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Editorial

Climate change and infectious diseases in Australia

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Key words: antibiotics, antiviral drugs, infection, malaria, travel.

(Aust Prescr 2009;32:58–9)

The mechanisms of global climate change are the subject of extended debate, but the fact that it is happening and our major part in its causation are generally accepted. The potential link between climate change and disease risk has been widely reported and reflects a growing concern about the health impacts of global warming.[1]

In the last decade analysis of detailed epidemiological, geographical and meteorological data has improved substantially, generating new insights into the interaction between complex weather systems and human disease. Some notable correlations between weather systems and specific infectious diseases have already been described, such as the correlation between the El Niño Southern Oscillation and cholera in Bangladesh.[2] Smaller scale events, such as a possible association between El Niño and outbreaks of highland malaria, are more difficult to attribute to climate change.[1,3] The effects of changing weather systems are difficult to show conclusively when non-climate factors such as human population density, migration and insect vector dynamics add to the risk of disease.

Closer to home, epidemiological studies have shown an association between high daytime temperatures, a low UV index, and presentations with gastroenteritis in children.[4] The major source of inter-annual climate variation in our region is the 3–6 yearly El Niño Southern Oscillation cycle, which affects temperature, rainfall and the probability of storms, floods and droughts. In north-western Australia some locations have recorded a doubling of the annual rainfall over two decades, and cyclical rainfall variation has been observed.[5] It is difficult to predict precisely how these complex changes are likely to impact on endemic infectious disease for which only limited environmental surveillance data are available.

The addition of an insect vector to the equation adds another layer of ecological complexity. Ross River virus disease is the most common and widespread mosquito-borne infection in Australia. A recent investigation found that rainfall, temperature and high tides were determinants of Ross River virus transmission, but that the nature and scale of the interrelationship between disease, mosquito density and climate variability varied with geographic location and socioeconomic conditions.[6] A predictive model based on surveillance data from Darwin found that a combination of rainfall, minimum temperature and three mosquito species predicted disease prevalence effectively. The model indicated that climate change may result in increased Ross River virus infections.[7]

Empiric data from the Northern Territory also show a clear correlation between the occurrence of acute melioidosis and the onset of the wet season.[8] This has been attributed to the wetting of soil and regeneration of surface water collections contaminated by the causal agent, *Burkholderia pseudomallei*. However, recent photobiology experiments raise the possibility of an alternative explanation – the loss of decontaminating ultraviolet light due to cloud cover.[9]

Looking to the future, we can predict that there will be an increase in the population at risk of dengue. This may translate to an increased frequency of dengue outbreaks in northern Australia and an extension of the at-risk area. Other arbovirus* diseases including Ross River virus, Barmah Forest and Kunjin virus infections, and Murray Valley encephalitis are likely to be affected by climate change, but the complex ecology of virus transmission makes location-specific prediction difficult.[6]

* arthropod-borne virus

In this issue…

The emergence of a new strain of influenza virus (H1N1) in Mexico has raised concerns about a pandemic. Prompt detection of cases is important, so the review of rapid tests for influenza by Hong Foo and Dominic Dwyer is timely.

Changes in the pattern of infectious diseases may result from changes in the global environment. A warming climate will have an effect on prescribing. In addition to the impact on infectious diseases discussed by Timothy Inglis, there will be implications for how medicines are stored and used.

Pharmacogenetic testing has the potential to influence how warfarin is used. Although knowing the patient's genome can help with predicting and adjusting the dose of warfarin, Jennifer Martin explains that pharmacogenetic testing is not yet ready to be part of routine management.

The re-emergence of malaria in Australia is more difficult to predict, though receptive mosquito species in northern Australia can propagate localised outbreaks after *Plasmodium* species parasites have been introduced by international travellers.[10,11] There is a clear consensus that the future spread of malaria within Australia can be minimised by a combination of surveillance and public health interventions.

Increased coastal flooding may lead to cholera and marine vibrio infections, and possibly increased melioidosis. Climate change-related increases in temperature will increase the risk of food-borne infections such as salmonellosis and listeriosis, and may also raise the risk of sporadic amoebic meningo-encephalitis. A greater reliance on seasonal air conditioning may lead to an increase in cases and outbreaks of Legionnaires' disease. These are all direct effects of a changing climate. More subtle are the indirect effects such as population shift due to changing land use, a changing epidemiology of zoonotic infections through major relocations of livestock, and a possible shift in avian-mediated viral infections due to shifts in the migratory flyways.

Changes in regional and global climates are fortunately not enough to cause catastrophic, immediately evident infectious disease outcomes. However, medical practitioners need to keep contemporary disease intelligence in view, while maintaining a low threshold of suspicion for unusual, and common but out-of-context infections. Any patient who presents with a fever or localised infection of unknown cause after travel within Australia needs to be asked about their recreational and occupational activities. Soil or water exposure, biting insect or animal contact, severe weather or air conditioning are all potentially relevant. Prolonged incubation periods (up to an extreme of 63 years in the case of latent melioidosis[12]) can cause diagnostic difficulties.

Some infections of the Australian tropics are not notifiable in some jurisdictions, but general practitioners, infectious disease specialists and public health authorities will all want to know if a group has been affected by a within-Australia travel-related infection.

Antiviral drugs are ineffective against the arbovirus diseases. Acute, septicaemic melioidosis can be rapidly fatal and presumptive intravenous antimicrobial drugs must be commenced as quickly as possible in accordance with the Antibiotic Guidelines (either meropenem or ceftazidime, then followed with prolonged eradication therapy).[13] Legionnaires' disease should be treated promptly with a macrolide (azithromycin or erythromycin plus either rifampicin or ciprofloxacin in severe cases). Diarrhoeal or food-borne infections can often be treated symptomatically without the need for antibiotics.

Although climate change is likely to change the risk of contracting many infectious diseases, neither surveillance data nor predictive modelling allow accurate forward prediction of time, place and specific infectious disease. Australian practitioners should maintain a high index of suspicion for changes in conventional epidemiology, and remain alert to exotic infections following travel within Australia. The predicted disease consequences of climate change can most likely be minimised by forward planning and public health measures.

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Conflict of interest: none declared

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issu

Over-the-counter misnomers

Editor, – I am appalled to find that there are now two 'over-the-counter' S3 medications bearing the Sudafed label which do not contain pseudoephedrine. The first is Sudafed PE tablets, the second Sudafed nasal spray.

The new products contain phenylephrine, which is an active vasoconstrictor and decongestant when administered intravenously or intranasally, but its efficacy in a per-oral tablet formulation is questionable, as most pharmacological data suggest its first-pass metabolism is almost complete.

My family's experience in using these tablets confirms this. Indeed, I was so appalled that I returned the Sudafed PE tablets to the pharmacy where purchased, pointing out that they were not as labelled.

Sudafed has been a registered, recognised name for pseudoephedrine for more than 40 years, so to have it used for a completely different compound is confusing and misleading. How can the Therapeutic Goods Administration justify allowing the misuse of this name? What data were submitted to justify using the Sudafed label on products which do not contain Sudafed?

John A Crowhurst
Senior Consultant Anaesthetist
Mercy Hospital for Women
Heidelberg, Vic.

Dr Peter Bird, Head, Office of Non-prescription Medicines, Therapeutic Goods Administration, comments:

In recent years, concerns about the diversion of pseudoephedrine to the illicit drug trade led to more stringent limitations being placed on the supply of medications containing this ingredient. These restrictions resulted in some companies formulating new products that replaced pseudoephedrine with phenylephrine hydrochloride.

In common with general retail practice, over-the-counter (OTC) medicine companies use brand extensions (umbrella/family branding) to market their products. The Therapeutic Goods Administration (TGA) has specific guidelines to determine the acceptability of proposed brand extensions for OTC medicines (see http://tga.gov.au/docs/pdf/argom_5.pdf).

While the safety and efficacy of phenylephrine has been documented in standard reference texts, it is recognised that there may be differences in effectiveness compared to pseudoephedrine. For this reason, where there are medicines containing either pseudoephedrine or phenylephrine with similar presentations, the TGA requires that the letters 'PE', together with other distinguishing features, are included prominently on the label of the product containing phenylephrine. This is consistent with practices in a number of other countries in which these medicines are marketed. Similarly, nasal sprays containing decongestant ingredients are required to include distinguishing features on their labels.

Prescription pricing demystified

In a recent article Dr Tatchell gives a comprehensive review of the pricing of prescription medicines (Aust Prescr 2009;32:6–8). While he addresses issues in the community setting, he fails to include the complexity of prescription pricing in public hospitals.

Access to Pharmaceutical Benefits Scheme (PBS) dispensing was introduced into public hospitals in 2002. While this was intended to parallel the structure in community dispensing, some pricing anomalies exist. Brand price premiums, therapeutic group premiums and special patient contributions do not generally apply. Safety net contributions also differ. Any patient co-payment is added to the patient's safety net, whether for PBS or non-PBS subsidised items. In some hospitals, patient co-payments for non-PBS items are capped at the patient co-payment contribution rate. For example, concession patients pay no more than $5.30 per item, and safety net exemption cardholders may find they are not charged for non-PBS items or even over-the-counter items.

The availability of chemotherapy under the Chemotherapy Pharmaceuticals Access Program[1] adds another layer of complexity. Patients can access PBS-subsidised chemotherapy under this program. While they do not pay a co-payment, the actual dollar value of the co-payment (for example, $5.30 per concession patient) is still added to their safety net.

In this era of continuum of care, patients need to be aware that pricing structures differ between the hospital and community setting. Physicians who work in both the public and private sectors must also have an understanding of this pricing anomaly.

Jim Siderov
Senior Pharmacist, Cancer Services

Robert McLauchlan
Dispensary Manager

Austin Health
Heidelberg, Vic.

Reference

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Preventing motion sickness in children

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Summary

Motion sickness is a normal response to abnormal stimuli. The peak incidence occurs in children under 12 years, but it is uncommon in infants. As this condition has central and vestibular origins, centrally acting drugs may be useful. There is no evidence to support the efficacy or safety of drugs for children less than two years old. Potentially effective drugs in older children include hyoscine and antihistamines. Both are associated with anticholinergic adverse effects. Ginger and acupuncture bands may be used, but have only been evaluated in adults.

Key words: antihistamines, hyoscine, travel.

(Aust Prescr 2009;32:61–3)

Introduction

Motion sickness is a common condition, with about 30% of the general population suffering some kind of symptoms during a voyage and 5% suffering heavily. There are no specific statistics for incidence in children. Children under two years old are highly resistant to motion sickness, as they are often supine and do not use visual cues for spatial orientation. Susceptibility peaks around 10–12 years of age. Motion sickness in children occurs mainly during car, train and air travel, but also may occur on amusement park rides and during virtual reality immersion.[1]

There are simple preventative measures which may reduce the likelihood of travel sickness (see box). If these fail, pharmacological therapies may be tried in children older than two years.

Rationale for pharmacological management

Conflicting signals from vestibular, vision and proprioception systems produce symptoms of pallor and cold sweat, which usually precede epigastric discomfort, nausea and emesis. Ataxia and dizziness may be a feature in younger children. Prolonged motion sickness may cause drowsiness, apathy and even a feeling of impending doom. Cortical centres may also be involved, explaining the effect of anticipatory nausea before travelling.

The first mention of a drug for motion sickness was in the 1860s in the Lancet, when tincture of belladonna was recommended. Promethazine was approved in the 1950s, but it is only since the 1970s that cholinergic stimulation has been the postulated basis of motion sickness. Primarily, antihistamines and anticholinergics are used. These drugs act on vestibular receptors and nuclei, the cerebellum and the vomiting centre.

Treatment options [2]

The following general points should be considered when managing children who are prone to motion sickness:

- As motion sickness induces gastric stasis, it slows drug absorption, so preventing symptoms from occurring is more effective than trying to treat them after symptom onset.
- There are no controlled studies of anti-motion sickness drugs in young children. Clinical use is based on pharmacology principles and extrapolation of data from adult studies.
- While most anti-motion sickness medicines cause drowsiness, they should not be used as sedatives for air travel, as excessive sedation combined with lower oxygen partial pressure can be potentially dangerous for some children.[3]
- All anti-motion sickness medications are also effective antiemetics.

