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Cost shifting and the quality use of medicines
Is it time for National Medicines Policy 2.0?

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Key words
cost of medicines, Pharmaceutical Benefits Scheme

From the Editor

The quality use of medicines requires that drugs are used safely and judiciously. A challenge for the Policy is that the cost of access to medicines differs between public hospitals and the community. This has implications for continuity of care and the shifting of costs in the health system. The problem is accentuated in some states by the incomplete implementation of the Medicare reforms around medicines funding and access to medicines subsidised by the Pharmaceutical Benefits Scheme (PBS) in public hospitals. These reforms (implemented in Victoria, South Australia, Queensland, Western Australia, the Northern Territory and Tasmania) provide patients with PBS-subsidised access to one month’s supply of medicines on discharge from public hospitals supporting the continuity of care. In states where the reforms have not been implemented, patients on discharge are provided with a limited supply of their medicines, sometimes only a few days, requiring them to visit their GP and pharmacy to access medicines on the PBS.

Public hospital pharmacies are required to purchase pharmaceuticals in accordance with the supply contracts for their state. This does provide an opportunity for public hospitals to negotiate prices which may be cheaper than the PBS price. These contracts can influence what brands of medicines are available on hospital formularies and the quality use of medicines in the public system. This situation may also provide an opportunity for hospitals to profit when they can purchase a medicine, which they supply on the PBS at discharge, at a price lower than the remuneration the hospital receives from the PBS.

For example, a patient in a public hospital with neuropathic pain may be offered gabapentin. This is an off-patent medicine and there are a number of alternative brands on the Australian market. This competition enables negotiations to achieve the best price for supplying public hospitals. When discharged from hospital into the community the same patient cannot obtain the drug at a subsidised price because gabapentin is not listed for neuropathic pain on the PBS. Pregabalin is a therapeutically equivalent drug for neuropathic pain which is listed on the PBS.

A second example would be a patient taking a fixed-dose combination of an antihypertensive drug who is admitted to a public hospital. The hospital may not stock all of the available fixed-dose combination products and is likely to supply alternative brands of the individual medicines included in the combination product while the person is in hospital. On discharge from hospital the patient is likely to receive a prescription for the individual medicines (incurring two dispensing fees) with the added risk of confusion (and double dosing) about whether they should recommence the combination product.

These scenarios have important implications for cost shifting in the health system and the continuity of care for the patient. Added to the complexity of the health system is the risk of confusion when switching between different brands of medicine when...
patients are discharged from hospital. The cheapest brand in the hospital may not be the cheapest in the community pharmacy. Interestingly, pharmaceutical companies may employ a ‘loss leader’ approach by providing their medicines to public hospitals at a discount price to ensure they are included on the formulary, knowing that many medicines commenced in hospital are continued after discharge. This will mean that a patient will then obtain that medicine through the PBS, once they return home from hospital, increasing the uptake of that medicine in the community.

Cost shifting in the health system and funding ‘workarounds’ seem to be the norm for healthcare professionals. They have to do their very best to ensure their patients have sustainable and affordable access to medicines especially when moving between settings of care. Cost shifting is not a new issue, but it is a continuing challenge. The Society of Hospital Pharmacists of Australia prepared a possible solution in a position paper more than a decade ago. It said:

A single national system for medicines funding would foster integration with many other government programs on medicines use and allow the benefits of hospital work to flow to the community sector and vice versa.²

The National Medicines Policy was originally developed almost two decades ago at a time when the Australian health system and medicines issues were substantially less complex. The NPS MedicineWise national census on medicines use in 2012 highlighted the increasing complexity of medicines-related issues in the health system, including the high prevalence of medicines use and polypharmacy in older Australians.³ Invariably this complexity has created gaps and tensions in the health system, including barriers to achieving the quality use of medicines. These structural issues highlight the need to revisit and refocus the National Medicines Policy in the context of the present health environment and likely future challenges related to medicines and health.

Revisiting the National Medicines Policy in the context of medicines use and access must retain the commitment to a partnership approach. This has been the hallmark of the policy, ensuring the health of Australians is at its core and engaging with all partners in the sector (health professionals, regulators, consumers and industry), including the layers of government that fund access to medicines.

In summary, while we continue to have a disjointed health system with partially implemented funding reforms we will continue to have problems with timely access to affordable medicines and conflict, confusion and discontinuity for consumers. There is now a need to reframe Australia’s National Medicines Policy and its implementation to ensure we remove barriers to achieving the quality use of medicines.

Andrew McLachlan is an investigator on the PRECISE clinical trial which has received in kind research support (provision of pregabalin and placebo) from Pfizer. He has also received funding from GSK to support a research student scholarship. Professor McLachlan is the chair of a Drug and Therapeutics Committee at a public hospital and a member of a number of Australian government committees related to medicines regulation and antidoping. He is the former chair of the National Medicines Policy Committee.

REFERENCES

Letters to the Editor

Cardiovascular drugs in older people

Editor, – The article on cardiovascular drugs in older people (Aust Prescr 2013;36:190-4) did not provide up-to-date evidence regarding the use of anticoagulants in older people. The elderly with atrial fibrillation are at the greatest risk of stroke.1,2 Risk from falls has been an excuse not to treat. It is estimated that patients with atrial fibrillation, with an average stroke risk of 5% a year, would have to fall approximately 300 times in a year for the risk to outweigh the benefit.3 In people aged 75 years and over with atrial fibrillation, the risk of stroke may be greater than 20% a year and can be reduced to less than 5%.4,5 In the ARISTOTLE trial,6 apixaban was compared to warfarin in 18 201 patients. In the 5678 patients aged 75 and older, the rate of stroke or systemic embolism per year was only 1.6-2.2%. There was significantly less intracranial haemorrhage with apixaban. Aspirin as a single drug may be marginally better than placebo, but with the risk of bleeding.6,7 Aspirin plus clopidogrel is better than aspirin alone, but the risk of bleeding is similar to warfarin.6 We agree with both the Canadian Cardiovascular Society and the European Society of Cardiology who no longer recommend antplatelet therapy as first line in stroke prevention, irrespective of age, in patients with atrial fibrillation and a CHA2DS2 score of at least one.6,8 Anticoagulants for stroke prevention in the elderly with atrial fibrillation are indicated in most patients, even if they are frail. Antiplatelet drugs are markedly inferior with similar or greater bleeding risk.6,8,9

