.

Research confirms that there is an important hereditary component to the disease.

Anti-vascular endothelial growth factors have improved the outlook for patients suffering from neovascular age-related macular degeneration. Recent work has concentrated on refining the frequency and pattern of delivery of these drugs to the vitreous cavity.

There are few treatment options for geographic atrophy.

Introduction

Age-related macular degeneration is the leading cause of irreversible visual loss in Australia, and as the population ages its prevalence is increasing. Although the macula is only a small part of the retina the disease results in the loss of the central field of vision.

Pathology

In the early stage of the disease, drusen as well as pigmentary disturbances develop in the deep layers of the retina at the level of the retinal pigment epithelium/Bruch's membrane complex. Drusen are small deposits of extracellular material which appear as pale yellow deposits on fundoscopy, and accumulate preferentially in the macula (Fig. 1). Although not usually associated with any visual symptoms, they represent a risk of progression to the vision-threatening complications of late age-related macular degeneration.

Two types of late age-related macular degeneration are responsible for visual loss. These are choroidal neovascularisation, or 'wet' age-related macular degeneration, and geographic atrophy, or 'dry' age-related macular degeneration. The wet form accounts for approximately 10% of all cases of late age-related macular degeneration, but it is responsible for up to 90% of cases of severe visual loss.

In choroidal neovascularisation a network or 'membrane' of abnormal blood vessels breaks through into the retinal layers from the underlying choroid. This leads to haemorrhage, oedema and exudate beneath and within the retina (Fig. 2), often resulting in a rapid and profound loss of central vision. The subsequent formation of a fibrotic disciform scar (Fig. 3) leads to permanent visual loss.

Geographic atrophy is a much more gradual process. The loss of visual function is the result of progressive loss of photoreceptors and retinal pigment epithelium at the macula (Fig. 4).

Risk factors

The main ocular risk factor for late age-related macular degeneration is the presence of drusen and pigmentary abnormalities in the central macula. The greater the area of drusen at the macula the greater the risk of progression to loss of vision. These early changes can be detected with the direct ophthalmoscope or a slit lamp.

The major risk factors associated with late age-related macular degeneration are advancing age, smoking and a family history of age-related macular degeneration.[1] Current smoking increases the relative risk by 1.8 compared to those who have never smoked.

The increased risk to siblings is estimated at between two- and six-fold. Less consistently associated risk factors are high body mass index, cardiovascular disease, hypertension and a variety of dietary patterns.[2]

Genetics

Over the last 10 years genetic research has led to a better appreciation of age-related macular degeneration as an inherited disease. Variations in the complement factor H gene on chromosome 1 have been linked to a significantly increased risk of the disease. The complement factor H protein is involved in the regulation of the complement cascade. Its link with age-related macular degeneration implicates inflammation in the disease pathway. Several other genetic associations have been identified, including other complement-related genes. Genetic associations have been found for both early and late age-related macular degeneration. Research into the interaction

of genes and environmental risk factors is currently an area of active investigation.[3]

Treatment

Treatment options for the atrophic form of late age-related macular degeneration are still only in the clinical trial phase. However, the efficacy of treatment for neovascular age-related macular degeneration has improved dramatically over the last 10 years. This is particularly because of the anti-vascular endothelial growth factor (anti-VEGF) therapies. The improvement in the visual prognosis that has followed their introduction has made it all the more important that patients with this form of the disease are referred promptly. The main symptoms that should prompt early referral to an ophthalmologist are the new onset of central visual distortion or painless blurred central vision.

Laser photocoagulation

The membrane of new vessels can be ablated by direct application of a thermal laser. As this treatment also destroys the retina overlying the new vessels, it is suitable only for lesions away from the central macula or fovea. While it can in some cases give a permanent regression of vessels, a large proportion of the membranes unfortunately recur after treatment. The main drawback is that more than 80% of lesions are under the fovea at the time of presentation, making them unsuitable for laser photocoagulation. It still remains a viable treatment today for lesions that are away from the fovea (extrafoveal).

Photodynamic therapy

In the early 2000s photodynamic therapy began to be used for subfoveal neovascular age-related macular degeneration. It involves the intravenous infusion of the photosensitve drug verteporfin, which preferentially accumulates in the neovascular tissue. Application of a low energy, non-thermal laser over the affected part of the retina results in free radical formation and secondary selective thrombotic closure of the abnormal vessels.

The effect is temporary and regular three-monthly treatments are often required. A further drawback