Simple ways to prevent travel sickness [2,4]

- Focus child's attention elsewhere, e.g. out of the window, on the horizon where practical
- Do not encourage reading or focusing on games while travelling
- Avoid unnecessary head movements by using pillows or a headrest
- If travelling by car, seat child near the front of the vehicle, that is, middle rather than third row in a larger vehicle
- If flying, sit over the aeroplane wing – the ride tends to be less bumpy
- Have the child recline as much as possible
- Feed the child a light snack before travelling – avoid heavy, greasy meals
- Ensure ventilation either from open window or air conditioning – avoid overheating
- Try to keep calm – motion sickness is more likely to happen if a child is worried about having an episode

Efficacy and safety

Hyoscine hydrobromide (scopolamine)

A systematic review of 14 controlled trials involving hyoscine found it to be more effective than placebo, but not superior to antihistamines. Studies were predominantly in adult males. Hyoscine is less sedating than antihistamines, but has more anticholinergic effects.[5]

Antihistamines

Given their lack of efficacy and potential to cause serious adverse drug reactions, such as hallucinations, agitation and breathing difficulties, antihistamines (H_1 receptor antagonists) should not be used to prevent or treat motion sickness in children less than two years of age and should be used with caution in older children. Fatalities have been reported when over-the-counter products containing antihistamines were given to young children to treat coughs and colds.[6] There are no specific paediatric data for these drugs in motion sickness and dosing has been extrapolated from studies done in adults. In Australia, sedating antihistamines have recently become prescription-only for children less than two years of age.[7] This is now in line with New Zealand regulations. These drugs cause anticholinergic adverse effects of excitability, agitation, drowsiness, dry mouth, blurred vision and constipation. They should be avoided in children with seizure disorders.

Promethazine theoclate, promethazine hydrochloride and dimenhydrinate are approved in Australia for prevention and treatment of motion sickness. Timing varies, but they should be given at least 30 minutes before travelling. While diphenhydramine is used overseas for motion sickness prophylaxis in children, this is not an approved indication in Australia.

Non-sedating antihistamines, such as loratadine and cetirizine, penetrate poorly into the central nervous system and are not effective against motion sickness.

Complementary alternatives

Studies in adults using acupuncture wristbands, which activate the P6 Neiguan acupuncture point (5 cm above the wrist), show relief of nausea in pregnancy and after chemotherapy, but evidence for efficacy in motion sickness is contradictory. There are no studies in children, although wristbands are marketed for this age group.

Placebos have provided benefit in up to 45% of cases in controlled studies.[8]

Ginger *(Zingiber officinale)* has been used for centuries for its antiemetic properties.[9] Studies have shown reduced nausea in patients with hyperemesis gravidarum, postoperative nausea and vomiting and in a study using a revolving chair simulating motion sickness. There has not been more than anecdotal evidence of the efficacy of ginger for prevention and treatment of motion sickness in children. Ginger inhibits thromboxane synthetase and in high doses may potentiate the effects of anticoagulants, for example aspirin, heparin and warfarin. It may cause mild gastrointestinal upset.

A study using prism glasses from the 1980s reported a significant decrease in vomiting episodes in children (n=201) prone to motion sickness. The prism glasses were thought to decrease the discrepancy between visual and vestibular cues and thus to reduce the negative effects of vertigo.[10]

Treatments available overseas [2,11]

Hyoscine as a transdermal patch is available overseas for children older than 10 years. These patches have been shown to provide effective motion sickness prophylaxis for 72 hours, but have not been evaluated in younger children. Toxic psychosis has been reported in children using this treatment.

Cinnarizine and its derivative flunarizine are piperazine antihistamines with vasodilating actions of calcium channel blockers. The only study of anti-motion sickness drugs specifically in children was in an open study with cinnarizine. It was rated by participants (n=79, mean age 8.4 years) to be effective in preventing car sickness, with a low level of adverse effects.[12]

Conclusion

Motion sickness is a common condition, with many marketed remedies for children. Few have undergone controlled trials and even fewer have been scientifically tested specifically in children. The recent changes in labelling and restriction of access of antihistamines for children younger than two years of age highlight the importance of continual review of medicines used in children.

Acknowledgement: Dr Madlen Gazarian, Paediatric Clinical Pharmacologist and Head, Paediatric Therapeutics Program, University of New South Wales and Sydney Children's Hospital, for helpful comments about the manuscript.

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Conflict of interest: none declared

Your questions to the PBAC

Patent expiry and 'new' drug approvals

The February issue of *Australian Prescriber* contains a review of desvenlafaxine with a comment on the expiry of the patent of modified-release venlafaxine (Aust Prescr 2009;32:22–3). There are other examples of 'new' drugs which are just small variations on the original molecule. These include perindopril erbumine becoming perindopril arginine and omeprazole becoming esomeprazole.

It appears that these small variations on a successful molecule are not great therapeutic advances. They seem to be produced only for commercial reasons. I would like to know why such products are added to the Pharmaceutical Benefits Scheme. They are unlikely to be more cost-effective than the old drugs already in use.

Bruce Sutherland
Pharmacist
St Arnaud, Vic.

PBAC response:

As the Schedule of Pharmaceutical Benefits is not a limited formulary, a 'new' drug such as these can be added even though several similar products are already listed.[1] As mentioned by your correspondent, these drugs are 'not great therapeutic advances' and are 'unlikely to be more cost-effective than the old drugs already in use'.

Perindopril arginine was accepted by the Pharmaceutical Benefits Advisory Committee (PBAC) as being bioequivalent to perindopril erbumine, while esomeprazole and desvenlafaxine were accepted on a cost-minimisation basis, where the evidence indicates that the new drug is no worse than an existing comparator (in this case, omeprazole and venlafaxine respectively). Once the new drug is considered to provide similar health outcomes to the comparator, the PBAC then makes a recommendation about the therapeutically equivalent doses of the two drugs, based on all the evidence submitted at the time of listing, from which pricing is determined by the Pharmaceutical Benefits Pricing Authority. In the case of desvenlafaxine for major depressive disorders it was recommended on a cost minimisation basis with the parent drug venlafaxine, with the equi-effective doses being desvenlafaxine 50 mg and venlafaxine 75 mg. The PBAC considered that desvenlafaxine would provide a further treatment option for major depressive disorders, however, no evidence was presented to suggest that desvenlafaxine would offer an advantage for any particular patient group over the parent drug venlafaxine.[2]

In addition, the relative prices are adjusted depending on the actual prescribed daily doses in the marketplace. Both esomeprazole and perindopril arginine are in 'weighted average monthly treatment cost' groups of drugs regarded as therapeutically equivalent (the proton pump inhibitors and the ACE inhibitors). Pricing information using relative volumes of use and prescribed daily doses are compared across the group to determine the lowest priced drug in the group. The PBS subsidy is only provided at this lowest price.[3]

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Diagnostic tests

Rapid tests for the diagnosis of influenza

***Hong Foo**, Microbiology Registrar, and **Dominic E Dwyer**, Clinical Professor of Medicine, Centre for Infectious Diseases and Microbiology, Institute of Clinical Pathology and Medical Research, Westmead Hospital, Sydney*

Summary

Diagnosing influenza clinically is often difficult because of the variability of symptoms and the numerous other causes of 'influenza-like illness'. An accurate result from an influenza test performed at the bedside, or within hours of presentation, may assist in diagnosis and patient management. Rapid influenza tests based on viral antigen detection with point-of-care tests and immunofluorescence may be useful for primary care clinicians. However, it is important to know how to use these tests and to understand their limitations.

Key words: antigen detection, immunofluorescence, point-of-care testing.

(Aust Prescr 2009;32:64–7)

Introduction

Influenza is a contagious acute self-limiting infection caused by influenza A and B viruses. It is classically characterised by an abrupt onset of systemic symptoms, with fever, chills, headache, myalgia, malaise and anorexia, in addition to respiratory symptoms such as cough, pharyngitis and rhinorrhoea.

A reliable clinical diagnosis of influenza can be difficult, due to the variability of its presentation. There is also a multitude of other respiratory viruses in both children and adults which may cause a similar constellation of symptoms. Rapid diagnostic tests may assist the clinician to make a definitive diagnosis of influenza. Prompt diagnosis is important because antiviral therapy is most efficacious when commenced in the first 48 hours of illness. Furthermore, unnecessary investigations and antibacterial therapy (with the possible ramifications of increased antimicrobial resistance) may be avoided. Rapid diagnosis will also allow the early recognition of outbreaks in 'closed' environments such as nursing homes and schools.

Diagnosis

In patients presenting with cough and fever, testing for influenza is indicated when the clinical diagnosis is unclear, if antiviral therapy is a consideration, and in cases of suspected pandemic influenza. A rapid laboratory diagnosis of influenza can be made by detection of influenza viral antigen or nucleic acid in respiratory tract samples (Table 1). Alternative laboratory methods include influenza viral isolation, which may take up to a week, and serological detection of influenza antibodies, which may take several weeks.

The choice of test depends on factors such as the duration of symptoms, prevalence of influenza in the community, the clinical setting and proximity to a laboratory.

Specimen collection

The type and quality of the specimen as well as the timing of its collection are all factors which may significantly affect the sensitivity of a test. Nasopharyngeal aspirates in young children and paired nasal and throat swabs (Fig. 1) in adults using specialised viral swabs are the most practical specimens to collect. Nasal washes and nasopharyngeal swabs are also appropriate. A good quality respiratory tract specimen is particularly important for rapid antigen detection tests, which rely on the presence of adequate numbers of infected respiratory epithelial cells.

Viral shedding peaks in the first 48–72 hours of illness, thus the sensitivity is greatest for specimens collected within this time period.

After collection, respiratory tract specimens should be transported to the laboratory promptly at 4°C.

Rapid antigen detection tests

These may take the form of 'point-of-care' tests or immunofluorescence assays.

Point-of-care tests

Point-of-care tests are usually immunochromatographic assays involving monoclonal antibodies directed against influenza A and B nucleoprotein or other conserved antigens impregnated on a strip or bound to a membrane.

The respiratory tract specimen is initially treated with an extraction buffer and then applied to either a filter paper or dipstick, depending on the test format. If influenza viral antigens are present, they react with the influenza-specific monoclonal antibodies which produces a visible colour change. Most kits

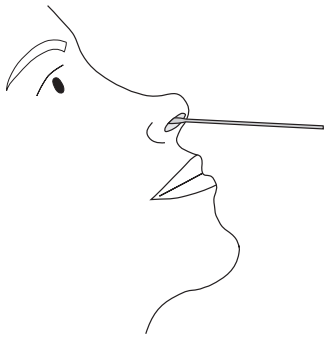
Table 1

Rapid tests for influenza [1,3]

Test	Turnaround time	Sensitivity	Specificity	Advantages	Disadvantages
Point-of-care test	15–30 minutes	59–93%	76–100%	Bedside test Fast Easy to perform No laboratory required	Occasional false positives Limited kit shelf-life Lower sensitivity No viral isolate for vaccine studies Subtyping not possible
Immunofluorescence assays	2–4 hours	70–90%	More than 90%	Fast Assessment of specimen quality Inclusion of other respiratory viruses Swab can be used for virus isolation Subtyping of influenza A possible	Labour intensive Laboratory and technical expertise required Less sensitive than nucleic acid tests
Nucleic acid test	24–48 hours	99%	99%	Highly sensitive Specimen quality less crucial Viable and non-viable virus detected Typing and subtyping of virus possible Batch testing possible	High infrastructure requirements Expensive May be affected by viral genetic drift

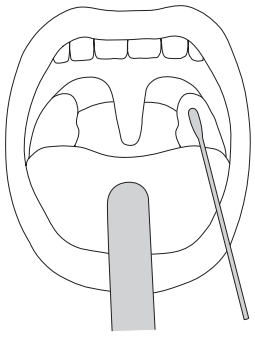
Fig. 1

Collecting specimens from the nose and throat



Nasal swab

1. Tilt patient's head back gently and steady the chin
2. Insert sterile swab into nostril and rub firmly against the turbinate (to ensure swab contains cells as well as mucus)
3. Insert swab into collection tube, break off shaft of swab and recap tube



Throat swab

1. Ask patient to open mouth and stick their tongue out
2. Use tongue spatula to press the tongue downward to floor of the mouth
3. Swab the posterior pharynx and the tonsillar area on both sides, without touching the sides of the mouth
4. Insert swab into same collection tube containing nose swabs, break off shaft and recap tube

distinguish between influenza A and B viruses, but do not allow further subtyping.