Vasi Naganathan, the author of the article, comments:

The letter raises an important question about the effectiveness and safety of anticoagulants for atrial fibrillation in older people. The authors are correct in their assertion that the evidence from clinical trials shows that anticoagulants are more effective than antiplatelets and have a similar low bleeding risk in the kind of older people who participate in clinical trials. The key question, however, is whether anticoagulants do more good than harm in older people who are frail, have multiple comorbidities and frequent falls. We do not have direct evidence about the efficacy or safety in this group because the inclusion and exclusion criteria in anticoagulant trials exclude most of them. In the ARISTOTLE trial,8 exclusion criteria included increased bleeding risk believed to be a contraindication to oral anticoagulation, severe comorbid condition with a life expectancy of less than one year, severe renal insufficiency and inability to comply with INR monitoring. Over 80% of the

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patients in the BAFTA trial\(^2\) were taking warfarin or aspirin before enrolment, which means the trial selected individuals who had already survived exposure to drugs that increase the risk of bleeding. In the much smaller WASPO trial\(^3\) which specifically enrolled octogenarians, people were excluded if they had had one or more falls within the last 12 months or a Mini-Mental State Examination (MMSE) score <26.

The assertion that a patient with atrial fibrillation must have 300 falls a year before the risk of warfarin outweighs the benefit comes from a Markov decision analysis that assumed participants had no disability at all before anticoagulation. It did not take into account the fact that patients who fall often have other risks for bleeding that can lead to major bleeds other than subdural haematomas.\(^4\)

Unless someone is brave enough to do the definitive trial that specifically looks at anticoagulation in older patients with atrial fibrillation who are truly frail, have comorbidities and are at risk of falling, or we have anticoagulation registries that include these kind of patients, we are left making clinical decisions in an ‘evidence-free zone’ and we will continue to see a wide variation in clinical practice.

REFERENCES


Classifying drugs in pregnancy

Editor, – With regard to the editorial ‘Classifying drugs in pregnancy’ (Aust Prescr 2014;37:38-40), we would like to comment on the statement that ‘topical or inhaled exposures are generally less concerning than oral or parenteral ones’. While this is an accepted generalisation, important exceptions should be highlighted including topical retinoids and cytotoxics, as well as transdermal opioid patches. According to several resources, topical tretinoin and isotretinoin (Australian category D) are not recommended during pregnancy.\(^1,4\) The Australian Medicines Handbook states that ‘although absorption via skin is minimal, in view of the teratogenicity of systemic retinoids, topical retinoids should not be used in pregnancy’. This is in line with the manufacturers’ recommendations.

Topical 5-fluorouracil cream (Australian category D) is another important example. Spontaneous abortion and two cases of malformations in infants exposed in utero due to maternal application of the cream have been reported.\(^1\)

Safety concerns of using transdermal fentanyl patches (Australian category C) during pregnancy should also be considered as the patch is designed to provide equivalent serum concentrations to parenteral formulations. The product information for Durogesic states that ‘neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of Durogesic during pregnancy’.

Felicity Prior

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REFERENCES

3. eMIMS. Sydney: MIMS Australia Pty Ltd. 2014.

Debra Kennedy, the author of the editorial, comments:

While Felicity Prior and Kate O’Hara have listed the exceptions to my statement that ‘topical or inhaled exposures are generally less concerning than oral or parenteral ones’, I do not feel this adds much to the broader debate about the pros and cons of drug classification in pregnancy. In fact, many of their statements actually highlight my contention that narrative labelling rather than simple categorisation is a more effective way of outlining the risks and that this needs to be made in an appropriate clinical context.

While they acknowledge that absorption of retinoids via skin is minimal, they then quote the somewhat contradictory Australian Medicines Handbook recommendations that ‘topical retinoids should not be used in pregnancy in view of the teratogenicity of systemic retinoids’. Clearly if a woman is seen before pregnancy was confirmed at eight weeks
she may consider a termination because of such warnings, and possibly, not fully understanding the differences between topical and oral preparations. Regarding topical fluorouracil, it is of some concern that the authors cite drug company product information about malformations and miscarriage, but then fail to quote the subsequent sentence in the reference guide which is far more important and says ‘it is not known if there is a causative relationship between the topically applied drug and these outcomes’. Also, malformations seen following topical use (with approximately 6% systemic absorption) were completely different to those seen after systemic exposure, making a causal relationship even more tenuous. If drug information specialists have difficulties interpreting such nuances, how is a poor patient or busy GP supposed to deal with this data.

We all want what is best for pregnant women and their babies and this starts with sound evidence-based advice and counselling about medication risks and benefits, not a simplistic alphabet soup.

Editor, – The recent editorial by Debra Kennedy (Aust Prescr 2014;37:38-40) describes a longstanding and complex problem in medicines information. Unfortunately, Dr Kennedy’s understanding of content found in the Australian Medicines Handbook (AMH) – that it ‘essentially consists of the Australian Drug Evaluation Committee categorisation and the company product information’ – is incorrect.

Great care and significant consideration of available evidence is taken in crafting the brief advice we provide. In the section on prescribing for pregnant women we say:

Our advice is based on human data and clinical experience. Animal studies are not used as the sole sources of information upon which advice is based, as their interpretation with respect to human risk is not clear. Advice provided may not mirror the approved product information. Absence of information in AMH does not imply safety. Australian categories of safety, from the database Prescribing medicines in pregnancy, are included where they exist.

For nifedipine, the product information states ‘Category C: nifedipine is contraindicated throughout pregnancy’. It then describes a range of potential fetal impacts on the basis of maternal hypotension, and adverse fetal effects seen in animal species. However, the AMH advises nifedipine is ‘used to suppress preterm labour and for hypertension in pregnancy’. This reflects current evidence and practice, as nifedipine is the preferred tocolytic in Australia. The AMH also includes preterm labour as an accepted indication for use of nifedipine.

It is impossible to reduce complex information to a one-letter categorisation. The plan announced by the US Food and Drug Administration over five years ago, to eliminate the pregnancy categorisation, and replace it with drug-specific interpretations of available data, confirms this.