Fig. 1 **Drusen in the central macula in age-related macular degeneration**

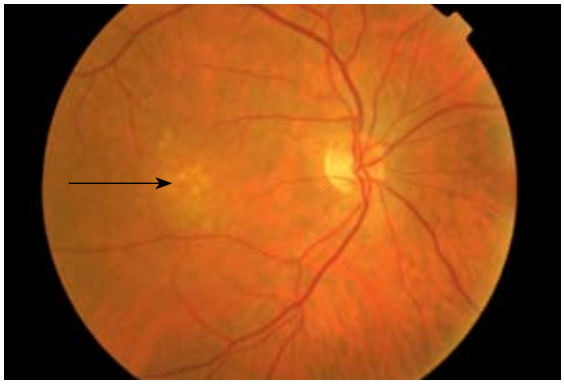


Fig. 2 **Subretinal haemorrhage in choroidal neovascularisation**

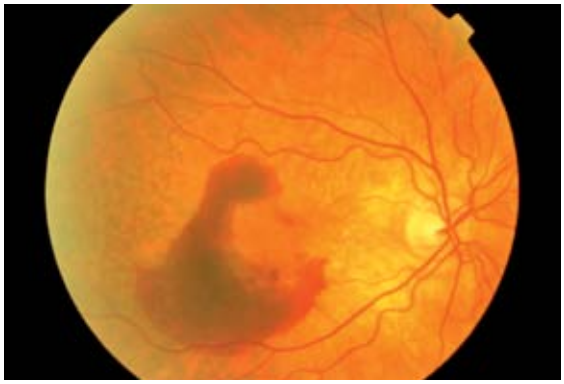


Fig. 3 **Fibrotic scar as the end result of late age-related macular degeneration**

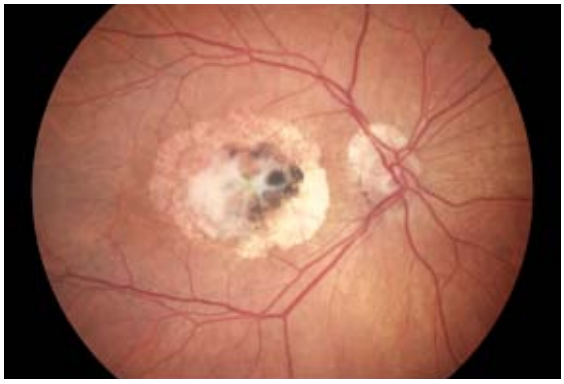
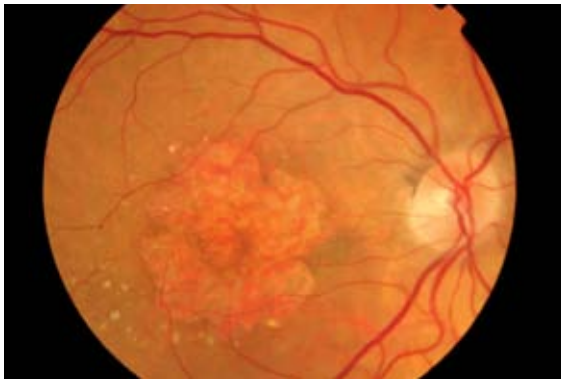


Fig. 4 **Geographic atrophy, one form of late age-related macular degeneration**



is that photodynamic therapy, while less destructive than thermal laser, usually results in atrophic areas within the central macula where the treatment was applied. The overall effect of photodynamic therapy is a slowing in the rate of progression of visual loss in neovascular age-related macular degeneration. It virtually never improves vision, but does continue to find a role in the treatment of some variants of age-related macular degeneration such as idiopathic polypoidal choroidal vasculopathy and other rare macular diseases.

Anti-vascular endothelial growth factor drugs

All previous treatments for age-related macular degeneration have now been almost completely superseded by anti-VEGF drugs. VEGF has long been suspected to be a mediator in choroidal neovascularisation.[4] Two anti-VEGF drugs, ranibizumab and bevacizumab, are currently in regular clinical use.

Ranibizumab

Ranibizumab is an antibody fragment directed against the A isoform of human VEGF. Two phase III clinical studies named ANCHOR and MARINA found vastly superior visual outcomes with four-weekly injections of ranibizumab compared to photodynamic therapy or sham injections, with all angiographic subtypes of sub-foveal membranes responsive to treatment.

In ANCHOR,[5] patients with the angiographically defined 'classic' form of choroidal neovascularisation were enrolled. The average change in vision at 12 months in the ranibizumab-treated group was an improvement of 11 letters on a standard acuity chart, compared with a loss of nine letters in the photodynamic therapy group.

The MARINA study[6] looked at the response in those defined angiographically as minimally-classic or occult choroidal neovascularisation, a subgroup which did not respond well to photodynamic therapy. After 12 months there was a 7-letter gain for ranibizumab-treated patients compared with a 10-letter loss in a sham treatment group. Stabilisation of vision was achieved in 94% of the treatment group, compared with 62% of the sham group.

Ranibizumab is expensive (around $2000 per dose). There is a large burden from ongoing monthly injections, in a large and growing population of patients, with treatment continuing for many years.

Bevacizumab

Bevacizumab is a significantly less expensive anti-VEGF drug. It is a full-length antibody used in the treatment of metastatic colorectal cancer. Although it is not approved for use in age-related macular degeneration, bevacizumab is frequently used 'off label' as an alternative to ranibizumab.

The Comparison of Age-related macular degeneration Treatment Trial (CATT)[7] was designed to compare the efficacy of bevacizumab to ranibizumab. It also investigated whether an 'as required' injecting regimen, based in part on high-resolution retinal imaging, could give visual outcomes as good as those with regular monthly injections. After 12 months there was equivalent efficacy both between the two drugs and between the two dosing regimens. Potentially, these data have important implications for the cost and streamlining of treatment services.