The point-of-care tests are generally simple to perform and interpret, and results are available within 15–30 minutes. For optimal results, some training is desirable in collecting respiratory specimens and performing point-of-care tests. As these tests can be performed outside of a laboratory setting they may have a role in doctors' surgeries and emergency departments, remote settings, or in outbreak situations where a rapid test result can significantly impact on clinical decision making.

The sensitivity of point-of-care tests is about 70% (59–93%)[1] depending on the test kit, the age of the patient (young children tend to shed higher viral titres for longer periods of time) and the timing of specimen collection (maximal sensitivity is achieved in early illness and falls significantly after day five of illness). The sensitivity of point-of-care tests is higher with influenza A compared to influenza B, and limited data suggest that they have reduced sensitivity for human cases of influenza A H5N1 infection (avian influenza). The specificity of point-of-care tests ranges from 76% to 100%.[2]

Point-of-care tests are most useful during the influenza season when the prevalence of influenza in the community is high, and the positive predictive value of the test is greatest.[3] A positive test result in this context is highly suggestive of influenza infection. Patients with suspected influenza who have negative point-of-care tests during the influenza season should undergo further testing with more sensitive methods. During periods of low influenza activity, point-of-care tests have a low positive predictive value, and a false positive result is more likely.[3] These tests are therefore recommended only during periods of high influenza activity.

The main drawbacks of point-of-care test kits are their expense and limited shelf-life (1–2 years). Poor specimen collection technique and misinterpretation of test strips by inexperienced staff can give inaccurate results. They do not provide a live isolate of the influenza strain needed for surveillance and annual vaccine design.

Immunofluorescence assays

These assays are based on the same principle as point-of-care tests (that is, detecting an interaction between viral antigen and specific antibodies) but are performed in a laboratory. Direct immunofluorescence assays involve placing the respiratory tract specimen onto a slide and staining with specific monoclonal antibodies conjugated to a fluorescent dye. Indirect immunofluorescence assays have an additional staining step with a second conjugated antibody, which increases the sensitivity of the test at the expense of an increased turnaround time.[3] Slides are examined with a fluorescent microscope to detect nuclear and cytoplasmic fluorescence staining. The quality of the sample can be assessed by observing the number of respiratory epithelial cells present. A repeat specimen can be collected if a poor quality sample leads to a negative test result.

Influenza immunofluorescence assays have a rapid turnaround time of 2–4 hours. Screening for other respiratory viruses (such as parainfluenza, respiratory syncytial virus and adenovirus) can be performed simultaneously, thereby enabling an alternative diagnosis or detection of viral co-infection. These assays distinguish between influenza A and B viruses. Specific monoclonal antibodies for H1, H3 and H5 viral antigens ('avian' influenza) are available and allow subtyping of influenza A viruses.

The sensitivity of influenza immunofluorescence assays is 70–90% and their specificity is over 90%.[1] Immunofluorescence assays need a specialised laboratory, fluorescent microscope and technical expertise, and are more labour intensive than point-of-care tests. Their use is therefore often restricted to working hours which may delay results.

Nucleic acid tests

There are a variety of commercial and in-house molecular assays for detecting influenza virus nucleic acid, either directly from the clinical specimen or from the viral isolate. Different nucleic acid tests may detect and characterise the influenza virus by type (A or B), usually by targeting the conserved matrix protein, or by subtype, using primers directed against the haemagglutinin or neuraminidase genes. The most common format involves a reverse transcriptase polymerase chain reaction.

After extraction of nucleic acid from the clinical sample, a set of enzyme primers are used to amplify a specific influenza nucleic acid region. A number of different methods exist for subsequent detection of the amplified gene product. A real-time polymerase chain reaction format simultaneously amplifies nucleic acid and detects product, and can significantly reduce turnaround time to 4–6 hours. Some assays can detect a number of different respiratory viruses in addition to influenza A and B.

Nucleic acid tests are the most sensitive diagnostic tests for influenza[1,3], with sensitivity and specificity approaching 100%.[1] Due to their high sensitivity and ability to detect both viable and non-viable virus, the quality and timing of specimen collection is less important than with antigen detection techniques. Nucleic acid tests are less labour intensive than immunofluorescence assays because they are automated and large numbers of specimens can be tested simultaneously. Although results can take six hours, transporting the specimen to the laboratory and the need for batch testing within working hours can delay results by 24–48 hours. Nucleic acid tests are also more expensive because technical expertise and specialised equipment are required.

Alternative tests

Viral isolation techniques are available in a limited number of laboratories. Standard influenza viral culture takes several days to a week, although rapid shell-vial viral culture techniques can reduce the turnaround time to 48 hours. Here, the clinical specimen is centrifuged directly onto a cell monolayer, which accelerates infectivity. Specific monoclonal antibodies can detect viral antigen after 24–48 hours. This negates the need to look for cytopathic effects of the virus, which may take up to a week, as in standard viral culture. Culture-based methods provide a viral isolate for surveillance purposes, detailed subtyping, antiviral resistance testing and annual vaccine development.

Serology offers a retrospective diagnosis of influenza, as it relies on detecting a rise in antibody titres between acute (within one week) and convalescent (four weeks) blood samples. Therefore, it is not useful in making an acute diagnosis of influenza.

Conclusion

The public health benefits stemming from a rapid diagnosis of influenza cannot be underestimated. Prompt detection of influenza is important not only for the individual, who may benefit from early commencement of antiviral drugs, but also for the community (including 'closed' environments such as households, nursing homes, schools and military facilities) by reducing transmission of the virus. Outbreaks of influenza may be prevented by treating individuals when they are most contagious, and by considering antiviral prophylaxis for exposed individuals at highest risk of complications from influenza.

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Further reading

For more information on interpreting diagnostic tests, see Attia J. Diagnostic tests. Moving beyond sensitivity and specificity: using likelihood ratios to help interpret diagnostic tests. Aust Prescr 2003;26:111-13.

Professor Dwyer has participated in laboratory evaluations of various commercial 'point-of-care' tests for influenza, and in clinical trials of various anti-influenza drugs.

Self-test questions

The following statements are either true or false (answers on page 87)

1. Viral subtyping is usually possible with point-of-care testing.
2. Nucleic acid tests are the most sensitive test for detecting influenza.

NPS RADAR
Rational Assessment of Drugs and Research

NPS RADAR update

The latest issue of *NPS RADAR* reviews hydromorphone, lanthanum and teriparatide listed on the Pharmaceutical Benefits Scheme on 1 May 2009.

Hydromorphone is a strong opioid that is approximately five times more potent than morphine. The once-daily tablets are available in 8 mg, 16 mg, 32 mg and 64 mg strengths. The 32 mg and 64 mg tablets equate to about 160 mg and 320 mg oral morphine respectively and so would be suitable only for patients who are highly opioid tolerant. *NPS RADAR* reminds prescribers of the risks of toxicity with inappropriate use or accidental overdose.

Lanthanum is a rare earth element that reduces serum phosphate concentration. It is listed as an authority prescription for adults with chronic kidney disease who are on dialysis.

Teriparatide is a recombinant human parathyroid hormone given as a daily subcutaneous injection using a pre-filled multidose delivery device (pen). Unlike antiresorptive agents, which inhibit bone loss, teriparatide stimulates bone formation. *NPS RADAR* discusses where teriparatide fits among the options for osteoporosis.

For more information about hydromorphone, lanthanum and teriparatide, see the complete reviews on the *NPS RADAR* website (www.npsradar.org.au).

Visit www.npsradar.org.au to register for your free email updates to keep track of the latest NPS RADAR news and reviews.

Long-term management of patients taking immunosuppressive drugs

***Denise C Hsu**, Immunology Registrar, Department of Immunology, Concord Repatriation General Hospital, Sydney; and **Constance H Katelaris**, Professor, Clinical Immunology and Allergy, University of Western Sydney*

Summary

The number of patients taking immunosuppressive drugs for the management of autoimmune inflammatory conditions is increasing. The general practitioner needs to be active in preventing, monitoring and managing the adverse effects of these drugs even long after the treatment has ceased. Monitoring is required because immunosuppressive drugs increase the risks of infection, malignancy, cardiovascular disease and bone marrow suppression. Some drugs have additional risks which require specific monitoring. Vigilance is needed as adverse effects may have atypical clinical presentations.

Key words: calcineurin inhibitors, corticosteroids, methotrexate.

(Aust Prescr 2009;32:68–71)

Introduction

General practitioners are increasingly likely to encounter patients who are taking immunosuppressive drugs for disease control in a variety of autoimmune inflammatory conditions. These include rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease and systemic vasculitis. The drugs are also used in transplantation. Although these drugs are usually started by specialists, general practitioners need to be aware of the long-term adverse effects so that there is no delay in detecting problems.

General risks of immunosuppressive drugs

Drugs which suppress the immune system are inevitably associated with increased risk of infection and malignancy. Many of these drugs also impact adversely on patients' cardiovascular risk.

Infections

Patients may be infected by common community-acquired and opportunistic organisms. The risk of infection increases with the degree of immunosuppression. Infections with *Pneumocystis jirovecii*, nocardia, aspergillus, cryptococcus and reactivation of varicella zoster, herpes simplex, cytomegalovirus, hepatitis B and C as well as tuberculosis are not uncommon in patients who are profoundly immunosuppressed.

Patients often present with atypical symptoms and disseminated disease. All patients taking immunosuppressants should have a thermometer at home and should seek urgent medical assessment if they develop a temperature over 38°C.

Annual influenza vaccination, and pneumococcal vaccination at baseline and one-time revaccination after five years, is recommended by the American College of Rheumatology. Patients with significant immunosuppression should not receive live vaccines. In those exposed to chickenpox or shingles, administration of herpes zoster immunoglobulin is an option.[1]

Malignancy

The risk of cancer, especially cutaneous and haematological malignancies, is increased. Patients taking immunosuppressive drugs should have at least yearly skin checks by their general practitioners, and be up to date with the normal recommended cancer screening programs such as faecal occult blood for those over 50, cervical smears and mammography.

Many autoimmune diseases are associated with an increased risk of malignancy. Dermatomyositis and polymyositis are associated with adenocarcinomas, while rheumatoid arthritis, systemic lupus erythematosus and Sjögren's syndrome are associated with lymphoid malignancy.

Marrow suppression and cytopenia

Bone marrow suppression is a common dose-limiting toxicity for most immunosuppressive drugs, apart from hydroxychloroquine and the glucocorticoids. The recommendations for monitoring are largely based on expert consensus and often differ slightly.[1,2] Table 1 has a suggested frequency of monitoring for patients who have been stable on maintenance doses of immunosuppressive drugs. Patients with white cell counts less than 3.5 x 10^6/L, neutrophils less than 2 x 10^6/L and platelets less than 150 x 10^6/L should have repeat testing within seven days and the specialist should be alerted if the results are low. Immunosuppressive drugs should be suspended if there is significant neutropenia (less than 1.5 x 10^6/L) and the specialist should be contacted immediately.