Simone Rossi
Managing editor
Neil Hotham
Specialist editor
Australian Medicines Handbook
Adelaide

Debra Kennedy, the author of the editorial, comments:

Thank you for pointing out my error in essentially lumping the AMH with other sources of information such as MIMS and the product information. I apologise if this caused any offence or confusion. I am the first to acknowledge the AMH as a valuable source of information regarding the use of medications in pregnancy. I did not intend to criticise its content.

I did, however, wish to point out that the AMH still includes the Australian Drug Evaluation Committee categorisation as well as some narrative and that therefore at times (in my opinion at least) it contains information that is somewhat internally contradictory. One example is hydroxychloroquine which is listed in the AMH as being indicated to treat ‘rheumatoid arthritis (mild), discoid and systemic lupus erythematosus and prophylaxis and treatment of malaria if chloroquine is not available’, but then goes on to say that it is ‘safe to use for malaria; for other indications contact one of the pregnancy drug information centres; Australian category D’. I am not sure that this is either helpful or accurate. Why is the drug safer in pregnancy for one indication than another? The reality is that in Australia far more women will be using it for rheumatological conditions than for malaria. Furthermore, it is unclear why the drug is actually category D as there is no compelling evidence, to my knowledge, of it increasing the risk of birth defects. This would be a more valuable statement than any of the above.
Drug treatments of childhood coughs

SUMMARY
Appropriate management of cough in children depends upon accurate assessment. The diagnosis is often unclear at the initial presentation.

Acute cough is frequently caused by a viral infection, and often no specific therapy is indicated. Urgent treatment may be needed if history suggests a more serious disorder such as a foreign body or pneumonia.

When treating children with chronic cough, paediatric-specific algorithms should be used. Empirical use of medicines without looking for a specific cause should be avoided.

In the absence of an alternative specific cause of cough, chronic wet cough (lasting at least four weeks) is most frequently due to protracted bacterial bronchitis. Antibiotics are indicated.

Introduction
Cough is the most common symptom presented to GPs and pharmacists in Australia. An Australian study found that ‘one in three (28.7%) respiratory episodes were associated with a doctor’s visit, and one in four (23%) necessitated time off school or work’. When a child first presents with cough, determining the precise diagnosis is not always possible.

Acute cough
Acute cough in a child may represent a variety of pathologies, from self-resolving viral-induced acute respiratory infection to acute severe respiratory disease or an acute presentation of an underlying chronic disorder. Appropriate management depends on accurate assessment. Patient history should include:• cough duration (acute <2 weeks, sub-acute 2–4 weeks, chronic >4 weeks)• characteristics of cough (whooping cough, wet vs dry cough)• questions about choking episodes and previous respiratory illness• associated wheeze• other symptoms such as weight loss, appetite or rash• immunisation history.

In the differential diagnosis, it is important to consider inhaled foreign body, pneumonia and other treatable infections like pertussis and underlying lung disease such as bronchiectasis.

Uncomplicated acute upper respiratory infections
It is commonly said that young children have up to 6–12 acute respiratory infections per year. However, a Melbourne-based community study involving 600 families showed fewer episodes and an age-dependent trend (see Table). The mean duration of episodes was 6.3 days (range 1–70 days) and younger children were more likely to have a longer duration of cough (6.8 days in youngest age group and 5.5 days in oldest group).

Management
Supportive therapy is the mainstay of treatment for viral acute respiratory infections. Paracetamol and ibuprofen are useful for related symptoms. Over-the-counter cough and cold medicines are not recommended due to a lack of proven efficacy and the possibility that they may present a safety risk. The Therapeutic Goods Administration now recommends that they should not be used in children under 6 years and only in children aged 6–11 years on advice from a doctor.

Honey,5,6 and menthol-based rubs7 may reduce the impact of nocturnal cough. It is reasonable to recommend one teaspoon of honey before bedtime for children aged over one year. Honey should be avoided in children under one year due to the risk of botulism.

Table
Australian rates of uncomplicated acute upper respiratory infections in children and young adults

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean number of episodes a year</th>
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</thead>
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<tr>
<td>0–1</td>
<td>3.8</td>
</tr>
<tr>
<td>2–3</td>
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<td>4–5</td>
<td>2.8</td>
</tr>
<tr>
<td>6–10</td>
<td>2.2</td>
</tr>
<tr>
<td>11–20</td>
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</tbody>
</table>

Key words
asthma, bronchiectasis, bronchiolitis, bronchitis, croup, pertussis, pneumonia

Aust Prescr 2014;37:115–9
Antibiotics should be avoided for the treatment of acute cough associated with mild upper respiratory tract infection, as the cough is most likely viral in origin. A recent Cochrane review reported that in cases of confirmed or suspected exposure to influenza in healthy children, oseltamivir shortens the time to first alleviation of symptoms by 29 hours (95% confidence interval 12–47 hours, p=0.001).6 No effect however was seen in children with asthma. Oseltamivir may reduce the risk of otitis media in children aged 1–5 years, especially if commenced within the first 12 hours, but is associated with a significantly increased risk of vomiting.6 Laboratory-based polymerase chain reaction (PCR) techniques enable rapid influenza diagnosis.10

Management of acute cough should include counselling and advice on:

• the expected duration of cough (typically 5–7 days, but up to 3 weeks)
• when to come back and see the GP and when to seek urgent medical review (for example suspected foreign body, tachypnoea, dyspnoea, vomiting, inability to feed, persistent fever, lethargy)
• avoidance of passive smoke exposure.

Specific causes of acute cough

A number of specific diseases need to be considered in a child presenting with acute cough. Many of these have specific symptoms and signs.

Croup
The acute or sub-acute onset of a barking ‘brassy’ cough, hoarse voice, stridor with or without evidence of upper airway obstruction, is characteristic of croup. It often begins with a viral upper respiratory tract infection (for example rhinorrhea, sore throat with or without fever) and typically affects children aged 1–6 years. Children outside this age range or with severe or recurrent stridor or other symptoms require careful evaluation for an underlying airway lesion. Children with bacterial causes of stridor such as tracheitis or epiglottitis usually appear more toxic.