Procedure

Anti-VEGF drugs are injected into the vitreous cavity. The standard technique involves instillation of local anaesthetic and dilute povidone iodine drops, and a sterile eyelid speculum. A dose of 0.05 mL of the anti-VEGF drug is then given by trans-scleral injection through a 30-gauge needle. This is commonly performed in a treatment room setting.

Adverse effects

The ocular risks are low and relate mainly to the mechanical process of injecting into the vitreous cavity. They include endophthalmitis, at a rate of approximately 1 in 2000, traumatic cataract, and retinal detachment. Transient symptoms of ocular surface discomfort, bruising and floaters are common, but severe discomfort, worsening vision, or a persisting shadow in the vision should prompt early review by the specialist.

There is a theoretical risk of systemic effects from the intravitreal administration of these drugs, based on those seen with systemic anti-VEGF treatments. These are mainly related to arterial thromboembolic complications such as stroke. A small increased risk of arterial thromboembolic complications in an elderly population is difficult to determine, with large numbers needing to be followed to confirm a small increase in risk. To date no statistically significant increased risk has been confirmed, although ongoing safety studies continue.

Prevention

The Age-Related Eye Disease Study (AREDS)[8] investigated the use of high dose antioxidants (vitamin C, vitamin E and beta carotene) combined with zinc over a five-year period to slow progression of disease. Results suggested a modest benefit in slowing progression in only certain subgroups of early age-related macular degeneration. Much debate has ensued regarding the risks and benefits

of long-term high-dose supplementation. The Age-Related Eye Disease Study 2 (AREDS2) is re-investigating the use of different combinations and doses of the antioxidant vitamins along with other supplements including lutein, zeaxanthin and omega-3 long-chain polyunsaturated fatty acids.[9]

Future therapies

Research is continuing to refine and tailor the delivery of the existing anti-VEGF therapies on an individual patient basis. This is according to the behaviour of an individual's neovascular membrane and the appearance of the retina on various imaging techniques during follow-up. Further efforts are looking into other anti-VEGF drugs, formulations with a longer half-life in the vitreous cavity, alternative means of delivery to the retina, and combination treatments. Predictors of the response to treatment are also being researched to further individualise the treatment protocols. Much effort is going into understanding the underlying pathophysiology of age-related macular degeneration to allow interventions that prevent or delay the onset and its progression.

Conclusion

Age-related macular degeneration is the leading cause of irreversible visual impairment in Australia, with the neovascular form of late age-related macular degeneration responsible for the large majority of cases of severe visual loss. The introduction of the anti-VEGF therapies has revolutionised the outlook for patients suffering this devastating form of the disease. When symptoms of visual distortion or central visual loss are reported, early review by an eye-care professional and referral as appropriate to specialised care remains key to improving an individual patient's prognosis. ◁

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

7. Photodynamic therapy improves vision in patients with neovascular age-related macular degeneration.

8. A persistent shadow in the vision after treatment with ranibizumab requires rapid referral to a specialist.

Answers on page 103

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Macular Degeneration Foundation

The Macular Degeneration Foundation is a national organisation based in Sydney, which aims to reduce the incidence and impact of macular degeneration in Australia.

The Macular Degeneration Foundation website contains fact sheets on macular degeneration, lifestyle advice, information for families and carers, quarterly newsletters with tips for those with low vision, and links to related websites.

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DIAGNOSTIC TESTS

Cytology

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cervical screening, fine needle aspiration, Pap smear

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SUMMARY

Cytology allows the diagnosis of malignancy from a small number of cells. Cervical Pap smears are the most recognised example of this kind of testing and have dramatically reduced the incidence of squamous cervical carcinoma.

Cytology provides a minimally or non-invasive means of obtaining samples and allows analysis of specimens such as exfoliated cells in sputum and urine, and pleural, pericardial, cyst and ascitic fluids.

Fine needle aspiration yields cell samples from palpable lesions, and under image guidance from inaccessible sites such as the mediastinum, lung, head of pancreas and para-aortic lymph nodes.

Specimens are often small and to obtain maximum value it is vital that the request clearly specifies the question that is being asked and gives all the relevant clinical information.

Introduction

Cytology is literally 'the study of cells' and is related to anatomical pathology. While histology uses tissue sectioning techniques, cytology uses various cell preparation technologies. Specimens are obtained mechanically, by scrapings or needle aspirates, or by collection of exfoliated material from various body fluids. Gynaecological cytology, in the form of Pap (Papanicolaou) smears, is the most recognised type of test. However a wide variety of specimens are analysed by cytologists and cytopathologists, including urine, sputum and other body fluids. Fine needle aspiration specimens are also taken from sites such as lymph nodes, breast, thyroid and liver.

As with many tests, appropriate clinical information and patient history are essential and enable directed ancillary testing of limited material. Unfortunately, when this information is not provided it can lead to delay or failure of diagnosis due to an exhausted specimen. Communication is important and patients will benefit if their doctor has a good relationship with the cytology department.