Table 1

Suggested frequency of monitoring during treatment with immunosuppressive drugs

	Full blood count	Electrolytes, urea, creatinine and fasting glucose	Liver function tests	Calcium magnesium phosphate	Fasting lipids	Eye review	Urinalysis
Corticosteroids	3 monthly	3 monthly	3 monthly	NR	6 monthly	If symptomatic	NR
Hydroxychloroquine	12 monthly	12 monthly	12 monthly	NR	12 monthly	12 monthly	NR
Azathioprine	1–3 monthly	1–3 monthly	1–3 monthly	NR	6 monthly	NR	NR
Cyclosporin/ tacrolimus	1–3 monthly	1–3 monthly	1–3 monthly	1–3 monthly	6 monthly	NR	NR
Leflunomide	1–3 monthly	1–3 monthly	1–3 monthly	NR	12 monthly	NR	NR
Methotrexate	1–3 monthly	1–3 monthly	1–3 monthly	NR	12 monthly	NR	NR
Mycophenolate	1–3 monthly	1–3 monthly	1–3 monthly	NR	12 monthly	NR	NR
Cyclophosphamide	Fortnightly to monthly	Monthly	Monthly	NR	12 monthly	NR	6 monthly

NR Not routinely recommended

Cardiovascular risk

The commonest cause of long-term morbidity and mortality in patients with autoimmune disease is cardiovascular disease. Women less than 45 years old with systemic lupus erythematosus are 50 times more likely, and patients with rheumatoid arthritis are twice as likely, to have a myocardial infarct in the next 8–10 years when compared with healthy age- and sex-matched controls. This increase in risk is attributed to the chronic inflammatory state as well as the hyperglycaemic and hyperlipidaemic adverse effects of immunosuppressive drugs such as glucocorticoids, cyclosporin and tacrolimus.

Patients should be encouraged to cease smoking and have regular monitoring of weight, blood pressure, fasting lipids and glucose. Although there are no evidence-based cardiovascular guidelines specifically for patients on immunosuppressive drugs, efforts to achieve risk factor reduction should be more rigorous than for the general population. The threshold for further cardiac investigation should be low in the presence of symptoms, even if they are atypical.

Specific long-term toxicities requiring monitoring

In addition to their general effects on the immune system, immunosuppressant therapies have drug interactions (see box) and adverse effects. Monitoring aims to detect these problems early.

Glucocorticoids

Corticosteroids are commonly used immunosuppressive drugs. They have potential adverse effects on multiple organs. Their toxicity is related to both the average dose and the cumulative duration of use. General practitioners need to be especially alert as many adverse effects are asymptomatic, but treatable with early diagnosis and intervention. Weight control and dietary advice at the outset of long-term treatment may assist in preventing weight gain and diabetes. Patients should also be screened for diabetes periodically.

Some important interactions with immunosuppressive drugs

Azathioprine	and	allopurinol
Calcineurin inhibitors	and	azole antifungals colchicine diltiazem erythromycin phenytoin atorvastatin, simvastatin
Methotrexate	and	non-steroidal anti-inflammatory drugs trimethoprim (and sulfamethoxazole)

Bone protection

Glucocorticoids alter bone metabolism. They reduce bone formation and increase resorption leading to substantial decreases in bone mineral density, especially in the first few months of use, and to increased fracture rates. Baseline bone mineral density should be measured if corticosteroid therapy is likely to be required for more than three months. Bone-protective therapy should be commenced at the time of starting corticosteroids in high-risk individuals, for example those aged 65 years or over, those with prior fragility fracture and those who are osteopenic.[3] There is evidence for the use of adequate doses of calcium and vitamin D with bisphosphonates for the prevention or reduction of steroid-induced bone loss and fracture.[4]

Patients need encouragement to remain active and to take regular weight-bearing exercise. They should also have their bone mineral density checked every 1–2 years.

Cardiovascular risk

A large cohort study has shown that even after adjustment for known covariates, the relative risk for cardiovascular events in patients receiving high-dose glucocorticoids was 2.56.[5] The risks of individual outcomes such as death, heart failure, myocardial infarction, stroke and transient ischaemic attacks are all significantly higher for those prescribed high-dose glucocorticoids. Tight control of cardiovascular risk factors is therefore essential for those taking corticosteroids.

Eyes

Glucocorticoids cause cataract formation and can increase intraocular pressure. Currently, there is no recommendation for regular ophthalmological review, however enquiry about eye symptoms and yearly optometry review with measurement of intraocular pressure is prudent.

Hydroxychloroquine

This antimalarial drug has immunomodulatory properties and is used in a variety of autoimmune diseases. It is relatively well tolerated at the commonly used dosages of 200–400 mg/day. Retinopathy has been well documented with doses greater than 6.5 mg/kg/day (a dose rarely used today). Hydroxychloroquine is contraindicated in patients with pre-existing maculopathy. Guidelines regarding the need for regular ophthalmological reviews vary. The American Academy of Ophthalmology recommends ophthalmological examination within the first year of treatment. If a patient is in the low-risk category (no liver disease, no retinal disease and age less than 60), no further ophthalmological testing is needed for the next five years. Patients at high risk require annual examinations.[6] The usual practice in Australia is annual ophthalmological review.

Leflunomide

Elevation of liver enzymes is a common toxicity of leflunomide. Three-fold elevations occur in up to 10% of patients, but these are generally reversible with dose reduction or discontinuation of the drug. Liver function tests should be done at regular intervals.

Blood pressure monitoring is required as a small percentage of patients become hypertensive. The risk is increased with concomitant use of non-steroidal anti-inflammatory drugs.

Methotrexate

Methotrexate is usually taken orally once a week on a nominated day, in combination with folic acid to reduce toxicity. The general practitioner needs to take special care as toxicity from methotrexate can occur during long-term use, with up to 30% of patients treated for more than five years discontinuing due to unacceptable toxicity in some series.

An interaction with non-steroidal anti-inflammatory drugs can increase toxicity, but this is less likely to occur with low doses of methotrexate. Penicillins and sulfonamides reduce the excretion of methotrexate. As trimethoprim also increases the risk of toxicity, the combination of trimethoprim and sulfamethoxazole should generally be avoided in patients taking methotrexate.

Myelosuppression

Myelosuppression is the major dose-limiting adverse effect of methotrexate. It is particularly likely in the elderly and patients with renal impairment or concomitant administration of antifolate drugs such as cotrimoxazole and phenytoin. A full blood count every 1–3 months is advisable.

Hepatotoxicity

Hepatotoxicity occurs at a frequency of 1 per 35 patient years. It is usually associated with a cumulative dose of at least 1.5 g. Alcohol is a major risk factor and should be avoided. The general practitioner should enquire regularly about the patient's alcohol intake. Coexisting hepatitis B and C also increases the risk of hepatotoxicity. The current recommendation is for 1–3 monthly monitoring of liver function. Liver biopsy is indicated if six of twelve tests are abnormal in any year (or five of nine if testing is performed at six-week instead of monthly intervals).[2]

Pulmonary toxicity

Methotrexate-induced pulmonary toxicity is an idiosyncratic reaction, occurring at a frequency of 1 per 108 patient years. Hypersensitivity pneumonitis is the most common manifestation. Evidence for screening is lacking. Patients with respiratory symptoms should have lung function testing and a chest X-ray, with specialist review for further investigations, such as a high resolution computed tomography scan, and treatment.

Azathioprine

Azathioprine can be associated with life-threatening myelosuppression and liver enzyme abnormalities. Most patients would have had their concentration of thiopurine methyltransferase measured before treatment.[7] Deficiency of this enzyme is associated with a significantly increased risk of serious adverse haematological events. While azathioprine is contraindicated in homozygous deficiency, individuals with heterozygous deficiency are likely to be prescribed a reduced dose and will need more frequent monitoring. Mild leucopenia can be managed by dose reduction. More severe cytopenia and liver function abnormality will require drug cessation, however this should be done in liaison with the patient's specialist. Myelotoxicity may be precipitated by an interaction with allopurinol, so this combination is best avoided.

Cyclophosphamide

Cyclophosphamide given in intravenous pulses is generally used for inducing remission in a variety of autoimmune

diseases as it has a better adverse effect profile than daily oral dosing. Nowadays, it is usually replaced by other drugs for maintaining remission so patients rarely take it for a long time.

While the patient is taking cyclophosphamide it is crucial to monitor for cytopenia, haemorrhagic cystitis and early signs of infections. Even after the drug is discontinued it is necessary to monitor for haematuria and check urine cytology 6–12 monthly as bladder transitional cell carcinomas can develop up to 15 years after stopping cyclophosphamide. Patients with new-onset non-glomerular haematuria or atypical urine cytology findings should be referred to a urologist for further evaluation, including cystoscopy.

Calcineurin inhibitors

The adverse effects and monitoring required for cyclosporin and tacrolimus are similar. The doses used in autoimmune disease are much lower than in transplantation so there is less toxicity, and regular monitoring of drug concentration is not mandatory. Nephrotoxicity characterised by rising urea and creatinine is a common dose-related adverse effect leading to discontinuation of the drug. Tubular dysfunction can also occur resulting in hypomagnesaemia and hyperkalaemia.

The drugs adversely impact on patients' cardiovascular risk, causing glucose intolerance and hyperglycaemia, hyperlipidaemia, hyperuricaemia and hypertension. These toxicities are usually responsive to dose reduction. Calcium channel blockers are the preferred antihypertensives as they reverse the vasoconstriction mediated by calcineurin inhibitors. Diltiazem also impairs calcineurin inhibitor metabolism, thereby allowing a lower dose to be given. If a lipid lowering drug is necessary, drugs metabolised by cytochrome P450 3A4, such as simvastatin, should be avoided as cyclosporin may increase the concentrations and thus adverse effects. A drug such as pravastatin would be a suitable alternative. Similar caution is needed if ezetimibe is prescribed for a patient taking cyclosporin and cyclosporin concentrations should be monitored.

Every 1–3 months check the patient's weight, blood pressure, full blood count, urea, electrolytes and creatinine, liver function tests, calcium magnesium and phosphate, uric acid, and fasting glucose. Check the fasting lipids every six months.

Mycophenolate

The main toxicity of mycophenolate which requires monitoring is cytopenia. As mycophenolate is renally cleared, dose adjustment is necessary in renal impairment.

Conclusion

Immunosuppressive drugs are efficacious in inducing and maintaining remission in organ threatening inflammatory diseases, but are also associated with significant adverse effects and toxicity. Health professionals involved in the patient's management need to be vigilant and proactive in preventing, monitoring and managing adverse effects. This surveillance may need to continue long after the drugs have been stopped.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 87)

3. Immunosuppressive drugs increase the risk of cardiovascular disease.
4. Patients taking methotrexate should not drink alcohol.

See **Dental notes: Immunosuppressive drugs** page 75.

Prescribing good oral hygiene for adults

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Summary

Good oral hygiene is necessary to maintain a healthy mouth. This involves effective, mechanical removal of bacterial plaque from the teeth and from between the teeth every day. Patients need information and instruction about tooth brushing, flossing and interdental brushing for optimal self-care of the teeth and gums. Teeth should be brushed twice a day, with once-daily cleaning of the interdental spaces with floss or an interdental brush.

Key words: dental plaque, periodontal disease, toothbrushing.

(Aust Prescr 2009;32:72–5)

Introduction

Periodontal disease and dental caries are caused by oral bacteria which form biofilms, called 'dental plaque', on the surfaces of teeth. Good oral hygiene describes procedures which mechanically disrupt and remove dental plaque from the tooth surface in order to maintain a healthy dentition and periodontium. Since plaque is constantly forming, it needs to be removed every day by brushing and by the use of interdental cleaning aids such as dental floss or interdental brushes. Professional evaluation of dental health is required since self-performed oral hygiene alone is insufficient to treat the more severe form of periodontal disease – chronic periodontitis.

The dental plaque biofilm

The mouth has a diverse resident flora and over 700 different species of oral bacteria have been identified. The majority of these bacteria live in biofilms on the oral mucosa, gingiva and tooth surfaces. Desquamation of mucosal and gingival surface cells provides a mechanism for constant shedding of attached bacteria back into saliva and clearance by swallowing. However, biofilms which form on non-shedding surfaces such as teeth are not washed away by the action of saliva or by rinsing with fluids.

Biofilms are complex structures of bacterial communities adhering to surfaces in aqueous environments. The bacteria are surrounded by an extracellular polysaccharide and protein matrix. This protects them by restricting diffusion of host antimicrobial factors, antiseptics and antibiotics[1], or by inactivating these agents within the biofilm. Dental plaque biofilms can only be removed from the tooth surface by mechanical means and therefore mechanical procedures are the mainstay of good oral hygiene.