Prednisolone 1–2 mg/kg orally for two consecutive days is effective for croup. Dexamethasone 0.15 mg/kg orally is an appropriate alternative therapy. In severe croup, when a child has ongoing stridor at rest, increasing fatigue and marked tachycardia with or without signs of impending hypoxaemia (for example, lethargy and increased irritability), urgent transfer to an emergency facility is recommended. Potentially distressing interventions, such as throat examination, should be avoided, as these may worsen respiratory obstruction.

Pneumonia
Children with pneumonia often have cough, fever and tachypnoea, but occasionally present with fever and upper abdominal pain. Signs of severity include grunt and intercostal recession. Wheeze is usually absent in bacterial pneumonia. A chest X-ray does not need to be performed routinely in all children with suspected pneumonia. However, it should be considered in any child with an atypical presentation (recurrent pneumonia, prolonged fever, signs of pleural effusion) or severe pneumonia requiring hospital admission.11

Recommendations for antimicrobial therapy vary according to the age of the child, context, presence of underlying disease (risk factors), presence of hypoxaemia, non-respiratory symptoms (such as vomiting), length and severity of symptoms and the presence of complications. Guidelines for antimicrobial therapy should be consulted.11–13 For a child with subacute onset and prominent cough (with or without headache or sore throat), or who is not improving, mycoplasma pneumonia should be suspected.15

Indications for hospitalisation for community-acquired pneumonia include:

• very young children (less than 6 months) with suspected bacterial pneumonia12
• clinical evidence of moderate to severe pneumonia, including hypoxaemia and signs of respiratory distress12
• significant comorbidities or factors which predispose to more severe disease e.g. immunodeficiency, congenital heart disease, bronchiectasis11
• pneumonia suspected or confirmed to be secondary to a pathogen with increased virulence e.g. community-acquired methicillin-resistant Staphylococcus aureus (MRSA)12
• dehydration or inability to tolerate oral therapies11
• significant parental concern or anxiety11
• family unable to provide appropriate care or adhere to management plan12
• toxic-looking child e.g. pale or cyanotic, lethargic or inconsolably irritable
• complicated pneumonia e.g. empyema
• poor response after 48 hours of oral antibiotics.

All children with suspected pneumonia should be followed up regularly to ensure complete resolution of their symptoms. A repeat chest X-ray is not routinely performed following simple pneumonia unless there are persisting symptoms.11

Bronchiolitis
Children under two years presenting acutely with cough, tachypnoea (with or without poor feeding) and often with a history of a viral prodrome may
have viral bronchiolitis. Clinical examination reveals hyperinflation with widespread wheeze and crackles on chest auscultation. Respiratory syncytial virus is the most common infection associated with bronchiolitis. Any infant with apnoeas, hypoxia (oxygen saturations ≤92%), dehydration or poor feeding requires hospital admission for supplemental oxygen with or without hydration therapy. Children frequently worsen in the first 72 hours before showing improvement. The cough can persist for 2–3 weeks after other symptoms resolve. There is no evidence for the routine use of antibiotics, steroids or asthma drugs in viral bronchiolitis.

**Pertussis**

Pertussis (whooping cough) typically presents with cough lasting two or more weeks with cough paroxysms, inspiratory whoop or post-tussive vomiting. Confirmation with a PCR-positive nasopharyngeal aspirate or swab is recommended. If there is a high clinical suspicion, start antibiotics before receiving the test results. Clarithromycin (7.5 mg/kg up to 500 mg orally, 12-hourly for 7 days) or erythromycin (10 mg/kg up to 250 mg orally, 6-hourly for 7 days) is recommended. Treat early to improve symptoms (within 1–2 weeks of start of symptoms) and reduce the infectious period. Patients are seldom infectious after having a cough for longer than three weeks and antibiotics are not recommended at this point.

**Chronic cough**

The common causes of chronic cough in children differ from those in adults so adult-type management approaches directed at asthma, rhinitis and gastro-oesophageal reflux disease do not apply. In a multicentre study involving 346 new referrals to respiratory paediatricians for chronic cough, the most common diagnoses included protracted bacterial bronchitis (41%), asthma (15.9%) and bronchiectasis (9%). In 13.9% of children, cough resolved without a specific diagnosis. A detailed respiratory history and examination as well as use of a chronic cough algorithm (see Fig.) assist in the assessment and diagnosis of chronic cough.

**Fig. Simplified paediatric chronic cough algorithm**

### ASSESSMENT

**History:** cough characteristics, specific features suggestive of an underlying diagnosis (e.g. pertussis), wheeze or recurrent lower respiratory tract infections, feeding difficulties, medications, neurodevelopmental problems, malnutrition, failure of previous treatment

**Examination:** chest wall deformity, clubbing, abnormal auscultation

**Consider:** chest X-ray with or without spirometry

<table>
<thead>
<tr>
<th>No specific diagnostic features</th>
<th>Features of specific diseases such as asthma or bronchiectasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wet cough</td>
<td>Investigate and treat according to likely diagnosis, consider specialist referral</td>
</tr>
<tr>
<td>Dry cough</td>
<td>Watchful waiting and review</td>
</tr>
<tr>
<td>Features of protracted bacterial bronchitis</td>
<td>If cough continues</td>
</tr>
<tr>
<td>Antibiotics + repeat course if necessary</td>
<td>Refer to specialist</td>
</tr>
<tr>
<td>If cough continues</td>
<td>Consider trial of therapy (e.g. bronchodilator), consider specialist referral</td>
</tr>
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</table>

Adapted from reference 16
The cough algorithm also significantly improves quality of life and reduces duration of cough. This approach is based on determining the cause of the cough (through systematic history taking and a thorough examination), in addition to spirometry (in a child >5 years of age) and chest X-ray. Indications for referral to a specialist are listed in the Box.

**Box Common indications for specialist referral in chronic childhood cough**

- Chronic cough (>4 weeks) of unclear aetiology (with or without failure to thrive)
- Suspected airway malformation e.g. tracheo-oesophageal fistula, vascular ring
- Cough and feeding difficulties (suspected aspiration disease)
- Clinical features of chronic lung disease e.g. clubbing
- Persisting auscultatory findings e.g. crepitations
- Recurrent pneumonias
- Abnormalities on chest X-ray or spirometry
- Failure to respond to treatment e.g. in asthma

**Protracted bacterial bronchitis**

Protracted bacterial bronchitis is the most common cause of chronic wet cough in Australian children. It is defined as:

- cough lasting more than four weeks
- response to two weeks of antibiotic therapy
- absence of specific pointers indicating an alternative cause.