Gynaecological cytology (Pap smears)

The cervical Pap smear is a long established screening test for cervical carcinoma. It identifies premalignant changes and allows selection of women with at-risk findings for more intense clinical examination, treatment and follow-up. It is very successful for detecting squamous lesions and can prevent most squamous cell carcinomas. In 1991, squamous cervical cancer occurred at a rate of 12.4/100 000. This had fallen to 5.4/100 000 by 2006.[1] Some glandular abnormalities including adenocarcinoma *in situ* can also be identified on Pap smears, however this is not the main aim of cervical screening programs.

Australian guidelines[2,3] recommend screening every two years for all women over 18 years of age or two years after onset of sexual activity. Women over the age of 70 with two negative screens in the preceding five years can reasonably stop. The biggest risk factor for cervical cancer in Australia is not being screened, with 65% of all carcinomas identified in women who have been underscreened. The current Medicare Schedule provides a rebate for a conventional Pap smear.

Human papillomavirus is the main cause of cervical cancer. The transformation zone of the cervix is the area most susceptible to this infection and is sampled when collecting a Pap smear. This involves scraping the cervix transitional zone with a spatula or brush, then smearing the sample onto a glass slide and fixing with alcohol while still wet. Sampling should be taken by rotating the device around the endocervical canal. Abnormality develops at the squamo-columnar junction. This is the edge of any visible eversion/ectropion and care should be taken to sample this area.

Alternative monolayer technologies are equally effective but are not eligible for a Medicare rebate. After sampling, the plastic, not wooden, collection implement is vigorously agitated into a fixative solution to produce a cell suspension. This is subsequently processed in the laboratory to generate a more homogeneous specimen and a slide with cells spread one cell thick (thin layer or monolayer), with reduced obscuring factors such as blood or inflammation. After preparation of a conventional Pap smear, the plastic sampling brush can be rinsed into solution which can then be used for monolayer technology. Microbiological testing for chlamydia, by

polymerase chain reaction, and DNA subtyping of human papillomavirus (HPV) can also be performed on this solution.

Currently, DNA human papillomavirus testing and subtyping for high-risk strains can be used as an indicator of risk of recurrence of high-grade abnormality and as a 'test of cure'. A concurrent negative Pap smear with no high-risk human papillomavirus subtypes detected for two consecutive years enables a patient with a previous high-grade lesion to return from yearly screening to routine two-yearly screening. This use is covered by Medicare.

Sputum cytology

Sputum cytology is a diagnostic test not a screening test. A series of three deep cough morning sputum specimens has a 66% sensitivity for confirming lung carcinoma.[4] A single sputum specimen has a sensitivity of 0.1–0.7, averaging 0.22 in a review of published studies.[5] There is a small gain in additional specimens (up to five). Post-bronchoscopy sputum samples sometimes give diagnoses not achieved by other means.

Critical to sputum specimens is 'deep cough'. Many specimens are oral and contain saliva, oral squamous cells and micro-organisms. Cytologists judge sample adequacy by the presence of pigmented pulmonary macrophages. Cytology can only examine a small quantity of material so technologists subsample by picking blood or streaked areas for slide production. Sputum is mostly mucus which interferes with the creation of a homogeneous representative subsample and limits the diagnostic yield. However, with some manipulation monolayer and similar technologies can be used.

Sputum is more likely to be diagnostic with large and central lung lesions and less likely with small and peripheral lesions. Cytology can usually make the therapeutically vital distinction between small cell and non-small cell carcinomas. There is greater difficulty in reliably distinguishing adenocarcinoma, squamous cell carcinoma and large cell carcinoma, particularly when poorly differentiated. The distinction has become important with oncologists wishing to screen adenocarcinomas for activating mutations of epidermal growth factor receptor to determine eligibility for specific inhibitors such as gefitinib. Currently this requires a tissue sample or a good cell block preparation (more than a hundred malignant cells on the slide). This would normally require fine needle aspiration or core biopsy.

Urine cytology

Urine cytology is very sensitive for detecting high-grade urothelial malignancy (papillary neoplasm, invasive and *in situ*) as these cells are recognisably malignant and shed readily. Cytology may be correctly positive when cystoscopy is negative for these malignancies. However, cytology is insensitive for diagnosing low-grade urothelial neoplasms and papillomas as these cells appear normal or near normal. The only abnormalities found may be increased cellularity and increased cell groups which are sometimes papillary. When made, the diagnoses of low-grade urothelial neoplasms and papillomas are sometimes incorrect, reflecting the difficulties.

Sensitivity for high-grade lesions makes urine cytology useful in screening high-risk groups such as workers with exposure to carcinogenic chemicals. It is also useful for investigating symptomatic patients and in follow-up of patients with previous urinary tract malignancy. There is no role in detecting solid renal tumours or prostatic carcinomas as these shed only small numbers of cells late in their natural history.

Confounding factors in diagnosis

Inflammation caused, for example, by therapeutic Bacillus Calmette-Guérin (BCG – the tuberculosis vaccination organism used to treat bladder carcinoma) can generate prominent reactive cytological changes. Instrumentation and catheters can result in increased cellularity and cell grouping. These can confound cytological diagnosis and it is helpful if this information is provided on the request form. Giving details of how the sample was collected (instruments used) is also vital.