Plaque formation

Following thorough cleaning of the tooth surface, bacteria from saliva begin re-attaching within minutes. It takes approximately 24–48 hours for sufficient plaque to form and be visible as macroscopic, milky-white, soft deposits on the tooth surface (Fig. 1). Plaque is a soft deposit so it can be easily removed with toothbrushes and interdental cleaning aids. However, when plaque becomes mineralised (calculus), it requires scaling for removal.

What is the best type of toothbrush?

Toothbrushes with soft bristles are recommended for effective plaque removal. They are able to splay beneath the edge of the gingival margin to remove plaque from the tooth surfaces in the crevice between tooth and gum. Hard bristle brushes should be avoided as these do not improve the efficiency of plaque removal and they can damage the gingival tissues and cause gum recession. They can also cause defects by abrading the tooth surface. Although manual toothbrushes can be purchased with soft, medium or hard bristles, all powered toothbrushes have only soft bristles. The head of the toothbrush should be small enough to allow access to all areas of the dentition, particularly the posterior teeth (Fig. 2). Most people do not clean the inner surfaces of the lower teeth effectively. A toothbrush with a small head helps in accessing these surfaces while the handle size and shape should suit the user's dexterity.

Are powered toothbrushes better than manual ones?

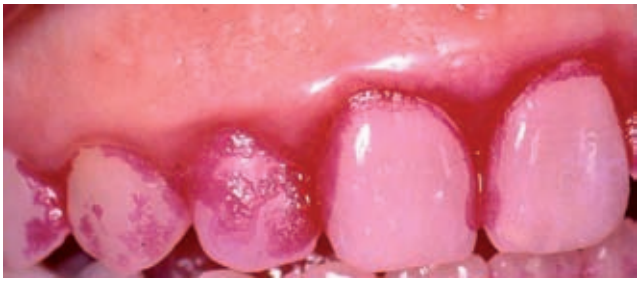
Powered brushes with a rotation oscillation action are the only type with adequate evidence of greater efficacy.[2] Compared with manual brushes, this type of powered toothbrush showed modest improvements in reducing plaque and gingival inflammation scores and was considered to be 'at least as effective' as manual brushes. Brushing for two minutes is the optimal duration necessary to achieve adequate plaque removal. A major advantage of powered toothbrushes is that individuals brush for longer with them as compared with manual brushing.[3] Powered toothbrushes are helpful for individuals with dexterity or disability problems and for carers of the elderly and infirm.

How often should toothbrushes be replaced?

Toothbrush manufacturers recommend replacement every three months. Both manual and powered brushes which are three months old are still as effective as new brushes in plaque removal[4,5] so toothbrush wear does not impede plaque control.

Fig. 1

Dental plaque



Deposits of bacterial plaque on the teeth are white in colour, but can be visualised with plaque disclosing rinses. Plaque forms quickly near the gum margin.

Fig. 2

Toothbrushes

Manual brushes with small heads and soft bristles, and rotation-oscillation type powered brushes are effective designs to remove plaque.

What is the most effective technique of toothbrushing?

No one technique has been shown to be consistently more effective than another. A recommended technique for manual brushes is to place the bristles at a 45° angle to the tooth surface at the gum edge and then move the bristles back and forth in short (tooth-wide) strokes or small circular movements. The tip of the brush is used in an up-and-down manner to clean the inner surfaces of the front teeth.[6] Powered toothbrushes should be held against the tooth surface so that the bristles splay into the crevice between the gum and the tooth. Since the bristles are already moving, there is no need for back and forth actions. Instead, the bristles are held against each tooth in turn in a systematic fashion ensuring that all outer, inner and chewing surfaces are brushed. When using a powered toothbrush, a low brushing force is more effective than a high force in plaque removal.

Is brushing with toothpaste necessary?

Brushing with toothpaste does not remove more plaque than brushing without paste.[7] However, toothpastes and gels are excellent vehicles for delivering fluoride to tooth surfaces to prevent dental caries, as well as delivering other agents to promote re-mineralisation or reduce sensitivity of tooth surfaces. Detergents and other additives in toothpaste may slow the rate of plaque formation. Although toothpastes can remove stains caused by tobacco or beverages, abrasive toothpastes can be harmful as they can cause tooth abrasion.

Is massaging of the gums required during brushing?

Massaging the gums does not resolve or prevent gum disease. This concept dates from an era before the causative role of dental plaque in periodontal disease had been identified and when it was thought that gingival tissues needed to be 'hardened' by physical stimulation to prevent absorption of 'toxins'. Periodontal disease is caused by plaque on the teeth and brushing the gums to 'massage' them does not remove this plaque, but can damage the gums and cause recession.

Does brushing clean between the teeth?

The interdental area is the site of rapid plaque development and the most common site for the onset of periodontal disease. It is also a common site for dental caries. Dental plaque cannot be effectively removed from this area with either a powered or a manual toothbrush since the ends of toothbrush bristles do not reach the tooth surfaces beneath the contact points of teeth. Dental flossing plus brushing removes more plaque from between teeth than brushing alone.[8]

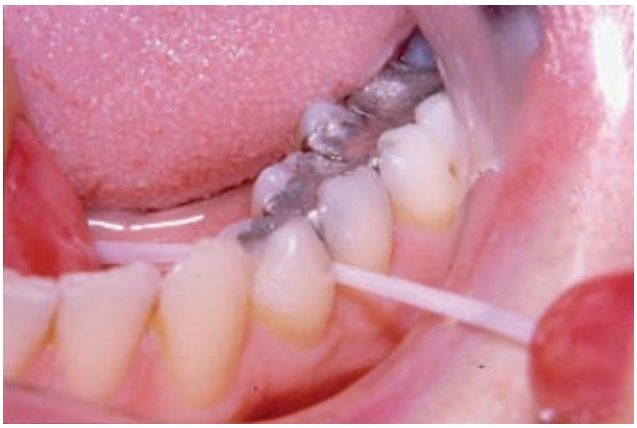
How should flossing be performed?

Flossing is not merely about removing food from between the teeth. The aim is to 'wipe' the interdental tooth surfaces with floss or tape to mechanically dislodge the plaque biofilm. This is particularly important within the crevice between the gum and tooth between adjacent teeth. An effective technique[6] involves gently moving floss through the contact area between the teeth with a back and forth action, ensuring that the floss does not suddenly slip through in an uncontrolled fashion and traumatise the top of the gum. The floss is then shaped into a C configuration so that it 'hugs' one proximal tooth surface and is then moved from the contact area to a position under the edge of the gum where it cannot penetrate any further and then back again to the contact area (Fig. 3). This up and down wiping action should be repeated several times and then the tooth surface on the other side of the interdental space cleaned in the same way.

Flossing can be a difficult exercise to master initially, and coaching and motivation are required. Studies have shown that floss-holding devices as well as various automated flossing

Fig. 3

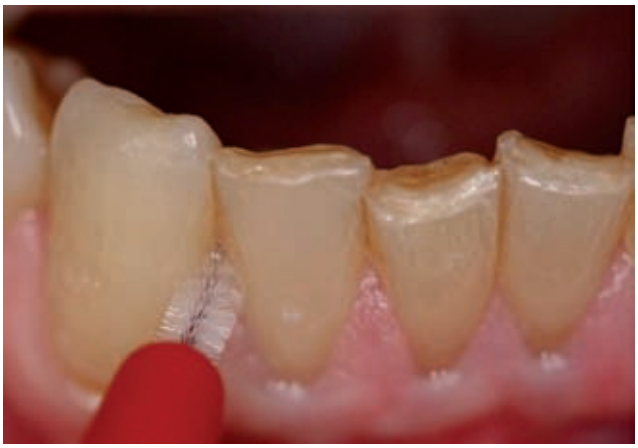
Dental tape



Dental floss or dental tape is required for removing plaque from interdental tooth surfaces

Fig. 4

Interdental brush



Interdental brushes are effective for removing plaque from between teeth

devices are as effective as manual flossing and that patients often prefer these to manual flossing. These devices require only one hand for operation and are available with various handle configurations. They are often helpful for those with dexterity or disability problems or for carers responsible for the oral hygiene of the elderly and infirm.

Are there alternatives to flossing?

Although interdental woodsticks are effective for removing food particles, they are less effective than dental floss for interdental plaque removal. In contrast, interdental brushes are effective in plaque removal. These are spiral brushes that can be pushed forwards and backwards through an interdental space below the contact point of the teeth. The tips of the bristles then mechanically dislodge plaque from the proximal tooth surfaces (Fig. 4).

A randomised blinded crossover trial found interdental brushes to be more effective than floss in removing plaque from accessible interdental spaces.[8] A three-month trial found that interdental brushes reduced plaque and gingival inflammation more than floss and that people became proficient in their use more quickly than with floss.[9] Water jets and other irrigation devices cannot remove plaque from between teeth since the biofilm structure of plaque prevents it being washed off the tooth surface.

How often should oral hygiene be performed?

There is little scientific evidence regarding the optimal frequency of oral hygiene procedures. Although thorough removal of plaque once every 48 hours has been shown to preserve gingival health in a dentally aware group, most people only reduce their plaque scores by 50–60% when they brush. It is therefore recommended that the teeth be brushed twice per day and interdental cleaning be performed once per day.[10] Patients who are susceptible to periodontal disease and those with extensive treatment histories require regular professional evaluation and maintenance care.

Specialised oral hygiene

Patients with dental implants, bridges, crowns which are joined together or those with orthodontic brackets and wires on the teeth will require specialised instruction in how best to perform plaque control. Use of special floss with a firm tip at one end or use of floss threaders is required for flossing under bridges, joined crowns and between teeth with orthodontic wires. Interdental brushes are also helpful in these situations. Plaque also forms on denture surfaces and therefore dentures need to be brushed to remove plaque.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 87)

5. Toothbrushes with hard bristles should be used for removing dental plaque.
6. Regular massage of the gums prevents periodontal disease.

Dental notes

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

Immunosuppressive drugs

See article on page 68

There is an increased likelihood of advanced periodontal disease in patients on long-term immunosuppressive medication.[1] Many patients also suffer from profound salivary hypofunction related to these drugs.[2]

The long-term care of these patients' dentition requires excellent oral hygiene measures, often including adjunctive agents, such as topical fluoride application. Regular dental reviews, professional vigilance and a strong emphasis on preventive dentistry are necessary for the stability of these patients' dental health. They may also often be taking other medicines, such as bisphosphonates, so dentists need to take time to undertake a thorough review of each patient's medical history and continually check which drugs are being used. For patients taking corticosteroids who require invasive procedures such as dental extractions, increasing the dose is recommended to minimise the risk of adrenal crisis.

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Pharmacogenetics of warfarin – is testing clinically indicated?

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Summary

Pharmacogenetics is genetic testing to optimise prescribing for individual patients. Warfarin is a potential candidate for pharmacogenetic testing as it is commonly used, has a narrow therapeutic window and its mechanism of action and elimination pathways involve receptors and enzymes that are polymorphic. Polymorphism is found in vitamin K epoxide reductase and cytochrome P450 2C9. Pharmacogenetic testing is not yet routine because alone it does not predict all the variability in a patient's response to warfarin so its contribution to improved clinical outcomes is uncertain.

Key words: anticoagulation, cytochrome P450 system, vitamin K.

(Aust Prescr 2009;32:76–80)

Introduction

Pharmacogenetics refers to testing based on an individual patient's genetic variation for the purpose of prescribing drug therapy. If it can successfully individualise treatment, pharmacogenetics could have the potential to vastly improve health outcomes. However, there is a long scientific journey from noting a genetic alteration in a drug target or metabolising enzyme to predicting a clinically relevant change in health outcomes.

A patient's response to warfarin is influenced by their genome, so pharmacogenetics could be used to determine warfarin sensitivity. However, there are a myriad of non-genetic factors affecting the relationship between warfarin dose and health outcomes.