A history of a preceding viral infection is common. Protracted bacterial bronchitis is more common in boys than girls and in those aged 1-3 years. Lower airway bacterial infection is frequently found on bronchoalveolar lavage sampling and is usually accompanied by elevated neutrophils suggestive of active airway inflammation. The major bacterial organisms found are *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*. After exclusion of other causes of chronic cough, a two-week course of amoxycillin-clavulanate is recommended. Children should receive follow-up after 2-3 weeks to ensure complete resolution of cough. A chest X-ray should be performed in any child with clinical suspicion of an alternative cause of chronic cough or if their cough persists despite antibiotic therapy.

**Bronchiectasis**

Bronchiectasis is another important cause of wet cough to consider, and should be suspected in any child with the following:

- chronic wet cough lasting longer than eight weeks
- two or more episodes of chronic wet cough (lasting ≥4 weeks) per year responding to antibiotics
- chest radiographic changes lasting more than six weeks despite appropriate antibiotic therapy.

Antibiotic therapy is usually started at the onset of wet cough in children known to have bronchiectasis. Antibiotic selection is based upon lower airway culture, local antibiotic susceptibility patterns and clinical severity. If symptoms do not respond promptly or adequately to oral antibiotic therapy patients should be hospitalised for intravenous antibiotics. Regular physiotherapy, physical exercise, avoidance of triggers (for example tobacco smoke) and routine vaccinations are recommended. Aboriginal and Torres Strait Islander children are at increased risk of bronchiectasis and doctors should be aware that cough may be under-reported by those from remote communities.

**Asthma and chronic cough**

While asthma can cause chronic cough, isolated chronic cough without any other symptoms in children is rarely due to asthma. Other symptoms usually present in asthma are wheeze, dyspnoea, chest tightness or exercise limitation. Risk factors such as eczema, hay fever, allergies or a family history of asthma in a first-degree relative are often present. Spirometry and measurements of airway responsiveness (for example exercise challenge) in children aged over five years can help to diagnose asthma. The presence of atopy does not distinguish asthma from other causes of chronic cough. Previous response to asthma therapies may be helpful, however response on a single occasion does not necessarily mean that the child has asthma. Guidelines for the management of asthma are available from the National Asthma Council of Australia (www.nationalasthma.org.au/handbook).

**Conclusion**

Accurate diagnosis of cough in children depends upon a thorough clinical history and examination to guide appropriate prescribing. The nature of the cough and its chronicity provide important diagnostic clues as to a specific cause of cough. Cough guidelines and algorithms further enhance diagnostic accuracy and may help to ensure more effective prescribing of cough therapies in children.

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**SELF-TEST QUESTIONS**

**True or false?**

1. Aboriginal and Torres Strait Islander children have an increased risk of bronchiectasis.
2. There is evidence for use of steroids in viral bronchitis.

Answers on page 143

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Malnutrition and nutritional supplements

SUMMARY
Malnutrition is common in the elderly, both for those living at home and those in care. A malnutrition screening tool can be used to identify people at risk.

In addition to correcting factors that may contribute to weight loss, the first step in improving oral intake is to use real foods. Small, frequent, nutrient dense meals are recommended.

Oral nutrition supplements are a useful adjunct to increase protein, energy and nutrient intake. There are standard supplements which are usually powders, but can be premixed liquids.

An Accredited Practising Dietitian can provide expert advice to improve nutrition status. They can advise on the use of specialised supplements for patients with conditions such as cancer cachexia and renal disease.

Introduction
Weight loss is not necessarily a normal part of the ageing process. However, undernutrition and malnutrition (see Box) are common in the elderly. This can result in significant morbidity and mortality, hospitalisation, pressure ulcer development, infection and an increase in falls and subsequent fractures.

Unintentional weight loss can result in a reduction in the ability to care for oneself, loss of mobility and independence and a poorer quality of life. People who are poorly nourished are more likely to be hospitalised and are less likely to live independently.

The rates of malnutrition in older people living at home are estimated to be as high as 30% and in aged-care facilities can be as high as 70%. Weight loss in the elderly generally results in loss of skeletal muscle mass and strength (sarcopenia). Sarcopenia has huge personal and financial costs and remains largely unrecognised.

There is wide publicity about the health impact of overweight and obesity and even the frail elderly and their carers can express satisfaction that they are finally losing weight. However, this may be the result of poor dietary intake or an undiagnosed illness. It must be remembered that obesity and malnutrition can exist simultaneously.

Causes of malnutrition
There are multiple factors that may contribute to weight loss and malnutrition. These include:

- financial problems
- social difficulties
- multiple comorbidities
- respiratory difficulties (for example dyspnoea)
- dysphagia
- poor dentition
- adverse effects of drugs
- polypharmacy
- depression, bereavement
- dementia
- reduced taste and smell
- poor appetite.

Correcting malnutrition
The first step in reducing malnutrition is to identify those who are at risk. There is a variety of malnutrition screening and assessment tools that are validated in various settings. These tools include questions about current weight, body mass index, weight change, appetite and comorbidities, and assign a score indicating level of risk. They can help to identify those who are losing weight and who are at risk, but they must be used together with a ‘pathway of action’. The factors contributing to poor intake must be treated where possible. Everyone involved in the care of the person can play a part in encouraging food intake and improving nutrition. The causes of poor intake should be closely examined and corrected. In addition the

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Box  Definition of malnutrition

The British Association for Parenteral and Enteral Nutrition (BAPEN) defines malnutrition as follows:

Malnutrition is a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function and clinical outcome. The term malnutrition does include obesity, however BAPEN is focused on the problem of ‘undernutrition’. The term ‘malnutrition’ is used commonly to mean ‘undernutrition’.
role of the dining environment and other social factors should not be underestimated.\(^6,7\) An Accredited Practising Dietitian can provide a comprehensive assessment and advise on strategies.

Most elderly people eat far less than they did when they were younger. Their energy needs are lower, but the requirements for some nutrients such as protein, calcium and riboflavin are actually higher.\(^8\) This means that their food must be more nutritious to meet their needs.