Urine is a harsh environment for cells and degenerative change is common. In combination with inflammation and instrumentation, it leads to a moderate number of specimens being called 'atypical'. A short series of three morning 50 mL specimens is preferred from ambulatory patients, but not first void of the day, as cells in these samples may have been sitting all night in urine.

Other specimens for cytology

Cytologists also examine other body fluids including pleural, ascitic and cyst fluid, as well as fine needle aspiration specimens from sites such as lymph nodes, breast, thyroid and liver.

Pleural, pericardial and ascitic fluid

Aspirated fluids are commonly sampled when looking for a malignancy. The preferred sample volume is 50–100 mL. While 1–2 L may have been removed from the patient, such specimens are simply too hard to manipulate and store. In contrast, smaller samples do not allow for production of a cell block and immunohistochemistry.

Synovial fluid

Ordering cytology on synovial fluid specimens is often unnecessary or wasteful. Where possible, diagnosis should be made by other means.

Cerebrospinal fluid

Cerebrospinal fluid specimens are usually examined cytologically. The composition of any cell content can be identified, such as neutrophils in bacterial meningitis or lymphoid cells in viral meningitis. Less commonly, malignant cells from haematopoietic malignancies (leukaemia, lymphoma), epithelial malignancies (breast cancer) and brain (ependymoma, medulloblastoma) can be found. Cerebrospinal fluid is a poor medium for cells and is ideally processed for slides within an hour of collection.

Fine needle aspiration

This involves collecting a specimen from a mass using a fine needle, paradoxically, usually without aspiration. The quality of the sample depends on the operator and their experience. Many pathology services provide clinics or appointments for patients with palpable lesions so specimens can be collected by an experienced pathologist.

Fine needle aspiration can be a very successful diagnostic strategy. It is as accurate and successful as core biopsies in the diagnosis of breast malignancy, but not for distinguishing invasive from *in situ* neoplasms (ductal carcinoma *in situ*).[5,6] This level of success can only be achieved with a sufficient flow of specimens through the laboratory to develop true expertise. Pathological assessment of a fine needle aspirate has been part of the triple test for breast malignancy with clinical and radiological assessment. When any of the assessments disagree, biopsy is performed – a strategy that has ensured quality. The tendency is for more core biopsies with prognostic and therapeutic markers to be done on the samples enabling presurgical hormone treatment or chemotherapy.

Image guidance

Image guidance, including ultrasound, computed tomography and conventional X-ray (for example angiography) is increasingly used by radiologists to sample impalpable, deep, intra-abdominal or intrathoracic lesions, such as para-aortic lymph nodes and lung masses. Attendance by cytology staff at the procedure can be an advantage as they can provide immediate feedback on the adequacy of a specimen. This reduces the need for repeat biopsies and additional patient anxiety.

Image guidance for palpable lesions is sometimes appropriate. For example, ultrasound guidance for thyroid nodule fine needle aspiration helps ensure that the tissue comes from the targeted nodule and not adjacent thyroid tissue.

Most recently, ultrasound-guided fine needle aspiration via endoscope has become possible with the endoscope serving as the ultrasound probe and the needle channel. In the upper gastrointestinal tract, this is being used to access the pancreas, bile duct and upper abdominal lymph nodes and allows pathological confirmation of carcinoma of the head of the pancreas. Ultrasound-guided fine needle aspiration via bronchoscope is being used to access mediastinal lymph nodes.

Cell blocks

The amount of material obtained in cytological preparations is small – a fine needle aspiration pass might yield 10 microlitres. This sample is used not only to make slides, from what will hopefully yield a diagnosis, but also for supplementary testing.

Table 1 **Examples of supplementary technologies used with cytology**

Technique	Indication	Purpose
Flow cytometry	Suspicious lymphoid population	Lymphocyte clonality to prove lymphoma, lymphocyte subtyping
Microbiology	Granulomatous	Culture
Immunostains*	Malignancy in pleural fluid	Distinguish between carcinoma and mesothelial cells
	Unidentified malignancy	Distinguish carcinoma and melanoma
	Carcinoma, unknown primary	Identify primary site of carcinoma
	Breast cancer	Detect prognostic markers on breast carcinoma: oestrogen receptor, progesterone receptor, HER2 amplification
		Determine eligibility for therapy
Molecular markers	Lung adenocarcinoma	Detect EGFR mutations to determine eligibility for therapy

HER2 human epidermal growth factor receptor 2
EGFR epidermal growth factor receptor
* While immunostains can be done on smears, cell blocks are a more effective and productive strategy

Specimens are often mixed with agar to lock the cells into a gel, a cell block, which can then be processed and sectioned using histology (Table 1). Cell blocks can be processed from most cytology specimens if required but are commonly made from fluid and fine needle aspirates when adequate material is received.

Immunohistochemistry

Immunostains are not one test but a selection of possibly hundreds of antibodies or stains that detect specific cell markers. The amount of sample and cost limit their use to a small number on any occasion. A clear request establishing what question needs answering together with basic clinical information can make all the difference in the outcome of the investigation. For example, a history of colonic carcinoma or a known ovarian mass would enable targeting of the test to markers for those malignancies.