Warfarin

Warfarin is the most commonly prescribed anticoagulant drug for the prophylaxis and treatment of venous and arterial thromboembolic disorders. It is now routinely used by many patients with atrial fibrillation. There is therefore interest in whether testing for genetic variations in warfarin metabolism could be useful for predicting the optimum dose, reducing bleeding risk and reducing the time to achieve a therapeutic prothrombin time (expressed as the international normalised ratio (INR)).

The efficacy and safety of warfarin is critically dependent on maintaining the INR within the therapeutic range.[1] Treatment may be ineffective if the INR is low, but there is a sharp increase in the risk of bleeding when the INR is above the upper limit of the therapeutic range.[2] However, with current management patients remain on average within their target range for only two-thirds of the time.[3] This is likely to be because current warfarin-dosing algorithms do not incorporate genetic and environmental factors that affect warfarin concentrations and effects.

Different patients can have highly variable responses to the same dose of warfarin. In order to understand the wide inter- and intra-patient variability in response, it is necessary to consider the pharmacokinetics and pharmacodynamics of warfarin and the effect of age, size and diet.

Cytochrome P450 2C9

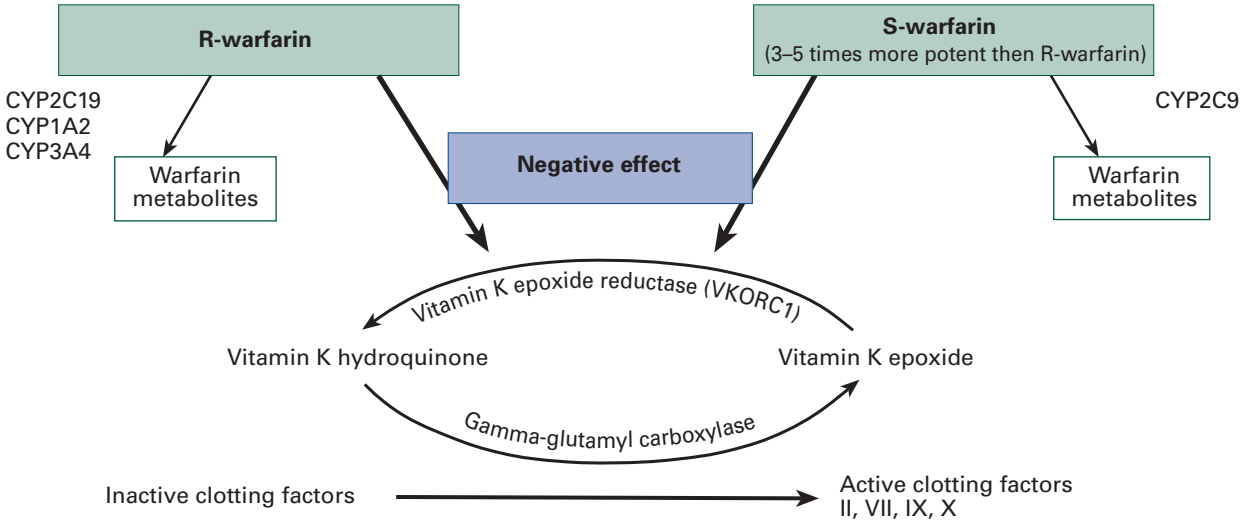
Warfarin is an equal mixture of the enantiomers S-warfarin and R-warfarin, with S-warfarin being approximately 3–5 times more potent than R-warfarin. Metabolism of S-warfarin occurs through the cytochrome P450 2C9 enzyme, while metabolism of the less potent R-warfarin occurs through CYP2C19, CYP1A2 and CYP3A4 (see Fig. 1).[4]

Patients who metabolise warfarin normally are homozygous for the usual (wild-type) allele CYP2C9*1. Two other clinically relevant single nucleotide polymorphisms have been identified in CYP2C9 (*2 and *3). These result in reduced enzymatic activity and therefore reduced warfarin metabolism. The *2/*2 homozygous genotype leads to a 12% reduction in CYP2C9 activity and the *3/*3 homozygous genotype has less than 5% of wild-type CYP2C9 activity. These single nucleotide polymorphisms are relatively common in Caucasians. Approximately 1% of the population are homozygous for CYP2C9*2 and 22% are heterozygous carriers of this allele. The corresponding figures for CYP2C9*3 are 0.4% and 15%. Another 1.4% of people are compound heterozygotes (CYP2C9*2*3).

Fig. 1

Schematic diagram of the action of warfarin

Warfarin is administered as a racemic mixture of S and R enantiomers. Cytochrome P450 2C9 inactivates the more potent S-warfarin enantiomer. Warfarin inhibits vitamin K epoxide reductase, preventing recycling of vitamin K leading to partially carboxylated sub- or non-functional coagulation proteins.



Patients requiring a low dose of warfarin (1.5 mg daily or less) have a high likelihood of having a CYP2C9 variant allele (*2 or *3) and an increased risk of major bleeding complications.[5] A number of studies have shown that knowing the patient's genotype helps in both predicting the optimal dose of warfarin and achieving the target INR more quickly.[6,7,8] However, using this knowledge to predict dose may not necessarily reduce bleeding events.[7]

Vitamin K 2,3 epoxide reductase complex

Even after adjusting the warfarin dose for the variability in CYP2C9 status, there is still an amount of dosing variability in patients who have similar CYP2C9 alleles. This variability appears to be partly attributable to genetic polymorphisms in the C1 sub-unit of the vitamin K 2,3 epoxide reductase complex (VKORC1). This enzyme complex is the rate-limiting step in the vitamin K-dependent gamma carboxylation system which activates clotting factors. Warfarin exerts its anticoagulant effect by inhibiting VKORC1 (Fig. 1).

A number of common polymorphisms in non-coding sequences have been identified in VKORC1. Polymorphisms of this receptor are associated with a need for lower doses of warfarin (see Table 1).[9] The VKORC1 genotype alone may explain nearly 40% of the variability in response to warfarin.[10]

Other genetic mutations

It is theoretically possible that point mutations in the genes for CYP2C9 or VKORC1 add to the variability in warfarin requirements when patients start therapy. There are at least two models which have demonstrated that the CYP2C9 and VKORC1 genotypes, together with known factors such as age and body size, only explain half to two-thirds of the inter-individual variability in warfarin requirements.[8,11] Although this is an improvement on current non-pharmacogenetic algorithms, at least one-third of the variability is still unaccounted for. There are at least 30 other genes involved in the pharmacodynamics of warfarin which may explain this variability, including polymorphisms in apolipoprotein E, multidrug resistance 1 (MDR1), genes encoding vitamin K-dependent clotting factors and possibly genes encoding additional components of the vitamin K epoxide reductase complex.

Environmental factors that affect warfarin dosage requirements

One of the difficulties with focusing solely on the effect of polymorphisms in the metabolising pathways of S-warfarin and vitamin K is that there are a number of non-genetic factors that affect the INR (Tables 1 and 2). Age, racial group and sex are well known, but increasingly recognised yet understudied is the effect of dietary and gut-derived vitamin K.

Vitamin K

Vitamin K is an essential cofactor for the normal production of clotting factors II, VII, IX and X. By inhibiting VKORC1, warfarin reduces the regeneration of vitamin K and thereby inhibits the activation of vitamin K-dependent clotting factors. It is known that a patient's vitamin K status when starting warfarin affects the time to reach a therapeutic INR. In addition, a daily dietary intake of more than 250 microgram reduces warfarin sensitivity. Interesting from a therapeutic perspective is the finding that giving patients with an unstable INR daily doses of vitamin K 150 microgram decreases the variability of INR and increases the time in the target range.[12]

Table 1

Factors associated with lower warfarin requirements

Factor	Effect
Age	Reduced requirements with age may be secondary to smaller liver size with age
Reduced vitamin K intake, e.g. starvation	Inadequate vitamin K to activate clotting factors
Genotypes	
VKORC1 3673	The AA genotype affects warfarin requirement less than GA or GG genotypes
CYP2C9 *2 or *3 CYP2C9 *2 and *3	Both heterozygotes of *2 or *3, or homozygotes of *2 and *3 result in reduced warfarin requirements
Medical conditions	
Advanced malignancy	Reduced requirements may be due to liver metastases, lower body weight and drug interactions
Malabsorption syndromes	Affects vitamin K production and absorption in gut
Liver disease	Affects synthetic functions of liver including production of clotting factors and warfarin metabolism
Heart disease	Causes hepatic congestion, resulting in abnormal liver function and reduced clotting factor synthesis
Pyrexia	Increases warfarin sensitivity by enhancing the rate of degradation of vitamin K-dependent clotting factors
Hyperthyroidism	Thyroxine increases the affinity of warfarin for receptor sites, decreasing production of vitamin K-dependent clotting factors. It also catabolises these factors more quickly.
Some racial groups	May be independent or secondary to known racially divergent CYP2C9 or VKORC1 mutations, different diet or additional factor
Gender	Gender did not make any significant contribution to the regression models, but it is likely that the differences in warfarin requirements noted clinically are attributable to females' smaller body size
Factor VII deletion genotype	Mildly lower reduction
Factor X insertion genotype	Small reduction

VKORC1 vitamin K epoxide reductase
CYP cytochrome P450

Is pharmacogenetic testing appropriate when prescribing warfarin?

Clinicians require easily available information that can help them to predict an individual's warfarin requirements with close to 100% accuracy in both the induction and maintenance phases of therapy. This is especially relevant when starting treatment as this is when the risk of bleeding due to over-anticoagulation is high. The induction regimens in current use (such as modified Fennerty regimens[13]) are only partly successful in achieving the target INR, especially in older people.[14]

Knowing the patient's CYP2C9 and VKORC1 status predicts less than half of the variation in the response to warfarin. Better predictions are achieved by incorporating pharmacogenetics into a dosing algorithm such as that based on the regression model of Sconce.[11] In this model the variables age, height, and the CYP2C9 and VKORC1 genotypes were the best predictors for estimating the starting dose of warfarin. This algorithm also confirmed that the mean warfarin daily dose requirement would be significantly lower with some genotypes.

As an example of the model's utility, the estimated daily warfarin dosage requirement for a 170 cm tall, 90-year-old man with CYP2C9*1/*3 and VKORC1-AA genotypes is more than six times lower than that for a 30-year-old patient of the same height with the CYP2C9 wild type and VKORC1-GG genotypes.

Table 2

Factors associated with higher warfarin requirements

Factor	Effect
Increased body weight	Higher total and lean body weight increase warfarin requirements, possibly through their effect on increasing body surface area
Smoking	Increased metabolism, particular of the R-enantiomer
Cytochrome P450 2C9 inducers	Induce metabolism of the S-enantiomer
High dietary vitamin K	Difficulty of carboxylating clotting factors with warfarin
Hypothyroidism	Decreased catabolism of vitamin K-dependent clotting factors

This model is a marked improvement on current algorithms, but it still only explains 55% of the variability in dose requirements. However, a recent paper has shown that, despite the shortcomings, a pharmacogenetics algorithm is clinically helpful to predict appropriate initial doses of warfarin in high-risk patients.[15]

Cost-effectiveness

As with all new technologies, it is important to evaluate the incremental cost-effectiveness of pharmacogenetics testing versus standard clinical practice. Pharmacogenetic testing for warfarin is relatively cheap compared to other new health technologies. The extra costs of this service include the polymerase chain reaction tests for the three CYP and two VKORC genes and the costs of clinical interpretation, estimated at $75–80 per person, with a turnaround time of three hours. The efficacy of the tests is measured as the reduction in the number of expensive adverse effects, time in hospital and improvement in quality of life due to less frequent INR monitoring. None of this has been accurately quantified in a prospective study, yet it is clear that even a reduction in hospital stay by one day would provide a sizeable cost offset. However, while testing seems relatively good value for money, there are additional issues to consider, for example the cost of screening all potential warfarin users. Additionally, although the prevalence of heterozygotes is relatively high (approximately 30% for CYP2C9), patients with a null genotype (those likely to get life-threatening and expensive adverse effects) are rare (less than 1%). The detection rate for a genotype associated with serious adverse events is therefore low. Lastly, we know that clinical outcomes such as bleeding are rare in patients followed in anticoagulation clinics because warfarin therapy is closely monitored and individualised. The INR is a well-validated and inexpensive surrogate marker for warfarin effects which is already in clinical practice. However, it is not helpful for predicting which dose of warfarin to use for starting anticoagulation.