A variety of dietary measures can be used to improve energy and nutrient intake. While the temptation might be to reach for a commercial oral nutrition supplement as a first step, there are many approaches that can improve oral intake with regular foods. Supplements have an important role, but the first step should be to find ways to increase the intake from familiar and preferred foods. There is a large element of taste fatigue with supplements and they are potentially an expensive option.

There are three main approaches to increase the intake of protein, energy and nutrient intake from food:

- **Small frequent meals** – encouraging snacks between meals
- **Increasing the nutrient density of meals** by additions of milk powder, grated cheese, margarine and cream
- **Nourishing fluids** such as milk drinks, smoothies, juice.

These strategies can increase protein and energy intake, but if the core food groups\(^9\) are not taken in recommended amounts, micronutrient deficiencies may develop. In this instance a multivitamin and mineral supplement may be recommended. Improvements in weight and nutrition status can be very difficult to achieve, and individual dietary advice from a dietitian may be needed. The dietitian can assess whether the use of commercial oral nutrition supplements is appropriate and which supplements may suit the individual person.

### Supplements

Studies have shown that judicious use of oral nutrition supplements can improve weight, protein and energy intake, nutritional status, physical function, quality of life and length of stay in acute care.\(^2,3\) When a supplement is required there are a number to choose from. The most common and readily available are milk based. They vary in their taste, nutrient profile and indications for use.

#### Standard oral supplements

Standard supplements are suitable for people who have some oral intake, but who are struggling to achieve adequate nutrition. These supplements are best taken as snacks between meals to complement normal meals. Most standard supplements are powder based. Some are ‘complete’, meaning that they will provide 100% of macro- and micronutrient needs if they are taken as the only form of nutrition. Some are supplemented with fibre, some are low in lactose. The standard dilution is one calorie per mL of fluid.

Examples include:

- Enprocal
- Ensure Powder
- Fortisip Powder
- Proform
- Sustagen hospital formula.

#### Standard liquid supplements

Some supplements come premixed in a liquid form. They are particularly useful in the acute-care setting as they do not require mixing and reduce waste. Some products may be more concentrated and provide more nutrition in a smaller volume. The formulations containing two calories per mL are frequently used in a ‘med pass’ program, where 50–60 mL of the supplement is provided at the same time as the medication round dispenses medicines, three or four times a day. This results in increased acceptance and a significant boost to nutrient and energy intake.

Examples of these products include:

- Ensure liquid, Ensure plus, TwoCal HN
- FMR (formulated meal replacement)*
- Fortisip

#### Clear liquid supplements

Clear liquid supplements have added protein and nutrients and are very useful for people who do not like milk drinks. Most are fruit flavoured. They tend to be quite sweet, but still provide significant nutrition even if they need to be diluted. They are suitable for use on a ‘clear fluid’ diet. Examples include:

- Enlive Plus
- Fortijuice
- Resource fruit flavoured beverage.

#### Puddings

The puddings are helpful for those who do not like milky drinks, but who are happy to take custards and milky desserts. The available products include:

- Ensure puddings
- FMR (formulated meal replacement) puddings*
- Forticreme
- Sustagen pudding powder (can be made to different thicknesses).
Nutritional supplements

**Supplements for diabetes**

Some supplements have been developed specifically for patients with diabetes. They have a lower glycaemic load, lower carbohydrate and low glycaemic index. In practice, patients with diabetes can usually tolerate the standard supplements. Most ordinary supplements have a low glycaemic index and are taken instead of regular foods. If blood glucose concentrations are elevated on the standard supplements then diabetes-specific options may be considered. They include:

- Diasip
- Glucerna
- Resource diabetic.

**Energy and protein boosters**

Some products are formulated to only boost protein or energy intake. While some have other additional nutrients they cannot be seen as complete foods. They are added to regular foods or drinks.

**Glucose polymers**

Glucose polymers have a neutral taste and can be added to sweet or savoury foods or drinks. They provide a source of pure carbohydrate only. They are not recommended for people with diabetes as they add significantly to the glycaemic load. Examples are:

- Carb plus
- Poly-Joule.

**Protein powders**

Protein powders can assist in increasing protein intake for individuals who will not eat meat or other protein foods and who do not like milk or its alternatives. The protein powders can be added into puddings, mashed potato and soups. Examples are:

- Beneprotein
- Protifar.

**Fat supplements**

Fat has a higher energy value per gram than protein and carbohydrate and is an excellent way of increasing energy intake in a small volume. Benecalorie has no carbohydrate, but contains protein and fat. It can be a useful way to add extra energy in a defined dose. Calogen is a 50% fat emulsion and is often used as part of a ‘med pass’ program.

**Biscuits, soups, desserts**

The commercial supplement companies are finding increasingly diverse ways to provide supplemented nourishing products that may tempt the taste buds of those with a poor appetite. These products are particularly useful when a person does not like the milky drinks. Examples include:

- bite sized cookies and desserts*
- Resource dessert fruit.

**Specialised supplements**

Many specialised supplements are available for a variety of medical conditions. The need for these should be assessed by a dietitian. Examples include:

- pulmonary supplements – lower carbohydrate
- renal disease – lower protein, potassium, sodium, phosphate
- supplements for a variety of metabolic disorders
- cancer cachexia supplements
- supplements for metabolic stress
- elemental (pre-digested) formulae.

**Wound management**

Adequate nutrition plays an important role in prevention and treatment of wounds and pressure ulcers. There is increasing interest in the role of specific nutrients, in particular arginine, in the healing process. A number of supplements have been designed as specific wound management support products. These include:

- Cubitan
- Recover
- Resource Arginaid.

**Conclusion**

The use of oral nutrition supplements can be a valuable adjunct to the nutritional management of an older person who is malnourished or at risk of malnutrition. They should not be used in isolation from other strategies to increase oral intake. The first step should always be to attempt to increase protein and energy from food, preserving the enjoyment of preferred food and maintaining quality of life.

* from Flavour Creations

Conflict of interest: none declared
REFERENCES


Book review

Anterior eye disease and therapeutics A–Z. 2nd ed.