The use of molecular markers to define eligibility for new anticancer drugs is increasing, putting pressure on fine needle aspiration as an adequate source of tissue. This may shift the diagnostic process towards more invasive core biopsies processed as histology specimens. However, new needle designs may increase the tissue recovery and provide larger and more consistent fragments for cell blocks. These have been developed initially for endoscopic fine needle aspiration and currently await approval from the US Food and Drug Administration.

Conclusion

Cytology is the original minimally invasive diagnostic technology beginning with exfoliated cells, aspirated fluid and subsequently fine needle aspirations. As endoscopic and imaging technologies have advanced, the surgical diagnostic specimen is being replaced by small image-guided fine needle aspirations and core biopsy specimens which provide a challenge for pathologists to do more with less. ◁

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

9. Urine cytology is sensitive for detecting solid renal tumours.

10. Fine needle aspiration is as effective as core biopsies for diagnosing breast cancer.

Answers on page 103

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Valediction

Dr Shanthi Kanagarajah

Dr Shanthi Kanagarajah joined the Editorial Executive Committee of *Australian Prescriber* in 1997. Despite a career which has seen her move between Newcastle, Wollongong, Melbourne, Sydney and Brisbane, she has always maintained her strong commitment to *Australian Prescriber*. Dr Kanagarajah firmly believes in the importance of independent information about therapeutics and helped to ensure editorial independence was maintained when the National Prescribing Service – now NPS, Better choices, Better health – took over the publication of the journal in 2002.

In view of Dr Kanagarajah's extensive experience with *Australian Prescriber*, it was appropriate that she concluded her time with the journal as the chair of the Editorial Executive Committee. The editorial team has appreciated Dr Kanagarajah's good humour in steering the Committee through many manuscripts. Dr Kanagarajah has a sound understanding of the matters which are important to practising clinicians and this has supported the continuing growth in the readership of the journal. She has particularly supported the journal's online development. Despite retiring from the Committee, Dr Kanagarajah will continue to contribute to the quality use of medicines in Australia.

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Volume 3, Number 3, June 2012

In this issue

Candesartan, fetal malformations and use in pregnancy

Health professionals are reminded that candesartan and other angiotensin II receptor antagonists, as well as ACE inhibitors, are contraindicated in pregnancy. Exposure to these drugs in pregnancy can cause fetotoxicity. Patients who are pregnant or planning a pregnancy should be switched to an alternative antihypertensive agent.

Reported cases

The TGA has received four reports of fetal abnormalities following candesartan use in pregnancy, including three reports in 2011. In one case, candesartan was started before conception and continued to 30 weeks gestation. The fetus was diagnosed with renal failure, nephrocalcinosis and congenital genitourinary system abnormalities. In another case, anhydramnios and possible renal dysplasia was diagnosed. Fetal death occurred at 34 weeks, seven weeks after ceasing candesartan. A third case reported renal failure and kidney malformation.

The TGA has also received reports of fetal abnormalities following the use of irbesartan, enalapril, lisinopril, perindopril and captopril during pregnancy.

Risk of fetal malformations

Angiotensin II receptor antagonists and ACE inhibitors are classified as Australian pregnancy category D. Their use is contraindicated in pregnancy.

Antihypertensives acting on the renin-angiotensin system have been associated with decreased renal function, oligohydramnios and retardation of skull ossification in the fetus. Their use in pregnancy has been associated with neonatal problems such as renal failure, hypotension and hypokalaemia.[1] The risk of fetal abnormalities is considered greatest with second and third trimester exposure.[2]

Advice for health professionals

Health professionals should review the use of angiotensin II receptor antagonists and ACE inhibitors in women of child-bearing age. These women should be advised of the risks to the fetus and counselled on the use of appropriate contraception to avoid inadvertent fetal exposure. Patients taking an angiotensin II receptor antagonist or ACE inhibitor should be advised to speak to their doctor if they may be pregnant, or planning a pregnancy. Women who are pregnant or planning a pregnancy should be switched to an alternative antihypertensive agent. Information on the use of antihypertensive drugs in pregnancy can be found in the April 2012 issue of *Australian Prescriber*.[3]

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Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

Zolpidem: continued reporting of abnormal sleep-related events and amnesia

The TGA continues to receive reports of potentially dangerous, complex sleep-related behaviours, amnesia and hallucinations associated with zolpidem use. Patients should be reminded of the risks associated with the use of hypnotics. Health professionals are encouraged to report cases to the TGA, including suspected cases.

Zolpidem, a non-benzodiazepine gamma-aminobutyric acid (GABA) receptor agonist, is indicated for the short-term treatment of insomnia in adults. It has been marketed in Australia since 2000 under various trade names, including Stilnox. The TGA has previously alerted prescribers to the spectrum of spontaneously reported adverse events and the risk of parasomnias associated with its use.[1,2]

In 2007, the Australian media drew attention to reports of parasomnias, amnesias, hallucinations and suicidality with zolpidem use. Subsequently, the following boxed warning was added to the zolpidem Product Information (PI):

> Zolpidem may be associated with potentially dangerous complex sleep-related behaviours which may include sleep walking, sleep driving and other bizarre behaviours. Zolpidem is not to be taken with alcohol. Caution is needed with other CNS depressant drugs. Limit use to four weeks maximum under close medical supervision.