Additional epidemiological studies are needed to assess the association between genotype and the absolute risk of adverse effects before a cost-effectiveness analysis can be completed.[16]

Conclusion

The variability in warfarin dosage requirements is multifactorial, although genetic polymorphisms play a part. Current warfarin-dosing algorithms fail to take into account genetics and other individual patient factors. Theoretically, including these factors could help in predicting an individual's loading and maintenance doses for safer anticoagulation. However, linear regression analysis, taking into account genetic polymorphisms of CYP2C9 and VKORC1 (additive effect), body weight, body surface area and height, has so far been able to capture only approximately half of the large inter- and intra-patient variation in dose requirements. Vitamin K status and alcohol intake, together with additional genetic factors, are likely to account for some of the remaining difference in warfarin requirements, but still need to be studied in a regression analysis. For now, incorporation of age, body surface area, CYP2C9 and VKORC1 genotype allow the best estimate of warfarin induction and maintenance dose.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 87)

7. Increased dietary intake of vitamin K reduces a patient's warfarin requirements.
8. Most of the inter-individual variation in warfarin requirements can be explained by genetic variation in cytochrome P450 2C9.

Dental notes

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

Pharmacogenetics of warfarin

The international normalised ratio (INR) is a simple test commonly used by dentists to gauge the likelihood that a patient taking warfarin will have excessive haemorrhage following tooth extraction. There is a clearly defined range of INR values within which simple local post-extraction measures, such as suturing, pressure and tranexamic acid mouth rinses, are adequate to control bleeding. Patients within this range can continue warfarin.[1]

The large variation in INR values, related to genetic and dietary factors, particularly the intake of vitamin K, reinforces the need to have this test undertaken shortly before the dental procedure.

The metabolism of warfarin can be reduced by azole antifungals such as miconazole. Topical oral miconazole can profoundly increase the INR and thus the risk of bleeding due to over-anticoagulation.[2,3] Similarly metronidazole, which is commonly used in the management of oral infections, can greatly increase the INR. Dentists therefore need to review patients' current medication before prescribing any drugs, even those topically applied, for possible interactions with warfarin.

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New drugs: transparency

Access to information about drugs is essential for the quality use of medicines. Since 2003 *Australian Prescriber* has therefore recorded details about the willingness of pharmaceutical companies to disclose the information that supported the Australian approval of their new products.[1] These details are published as the T(ransparency)-score at the end of each new drug comment in *Australian Prescriber*.

Table 1 shows the responses to requests for evaluation data between January 2007 and January 2009. The Editorial Executive Committee of *Australian Prescriber* is pleased to report that there has been an improvement since the previous reports were published.[1,2] Most manufacturers now provide some information to assist in the preparation of the new drug comments. The Editorial Executive Committee hopes this trend to increased transparency continues.

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Table 1

Pharmaceutical company responses to requests for clinical evaluation data 2007–2009

Company	Drug
TTT manufacturer provided clinical evaluation	
Amgen	romiplostim
Baxter Healthcare	factor VIII inhibitor bypassing fraction
Bristol-Myers Squibb	abatacept, dasatinib, perflutren
Ferring	carbetocin
Genzyme	anti-thymocyte globulin
Hospira	ibandronic acid
Pfizer	maraviroc, varenicline, ziprasidone
Wyeth	temsirolimus
TT manufacturer provided additional useful information	
Boehringer Ingelheim	pramipexole
Janssen-Cilag	paliperidone
Merck Sharp & Dohme	fosaprepitant
Servier	ivabradine
T manufacturer provided only the product information	
Abbott	paricalcitol
Amgen	panitumumab
Baxter Healthcare	human protein C
Biogen Idec	natalizumab
Boehringer Ingelheim	tipranavir
Cedarglen Investments	galsulfase
CSL	sitaxentan
Delpharm	nitric oxide
Eli Lilly	duloxetine
Genzyme	idursulfase, laronidase
GlaxoSmithKline	human papillomavirus vaccine, lapatinib
Merck Sharp & Dohme	zoster virus vaccine
Novartis	nilotinib, ranibizumab, telbivudine
Pharmatel Fresenius Kabi	pentastarch
Sanofi-Aventis	insulin glulisine
Schering-Plough	olmesartan
UCB Pharma	rotigotine
T manufacturer declined to supply data	
AstraZeneca	fulvestrant
Celgene	lenalidomide
Eli Lilly	exenatide
Janssen-Cilag	darunavir
X manufacturer did not respond to request for data	
Genzyme	alglucosidase
Merck Sharp & Dohme	raltegravir, sitagliptin

New drugs

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

Cilostazol

Pletal (Pharmalink)

50 mg and 100 mg tablets

Approved indication: intermittent claudication

Australian Medicines Handbook section 6.8.1

Cilostazol is a phosphodiesterase III inhibitor. It is indicated for intermittent claudication in patients with peripheral arterial disease who do not have rest pain or evidence of peripheral tissue necrosis. Intermittent claudication is characterised by pain in the legs or buttocks during exercise which subsides with rest. These patients are usually managed by lifestyle modification, including stopping smoking and a supervised exercise program, plus drug therapy to reduce cardiovascular risk.

It is not clear exactly how cilostazol improves the symptoms of intermittent claudication. Its main physiological effects are vasodilation and inhibition of platelet aggregation. Other antiplatelet treatments with similar effects may reduce vascular events in peripheral artery disease, but they have not been shown to improve walking distance in patients with intermittent claudication.

A meta-analysis (seven trials involving 1500 patients) of cilostazol found that 50 mg and 100 mg cilostazol doses (given twice daily for 12–24 weeks) significantly increased absolute walking distance (maximum distance walked on a treadmill) from baseline by 32 m and 50 m more than placebo. A higher dose of cilostazol (150 mg twice daily) also increased walking distance, but the effect was not statistically significant.[1] Exclusion criteria varied between the trials but many excluded patients with ischaemic rest pain, hypertension, obesity and bleeding disorders. Patients taking antiplatelet, anticoagulant or anti-inflammatory drugs were also excluded from some of the trials.[1]

Only one of the studies in the meta-analysis compared cilostazol to an active comparator, pentoxifylline (400 mg three times daily). In this study, 698 patients with moderate to severe claudication received treatment for 24 weeks. Absolute walking distance increased by an average of 107 m for patients taking cilostazol, 64 m for pentoxifylline and 65 m for placebo.[2]

Cilostazol has not been directly compared to lifestyle interventions. However, a meta-analysis of supervised exercise programs found that after three months patients with intermittent claudication could walk 150 m further than those following an unsupervised exercise program. Before treatment, these patients could walk 300 m.[3]

The most common adverse events in the clinical trials were headache (more than 30% of patients), diarrhoea, palpitations and abnormal stools (more than 15%). Oedema resulted in some patients discontinuing cilostazol treatment.[4]

Phosphodiesterase inhibitors have previously been associated with increased mortality in patients with heart failure.[5] When cilostazol was approved in the USA, the Food and Drug Administration requested an additional long-term safety trial to assess all-cause mortality. Consequently, a postmarketing study followed 1435 patients with peripheral artery disease on cilostazol for up to 3.5 years. Patients taking aspirin, clopidogrel, pentoxifylline, anticoagulants, or who had had heart failure in the past, were allowed in the trial. It is important to note that patients with clinical evidence of current heart failure were excluded from this trial. From the data obtained, the number of deaths (from any cause or cardiovascular) and serious bleeding events were similar for cilostazol and placebo. There seemed to be no increase in bleeding events in patients taking aspirin, clopidogrel or anticoagulants.[4] However, long-term adherence in this study was low, with more than 60% of patients discontinuing before the end of the trial. This resulted in the study being underpowered to meet its primary end point – all-cause mortality – and limits the interpretation of the safety data.

After oral administration, cilostazol is readily absorbed and steady-state concentrations are reached after four days. A high fat meal increases the absorption of this drug and the recommendation is to take it at least half an hour before or two hours after breakfast and the evening meal. Smoking decreases exposure to cilostazol by approximately 20%.

Cilostazol is extensively metabolised mainly by CYP3A4 but also by CYP2C19 and CYP2D6, and is contraindicated in patients with moderate or severe hepatic impairment. The majority of metabolites are excreted in the urine so cilostazol is also contraindicated in severe renal impairment. Cilostazol may lead to increased plasma concentrations of drugs that are substrates of CYP3A4 or CYP2C19, such as midazolam, nifedipine and verapamil, so caution is recommended during co-administration.

Patients who are predisposed to bleeding, including those with active peptic ulceration, recent haemorrhagic stroke, surgery within the last three months, or proliferative diabetic retinopathy, should not take cilostazol. Cilostazol is also contraindicated in patients with congestive heart failure, prolonged QT_c interval, multifocal ventricular ectopic beats or

a history of ventricular tachycardia or ventricular fibrillation.

Haematological abnormalities (including thrombocytopenia, leucopenia, agranulocytosis, pancytopenia and aplastic anaemia) have occurred with cilostazol. Some of these were fatal so patients should have their blood counts monitored closely. Patients should be advised to report any signs of blood dyscrasia such as fever or sore throat, and if infection is suspected a full blood count should be done. Treatment should be stopped immediately if any haematological abnormalities develop. For patients having elective surgery, cilostazol should be stopped five days before the procedure.

Caution is urged when giving cilostazol with drugs that lower blood pressure as cilostazol may have an additive hypotensive effect with reflex tachycardia. Caution is also recommended when giving cilostazol to patients with atrial or ventricular ectopy or with atrial fibrillation or flutter.

Patients already taking anticoagulant or antiplatelet drugs should be monitored for bleeding events. Cilostazol has not been assessed in patients who are taking clopidogrel and have a high risk for bleeding such as coronary stent insertion. Cilostazol could potentiate the effects of nitric oxide donors such as sildenafil and should be used with caution in patients taking these drugs.

Cilostazol helps with the symptoms of intermittent claudication, however the overall gains were modest and show little advantage over supervised exercise programs.[3] Cilostazol should not be used in patients with congestive heart failure.

T T T manufacturer provided clinical evaluation

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Doripenem

Doribax (Janssen-Cilag)

500 mg powder for reconstitution and infusion

Approved indication: specified infections

Australian Medicines Handbook section 5.1.2

Doripenem is a new carbapenem with broad spectrum activity against Gram-negative or Gram-positive bacteria. However, it does not work against infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). This antibiotic is indicated for complicated intra-abdominal infections, nosocomial pneumonia (including ventilator-associated pneumonia) and complicated urinary tract infections (including pyelonephritis and cases of concurrent bacteraemia).

Doripenem is structurally related to the other carbapenems (ertapenem, imipenem, meropenem) which all have a beta lactam ring. The bactericidal activity of these antibiotics comes from their ability to inhibit cell wall synthesis by targeting the bacterial penicillin-binding proteins. In *in vitro* studies, doripenem has greater activity against *Pseudomonas aeruginosa*.

Doripenem is given by intravenous infusion every eight hours. For complicated intra-abdominal and urinary tract infections the infusion should be given over one hour, and over one or four hours for pneumonia. Doripenem is not extensively metabolised and most of the dose is excreted unchanged in the urine. Its half-life is approximately one hour in healthy adults.

A lower dose of doripenem is recommended for patients with moderate and severe renal impairment. Doctors should be particularly cautious when using this drug in patients with severely impaired renal function. Although doripenem is haemodialysable, there is insufficient evidence to recommend dose adjustment in those on dialysis. It is probably best avoided in these patients.