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A Bruce, M Loughnan
Sydney: Elsevier Australia; 2011.
380 pages
Also available as an ebook

The authors of this book have attempted to summarise common and important conditions affecting the anterior eye in a concise and simple-to-read format. Particular emphasis is placed on the role of therapeutics in the management of these conditions. An explanation of common office-based ophthalmic procedures is also provided.

The standardised double-page format provides an excellent summary of each condition. It is easy to read and provides the reader with an efficient way to find relevant content. The pictorial images are of high quality. Each condition has at least one large colour illustration (clinical photograph or diagram) that clearly depicts the relevant pathology. The size and weight of the book makes it ideal to carry in a handbag or briefcase. This is particularly useful for registrars to carry while on call, or read on public transport.

The summaries in the appendices covering therapeutics and office-based procedures are comprehensive and a very useful inclusion. The book is written by Australian authors so is particularly relevant to Australian prescribers. A number of texts published overseas recommend drugs that are not available or preferred in Australia, which can lead to confusion.

However, there are downsides to the book. It only covers the anterior eye which reduces its usefulness, especially for registrars on call. While a separate book on the posterior segment is available, other similar texts manage to cover the whole eye in a single volume.

The book organises conditions in alphabetical order. This unfortunately makes the book quite difficult to read from cover to cover for study purposes. Further, unless the diagnosis is known with certainty, it makes the book less useful in looking up possible differential diagnoses or related conditions. Schematic diagrams are of limited value and the use of schematic icons throughout the book, and in particular the opening groupings of conditions, adds little to the content.

The authors are to be commended for their efforts in producing this easy-to-read, well-illustrated textbook of conditions affecting the anterior eye. Its particular strength is its relevance to an Australian readership. Many readers, however, may prefer more established manuals that have a broader coverage and are organised in an anatomical rather than alphabetical format.
Safe use of sodium valproate

VALPROATE, also known as sodium valproate, has been widely used in the treatment of epilepsy for many years. It is a broad spectrum anticonvulsant drug which is approved for use in epilepsy and bipolar disorder. It has also been used for neuropathic pain and migraine prophylaxis. Valproate is available in tablet (immediate-release or enteric coated), syrup and intravenous formulations. There is no single mechanism of action that can explain valproate’s broad effects on neuronal tissue. Its pharmacological effects include:

- Increased gamma-aminobutyric acid transmission
- Reduced release of excitatory amino acids
- Blockade of voltage-gated sodium channels
- Modulation of dopaminergic and serotonergic transmission.

Valproate is almost completely metabolised in the liver, mainly by glucuronidation. It then undergoes further metabolism with oxidation, which is complex and involves several cytochrome P450 enzyme systems. It has multiple metabolites which may contribute to both its efficacy and toxicity. There are many potential drug interactions.

Summary

Valproate is an anticonvulsant drug which is approved for use in epilepsy and bipolar disorder. It has also been used for neuropathic pain and migraine prophylaxis. Valproate is available in tablet (immediate-release or enteric coated), syrup and intravenous formulations. There is no single mechanism of action that can explain valproate’s broad effects on neuronal tissue. Its pharmacological effects include:

- Increased gamma-aminobutyric acid transmission
- Reduced release of excitatory amino acids
- Blockade of voltage-gated sodium channels
- Modulation of dopaminergic and serotonergic transmission.

When fasting, oral valproate is rapidly absorbed and reaches peak plasma concentrations within four hours (immediate-release formulation) to seven hours (enteric coated formulation). It is highly plasma protein bound and has a half-life of 8–20 hours in most patients, but this may occasionally be much longer, for example in renal impairment or overdose. The relationship between dose, plasma concentration and therapeutic effect is not well understood.

Valproate is almost completely metabolised in the liver, mainly by glucuronidation. It then undergoes further metabolism with oxidation, which is complex and involves several cytochrome P450 enzyme systems. It has multiple metabolites which may contribute to both its efficacy and toxicity. There are many potential drug interactions.

Indications

Although there is clinical experience with valproate in epilepsy, some of its other accepted indications, such as migraine prophylaxis, have not been approved by the Therapeutic Goods Administration.

Epilepsy

Valproate is a broad spectrum antiepileptic drug and is used to treat either generalised or focal seizures. It is recommended in Australian and international clinical practice guidelines. There is evidence that it is more effective than lamotrigine or topiramate in treating:

- Idiopathic generalised epilepsy syndromes
- Seizures that are difficult to classify.

Some authors have expressed concern that there remains a dearth of well-designed, properly conducted, randomised controlled trials for adults with generalised seizures/epilepsy syndromes and for children in general.

Bipolar disorder

Valproate was first used for the maintenance treatment of bipolar disorder in Europe in 1966. Over the past two decades there has been a dramatic rise in its use for this condition. However, the authors of a recent Cochrane review said that, in view of the lack of clear findings in their review and the limited available evidence, conclusions regarding the efficacy and acceptability of valproate compared to placebo or lithium cannot be made with any degree of confidence. Longer-term and larger sample size randomised controlled trials are required to better assess the clinical utility of valproate in the maintenance therapy of bipolar disorder.
**Neuropathic pain**

Although the guidelines of the UK National Institute for Health and Care Excellence\(^1\) do not recommend valproate for neuropathic pain, an American Academy of Neurology practice parameter\(^1\) suggests that it should be considered for the treatment of painful diabetic neuropathy. A Cochrane review concluded that, in view of the limited available evidence, valproate use should be reserved for cases of neuropathic pain where other proven treatment options have failed, are not available, or are not tolerated.\(^1\)

**Migraine**

Preventative therapy for migraine is often undertaken if patients have more than one attack per month. First-line drugs for migraine prophylaxis include amitriptyline, propranolol and pizotifen. A systematic review found that valproate is also effective in reducing migraine frequency and is reasonably well tolerated.\(^3\)

**Adverse reactions**

Common adverse effects of valproate include nausea, upper abdominal cramps, abnormal liver function, weight gain and diarrhoea. Neurological adverse effects such as tremor, fatigue, sedation, confusion and dizziness are often observed. Other potential adverse effects include alopecia, reduced bone density, thrombocytopenia, anaemia, leucopenia and hyperammonaemia.

There are several cutaneous adverse effects of valproate. They include pruritus, urticaria, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS).