Reported cases

A study of reports received by the TGA between 2001 and 2008 concluded that there was 'an association between zolpidem exposure and parasomnias, amnesia and hallucination both before and after the cluster of media publicity beginning in early 2007'.[3] Despite the publicity, reporting of these adverse events has persisted at high levels (see Table).

A recent study which found that hypnotics (e.g. temazepam, zolpidem) are associated with a substantially elevated hazard of dying has revived the debate about the risks of hypnotic use.[4]

The use of zolpidem may unmask pre-existing depression and suicidal tendencies; the current PI for zolpidem has a precaution regarding depression, psychosis and schizophrenia. More than half of the deaths reported to the TGA in patients taking zolpidem have occurred in conjunction with either alcohol use (which is contraindicated) or concomitant use of antidepressants or antipsychotics, which suggests a pre-existing psychiatric diagnosis.

Information for health professionals

Five years after increased media attention there continues to be reporting of potentially dangerous complex sleep-related behaviours, amnesia and hallucinations. When considering the use of zolpidem in the management of insomnia, prescribers should advise patients of the contraindications and precautions listed in the PI, and of the spectrum of adverse effects associated with zolpidem use.

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Table
Commonly reported adverse events for zolpidem Jan 2009 – Apr 2012

Adverse event	All medicines (Zolpidem)
Somnambulism	54 (29)
Abnormal sleep-related event	36 (28)
Amnesia*	201 (27)
Hallucination	536 (12)
Drug dependence	96 (7)
Abnormal behaviour	190 (7)
Road traffic accident	40 (6)

* Includes the following terms: amnesia, anterograde amnesia, dissociative amnesia, paramnesia, retrograde amnesia, transient global amnesia

MEDICINES SAFETY UPDATE

Renal function assessment in prescribing

The Cockcroft-Gault (CG) formula to calculate creatinine clearance (CrCl) should be used to estimate renal function in patients being prescribed drugs which are preferentially renally excreted.

True glomerular filtration rate (GFR) is most accurately assessed by radioisotopic measurement. However, as this test is time consuming, expensive and likely to delay appropriate clinical management, it has a limited role in the immediate management of most patients.

Measured CrCl has historically been used to estimate GFR, however it is also time and labour intensive, and can be unreliable; the gain in accuracy is minimal compared to using estimates of GFR.

Estimates of GFR

GFR can be estimated using either the Modification of Diet in Renal Disease formula (MDRD, used to calculate eGFR) or CG formula for CrCl.

In Australia, eGFR is routinely supplied with laboratory measurement of serum creatinine, providing a potentially convenient screening tool. However eGFR assumes a body surface area (BSA) of 1.73 m^2 and there is the potential to overestimate GFR at low BSA. In such circumstances, reliance on eGFR could result in an excessive dose being prescribed.

The CG formula for CrCl is an alternative estimate of GFR. This formula takes into account the patient's weight, age and gender. It can be ordered from pathology laboratories or alternatively can be calculated by the prescriber. CG is relatively simple to determine, is familiar to clinicians, and most clinical software is able to perform this calculation.

Limitations of formulae to estimate GFR

In certain situations, there is an important and clinically significant disparity between the CG formula for CrCl and eGFR, including in the following patient populations:

- age greater than 70 years
- ethnicity (e.g. Asian)
- low muscle mass (e.g. elderly, amputee, malnourished patients)
- low intake of dietary protein (e.g. vegan)
- obesity.

In these patient populations, the estimation of GFR by either method could lead to overestimation of GFR. If there is evidence of renal insufficiency in the patient populations listed above, use caution and thoughtful clinical judgement when deciding on appropriate drug dosing adjustments.

Advice for health professionals

Most guideline groups recommend using the CG formula for drug dosing until more clinical studies with the MDRD eGFR formula are conducted. There are, however, published statements indicating that for most drugs in primary care, and for most patients of average age and body size, dosage adjustments based on eGFR should be similar to those based on CrCl.[1,2]

eGFR should not replace CG for determining dosage adjustments for drugs that have a narrow therapeutic index until more studies of eGFR are conducted. Nevertheless, eGFR has a role in alerting treating clinicians to the possibility of reduced renal function and to prompt consideration of dosage adjustments.

Renal function should be assessed in circumstances where there is clinical suspicion of a deterioration in kidney function due to acute kidney injury (examples include hypovolaemia, septicaemia, causes of nephrotoxicity or any other major acute medical illness).

Chronic kidney disease classification

The stages of chronic kidney disease (CKD) as defined by Kidney Health Australia are as follows:

Stage 1
Kidney damage with normal or ↑ GFR ≥90 mL/min

Stage 2
Kidney damage with mild ↓ GFR 60–89 mL/min

Stage 3
Moderate ↓ GFR 30–59 mL/min

Stage 4
Severe ↓ GFR 15–29 mL/min

Stage 5
Kidney failure GFR <15 mL/min (or dialysis)

At the present time, information on dosage adjustments in patients with renal impairment may be presented in the Product Information in terms of CrCl, not CKD.