The efficacy of doripenem for complicated intra-abdominal infection was similar to that of meropenem in a randomised trial of hospitalised patients. Clinical cure rates (complete resolution or significant improvement of symptoms) were 86% for doripenem and 85% for meropenem in 319 microbiologically evaluable patients (21 to 60 days after completing treatment). More people with *P. aeruginosa* infections responded to doripenem than meropenem (favourable outcomes in 18/19 patients vs 15/19 patients), however this difference was not significant.[1]

Two open-label trials assessed the efficacy of doripenem for nosocomial pneumonia. The first trial compared doripenem to a combination of piperacillin and tazobactam in 444 patients, including some who were ventilated. The median duration of treatment was 11 days. Most patients also received amikacin because of the risk of *P. aeruginosa* infection. Clinical cure rates

were similar for doripenem and piperacillin/tazobactam (81% vs 80%) in the 253 clinically evaluable patients. Not surprisingly, cure rates were lower for patients who were ventilated (69% for doripenem vs 58% for piperacillin/tazobactam). In the doripenem group, four patients had emergent infections associated with drug-resistant bacteria, including *P. aeruginosa*, *Acinetobacter baumannii* and MRSA.[2]

In the other open-label pneumonia trial, doripenem (given as a 4-hour infusion) was found to be comparable to imipenem in 525 patients who required ventilation. Clinical cure rates were 68% for doripenem and 65% for imipenem in the clinically evaluable population (248 patients). More patients (microbiologically evaluable) with *Escherichia coli, Klebsiella pneumoniae* and *P. aeruginosa* infections responded to doripenem than imipenem. Drug resistance emerged in *P. aeruginosa* isolates during the trial, however this was more common with imipenem than with doripenem.[3] (Overall, 38% of patients in the trial were given adjunctive antibiotic treatment for either *P. aeruginosa* or MRSA.)

The efficacy of doripenem for complicated urinary tract infections and pyelonephritis was found to be comparable to levofloxacin in two trials totalling 1171 patients. One of the trials directly compared doripenem to levofloxacin, and the other trial was an open-label design which used the levofloxacin arm from the other trial for comparative analyses. (As yet, the results of these trials have not been published in full.)

In the pooled microbiologically evaluable populations, cure rates after 10 days of treatment were 82–84% for doripenem and 83% for levofloxacin. Microbiological cure rates were lower for renally impaired patients who received a lower dose of the intravenous study drug (75% (54/72 patients) for doripenem and 58% (15/26 patients) for levofloxacin). More infections emerged during doripenem treatment than levofloxacin treatment. Isolates included *Enterococcus faecali, E. coli, Enterobacter cloacae, K. pneumoniae, P. aeruginosa* and *Serratia marcescens*. Similarly, super infections (those caused by resistant pathogens) were more common with doripenem. Resistant organisms included *Candida* species, *Enterococcus* species, *E. coli, Myroides* species, *S. aureus* and *S. maltophilia*.

The most common adverse events with doripenem in the clinical trials were headache (10%), diarrhoea (9%) and nausea (8%). Occasionally more serious adverse events have occurred that were thought to be related to doripenem. These included atrial fibrillation, atrial flutter, acute renal failure, renal impairment, cholestasis, abnormal liver function test, convulsion and hypotension. Treatment was discontinued in 1 in every 1000 patients – reasons included nausea, diarrhoea, pruritus, vulvomycotic infection, increased hepatic enzymes and rash.

As with other carbapenems, doripenem may reduce sodium valproate concentrations in serum, so concentrations should be monitored. An alternative antibiotic or anticonvulsant may be needed if therapeutic doses of valproate cannot be maintained or if seizures occur. Probenecid reduces the renal clearance of doripenem therefore co-administration of these drugs is not recommended. Doripenem is contraindicated in patients who are allergic to penicillins and other beta lactam antibiotics.

Doripenem offers an alternative for patients with serious infections when other treatments have failed, however the approval of this drug is mainly based on data from non-inferiority trials.[4] As with the other carbapenems, bacterial resistance is a problem. Although *in vitro* studies show that doripenem has increased activity against *P. aeruginosa*, there are limited data from the trials to suggest this is also the case in infected patients.

T manufacturer provided only the product information

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Japanese encephalitis vaccine

Jespect (CSL)

0.5 mL suspension in a pre-filled syringe

Approved indication: prevention of Japanese encephalitis

Australian Medicines Handbook section 20.1

Japanese encephalitis is a viral infection transmitted by mosquitoes. Although most infections are asymptomatic, symptomatic infection is often serious and can lead to neurological sequelae or death. The virus has been found throughout Asia and Papua New Guinea and vaccination is indicated for adults who live in or travel to these endemic areas, or who work with the virus in laboratories.

Production of the currently approved vaccine for Japanese encephalitis has been discontinued because of safety concerns regarding hypersensitivity reactions. This was an inactivated vaccine made from Nakayama and SA_{14}-14-2 virus strains propagated in mouse brains. A new inactivated vaccine has been developed in which the virus (strain SA_{14}-14-2) is grown in

tissue culture using Vero cells and not in mice.

In a comparative study of the two vaccines, 863 adults received either two intramuscular injections of the Vero cell-derived vaccine (days 0 and 28) or three doses of the vaccine derived from infected mouse brains (days 0, 7 and 28). Efficacy was assessed by measuring titres of virus-specific antibody in serum. The ability of this antibody to neutralise virus was also measured. The seroconversion rate was the percentage of participants whose serum (diluted at least 1:10) reduced the ability of the SA_{14}-14-2 virus to infect a cell monolayer by 50%. Four weeks after the final injection, the seroconversion rate for the test vaccine was similar to that of the comparator (98% vs 95%), and mean antibody titres were twice as high as in the comparator group. (This analysis was done on the per-protocol population of 735 people).[1] In a long-term uncontrolled follow-up study, 83% of people who had received a course of the Vero-derived vaccine 12 months earlier (181 vaccinees) had seroconverted. Mean titres had dropped at this time point.[2]

Systemic adverse reactions to the vaccines were similar, with headache (26%), myalgia (21%), influenza-like illness (13%) and fatigue (13%) being most commonly reported in the Vero-derived vaccine group. Localised reactions to the Vero-derived vaccine were much lower than with the comparator. For instance, redness was reported by 1% of people given the Vero-derived vaccine compared to 11% of those given the comparator vaccine. Swelling, hardening and tenderness after injection were also less frequent.[1] Similar tolerability to the Vero-derived vaccine was found in a placebo-controlled safety trial of 2650 participants.[3]

Due to lack of data, this vaccine should not be given to pregnant or breastfeeding women unless it is clearly needed. Likewise, it is not known how safe or effective this vaccine is in children.

Co-administration with inactivated hepatitis A vaccine did not interfere with the immune response to the Vero-derived vaccine. If other vaccines are indicated, injections should be given in the opposite arm. Response may be reduced in people who are immunosuppressed.

The actual effectiveness of this new vaccine is unknown. However, it has been inferred from previous studies that if an individual seroconverts to produce virus-neutralising antibody they will be protected against infection. Based on seroconversion rates in the trials, the vaccine should protect most people from Japanese encephalitis for up to a year. It is not known if further vaccinations will be needed after this.

Another way to assess immunogenicity of the vaccine is to measure cell-mediated immunity (which involves T cells directly and not humoral antibody), an important defence against viruses. There are no data on this from the trials but studies are underway.

T T manufacturer provided additional useful information

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Sugammadex

Bridion (Schering Plough)

vials containing 100 mg/mL solution for injection

Approved indication: reversal of neuromuscular blockade by rocuronium or vecuronium

Australian Medicines Handbook section 2.4.4

Drugs that reverse neuromuscular blockade are used by anaesthetists at the end of surgery to accelerate recovery from drug-induced muscle relaxation. Sugammadex is a modified gamma cyclodextrin designed to selectively reverse the effects of the neuromuscular blockers rocuronium and vecuronium. It works by forming a complex with these drugs, reducing their availability to bind to nicotinic receptors in the neuromuscular junction. There are no safety and efficacy data to support the use of sugammadex for reversing other neuromuscular blockers including suxamethonium, and benzylisoquinolium compounds such as atracurium and cisatracurium. Similarly, sugammadex should not be used to reverse pancuronium-induced blockade.

Until now, cholinesterase inhibitors such as neostigmine and edrophonium have been used to reverse neuromuscular blockade after surgery. However, these drugs have a relatively slow onset and have adverse effects associated with stimulation of muscarinic receptors. In addition, neostigmine cannot be used to reverse profound blockade.

The dose of sugammadex depends on the degree of neuromuscular blockade required. In a comparative trial of 182 randomised patients, sugammadex (4 mg/kg) was more effective than neostigmine (70 microgram/kg) at reversing profound neuromuscular blockade induced by rocuronium or vecuronium. The mean time to recovery of muscle function (measured using an acceleromyograph) was three minutes after the sugammadex injection compared to 50 minutes after neostigmine.[1,2] Sugammadex (2 mg/kg) was also quicker than neostigmine (50 microgram/kg) at reversing moderate neuromuscular blockade (mean recovery times of 1–2 mins vs 16–18 mins) in a trial of 189 patients.

In situations where immediate reversal of rocuronium-induced blockade is required, the recommended dose is 16 mg/kg of sugammadex three minutes after rocuronium administration. This recommendation is based on a trial comparing sugammadex for immediate reversal of rocuronium-induced blockade with spontaneous recovery of 110 patients given the short-duration muscle relaxant suxamethonium. Mean recovery times were quicker with sugammadex than with the comparator (4 mins vs 7 mins). There are no clinical data to recommend sugammadex for immediate reversal of vecuronium-induced blockade.[3]

Following intravenous administration, sugammadex has an elimination half-life of 2.2 hours. This is increased in elderly patients and decreased in children. After injection, most of the sugammadex dose is excreted unchanged in the urine, so its use in people with severe renal impairment is not recommended. Longer recovery times may be observed in older patients as well as people with cardiovascular disease, oedema or severe hepatic impairment.[3]

If re-administration of rocuronium or vecuronium is required after reversal with sugammadex, a waiting period is recommended. The duration depends on the dose of sugammadex, the dose of rocuronium or vecuronium, and the patient's renal function.

The most common adverse effect of sugammadex is a disturbance in taste (metallic or bitter taste), which was reported by 12% of patients in a dose escalation trial (mainly after a higher dose of 32 mg/kg). Recurrent blockade has occurred with sugammadex (2% of patients), however this was mostly associated with a suboptimal dose of sugammadex (less than 2 mg/kg). Anaesthetic complications such as body movement, coughing or grimacing during the anaesthetic (which are signs of restoration of neuromuscular function) were thought to be related to sugammadex treatment in about 1% of patients. Allergic reactions, such as flushing or erythematous rash, have been observed with sugammadex.

Sugammadex should not be used in children less than two years. In older children and adolescents, there are limited efficacy and safety data to support its routine use. Immediate reversal in children has not been assessed.

Although no direct drug interactions are expected with sugammadex, drugs interacting with vecuronium or rocuronium could potentially affect the efficacy of sugammadex. Toremifene, fusidic acid and flucloxacillin can displace vecuronium or rocuronium from the complex with sugammadex. This would potentially delay recovery time. High doses of flucloxacillin (500 mg or more) should be avoided in the postoperative period.

Prescribers need to be aware that sugammadex may decrease progestogen concentrations, similar to the decrease observed after missing a daily dose of an oral contraceptive. Women on the pill should refer to the missed dose advice for their contraceptive. Likewise, women using non-oral hormonal contraceptives, such as depot formulations, should be advised to use additional contraception for the next seven days.

Sugammadex may affect haemostasis by interfering with the coagulation cascade. Patients with pre-existing coagulation abnormalities should therefore be monitored for activated partial thromboplastin time, prothrombin time and INR after receiving sugammadex.

Prolongation of the QT_c interval has been noted in some patients receiving sugammadex, however torsades des pointes has not occurred. QT_c prolongation is a concern in situations where sugammadex is given with other drugs that affect the QT interval such as the anaesthetics sevoflurane and propofol.

Sugammadex is the first selective relaxant binding agent. It rapidly reverses neuromuscular block induced by rocuronium or vecuronium regardless of the depth of the block. However, recurrence of neuromuscular blockade has been reported with this drug so close monitoring of respiratory function remains vital during the recovery period. This drug has not been assessed in intensive care units.

T manufacturer provided only the product information

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The T-score (T) is explained in 'New drugs: transparency' on pages 80–1 of this issue.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.emea.europa.eu).

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