Acknowledgement: The TGA wishes to acknowledge advice from the Advisory Committee on the Safety of Medicines, used in the preparation of this article.

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MEDICINES SAFETY UPDATE

Anaphylaxis with chlorhexidine-impregnated central venous catheters

Clinicians are reminded that certain brands of central venous catheter (CVC) are impregnated with chlorhexidine to reduce the likelihood of CVC-associated bloodstream infections. A history of chlorhexidine hypersensitivity should be sought before choosing this type of CVC.

Chlorhexidine is known to cause IgE-mediated immune responses.

Chlorhexidine hypersensitivity is considered rare (estimated to occur at a rate of one case for every 385 000 catheter insertions),[1] but is probably under-reported. There are warnings on the packaging of CVCs regarding chlorhexidine hypersensitivity.

Antimicrobial surface-treated CVCs have been available since the 1990s. In 1998, the US Food and Drug Administration alerted clinicians to the possibility of hypersensitivity reactions to chlorhexidine-impregnated CVCs and other products containing chlorhexidine.[2] Over time sporadic case reports of anaphylaxis have appeared in the literature.[3]

The TGA has received three reports of anaphylaxis associated with the insertion of a chlorhexidine-impregnated CVC.

A high index of suspicion should be maintained by critical care clinicians faced with anaphylaxis temporally associated with the insertion of a chlorhexidine-impregnated CVC. Clinicians are encouraged to report all adverse events associated with chlorhexidine-impregnated CVCs to the TGA.

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2. FDA Public Health Notice: Potential hypersensitivity reactions to chlorhexidine-impregnated medical devices. US Food and Drug Administration. 1998.
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What to report? You don't 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, or birth defects.

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NEW DRUGS

New drugs

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

Boceprevir

Approved indication: hepatitis C
Victrelis (Merck Sharp & Dohme)
200 mg capsules
Australian Medicines Handbook section 5.4.3

The standard treatment for patients with chronic hepatitis C is a combination of peginterferon alfa and ribavirin. However, susceptibility to treatment varies depending on the viral genotype. Only 40–50% of patients with genotype 1 achieve a sustained virological response. In Australia, 55% of patients are infected with genotype 1.[1] Boceprevir is a protease inhibitor that can be added to standard therapy for these patients. It blocks viral replication by binding to the NS3 (non-structural 3) protease.

In phase III trials, boceprevir (800 mg three times a day orally) added to peginterferon alfa and ribavirin (after a four-week lead-in period) significantly improved the sustained virological response in patients with chronic hepatitis C genotype 1 (Table 1). One trial enrolled patients who had not responded or had relapsed after previous therapy[2] and the other enrolled previously untreated patients.[3] Interferon responsiveness predicts a sustained response to boceprevir. This was an inclusion criteria in the trial of previously treated patients.[2]

The most common adverse events with boceprevir were fatigue, anaemia, nausea, headache and dysgeusia. Almost half of the patients given boceprevir developed anaemia compared to about a third of patients given peginterferon alfa and ribavirin alone. Most of these patients were treated with erythropoietin.[2,3] In the trial of previously treated patients, more patients required a blood transfusion for their anaemia with boceprevir than with standard treatment (9% vs 0%).[2] Neutropenia also increased when boceprevir was added to standard treatment.

Complete blood counts should be done before starting treatment with boceprevir and regularly after that. Treatment may need to be modified if haemoglobin or neutrophils fall.

This drug should be taken with food as it increases bioavailability. Boceprevir is a strong inhibitor of cytochrome P450 3A4/5 so there is a potential for many drug interactions. The concomitant use of midazolam, triazolam, amiodarone, cisapride, alfuzosin, sildenafil or tadalafil for pulmonary arterial hypertension, and ergot derivatives is contraindicated. In addition, rifampicin, carbamazepine, phenobarbitone and phenytoin use is not recommended. Boceprevir may increase plasma concentrations and therefore the adverse effects of simvastatin.

Boceprevir is contraindicated in patients with decompensated liver function (Child-Pugh score >6), and in pregnant women because of risks to the fetus. This drug should not be given to patients with rare galactose intolerance disorders such as Lapp lactase deficiency or glucose-galactose malabsorption.

Adding boceprevir to standard hepatitis C treatment is a promising option for patients with genotype 1 disease. However, not all patients will have a sustained response. Regular blood monitoring is important as anaemia is a common adverse effect. The safety and efficacy of boceprevir has not been tested in people co-infected with HIV or hepatitis B.

T T manufacturer provided additional useful information

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Table 1 **Sustained virologic responses in patients with chronic hepatitis C genotype 1** [2,3]

Treatment for 44 weeks	Sustained virologic response *	
	Previously treated patients	Previously untreated patients
Placebo plus peginterferon/ribavirin	21% (17/80)	38% (137/363)
Boceprevir plus peginterferon/ribavirin	66% (107/161)	66% (242/366)

* undetectable viral RNA for six months after treatment

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

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ANSWERS TO SELF-TEST QUESTIONS

1	False	2	False
3	False	4	True
5	False	6	True
7	False	8	True
9	False	10	True

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