Cases of polycystic ovarian syndrome and male infertility have also been reported.

There is a risk of hepatic dysfunction (>1%) and pancreatitis (<0.1%). Both adverse effects can be fatal. If liver failure occurs, it is usually in the first six months, but pancreatitis can occur after years of use. Although liver function tests may alter during treatment they are not reliable in predicting which patients will develop liver failure.

A pooled analysis of 199 clinical trials of 11 antiepileptic drugs (including valproate) by the US Food and Drug Administration (FDA) found that patients who were randomised to receive an antiepileptic drug had almost twice the risk of suicidal behaviour or ideation (0.43%) compared to patients randomised to receive placebo (0.24%).\(^13\) This suggests that there would be one additional case of suicidal thinking or behaviour for every 530 patients treated with any antiepileptic drug.\(^13\)

**Contraindications and precautions**

Valproate should be avoided in patients with liver disease or a family history of liver disease. Although uncommon, patients with a urea cycle disorder or porphyria should also avoid valproate. Renal failure can impair protein binding and lead to the accumulation of metabolites, so a lower dose may be required in patients with impaired renal function.

Routine laboratory studies should be performed before commencing therapy, but regular monitoring is not required for most patients.\(^6\) The onset of lethargy, vomiting or ataxia is an indication to measure serum ammonia to exclude hyperammonaemic encephalopathy. Spontaneous bruising or bleeding may occur and necessitates clinical review and investigation. Such patients may have developed thrombocytopenia or altered platelet function.

**Pregnancy and lactation**

Maternal exposure to valproate was first linked to an increased risk of congenital spina bifida in the 1980s. Valproate has an increased risk of major congenital malformations and poor cognitive outcomes compared to other antiepileptic drugs.\(^14\)

In the Australian categorisation system valproate is in pregnancy category D, so women of childbearing age should use effective contraception (e.g. oral contraceptive, intrauterine device, subdermal etonogestrel). The safe use of valproate in women of childbearing age is fraught with challenges.\(^15\) Ideally, the indications for using valproate should be reviewed and its risks discussed before pregnancy occurs.

A recent systematic review\(^16\) of the teratogenicity of antiepileptic drugs advised clinicians to:

- avoid valproate if equally effective antiepileptic drugs are available
- aim for monotherapy
- prescribe the lowest effective dose whenever possible, avoid valproate doses of 700 mg daily or above (if possible)
- avoid withdrawal or changes of antiepileptic drugs after conception has occurred.

The FDA has announced that valproate is contraindicated for the prevention of migraine during pregnancy. It should only be used during pregnancy by women with epilepsy or bipolar disorder if other drugs are ineffective or unacceptable.

Folic acid supplementation (at least 0.4 mg daily), one month pre-conception and during the first trimester, is recommended for all women to reduce the risk of fetal neural tube defects. Women taking antiepileptic drugs, particularly valproate, are at greater risk of having a child with neural tube defects and other
Sodium valproate

malformations which may be related to altered folate metabolism. Consequently, they require a higher dose of folic acid supplementation (5 mg daily). An American Academy of Neurology systematic review of the available literature concluded that, although the data are insufficient to show that folate supplementation is effective in women with epilepsy, there is no evidence of harm and no reason to suspect that it would not be effective in this group.

Although valproate probably does not enter breast milk in clinically important amounts, the drug’s manufacturers advise against breastfeeding. Women with epilepsy who are currently pregnant or who have given birth recently are encouraged to contact the Australian Pregnancy Register at www.neuroscience.org.au/apr or 1800 069 722.

Drug interactions

For a variety of pharmacokinetic and pharmacodynamic reasons, valproate use has the potential to interact with a large number of drugs (see Box). The consequences of such interactions range from mild to life-threatening. Of particular clinical relevance is valproate’s effect on other antiepileptic drugs (for example carbamazepine, lamotrigine, phenobarbitone, phenytoin, topiramate).

Drug monitoring

With the exception of phenytoin (and possibly lamotrigine), antiepileptic drugs do not require routine therapeutic drug monitoring assays. Although measuring serum valproate concentrations may be useful in screening patients for toxicity or poor compliance, there is little evidence linking concentration to clinical efficacy.

A retrospective study within a major Australian teaching hospital found that most requests were ordered inappropriately and many tests were not taken at the correct time (at least eight hours after the last dose).

Signs and management of toxicity

The majority of patients with acute valproate intoxication experience mild to moderate lethargy and recover uneventfully. Central nervous system dysfunction is the most common manifestation of toxicity and this can range in severity from mild drowsiness to coma or fatal cerebral oedema. Hypernatraemia, metabolic acidosis, hyperammonaemia and liver failure may develop in some patients. Toxicity can occur within the therapeutic range and includes hyperammonaemic encephalopathy. This can present with confusion, increased seizures and focal neurological signs.

Supportive care is the principal treatment for valproate intoxication and results in good outcomes in the vast majority of cases. Activated charcoal may be considered for alert patients who have taken a severe overdose.

Withdrawal

Some doctors favour a gradual withdrawal of antiepileptic drugs (for example over a six-month period) to lessen the risk of seizure recurrence. However, a Cochrane review has highlighted the lack of evidence to guide clinicians on the optimal rate of withdrawal in patients whose seizures are well controlled. There is little evidence to guide antiepileptic drug withdrawal tapering periods in non-epileptic patients. The Austroads Assessing Fitness to Drive guide recommends that private licence holders do not drive while withdrawing antiepileptic drugs and for three months afterwards. Commercial licence holders with epilepsy will not be eligible to drive if their antiepileptic drug is ceased. The Austroads guidelines do not specifically address antiepileptic drug withdrawal by patients without epilepsy.

<table>
<thead>
<tr>
<th>Box</th>
<th>Potential drug interactions with valproate</th>
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<tbody>
<tr>
<td>aspirin</td>
<td>large doses increase valproate concentration</td>
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<tr>
<td>carbamazepine</td>
<td>reduces valproate concentration</td>
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<tr>
<td>valproate increases the concentration of the active metabolite of carbamazepine</td>
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</tr>
<tr>
<td>carbapenems</td>
<td>reduce valproate concentration</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>valproate increases lamotrigine concentration (risk of Stevens-Johnson syndrome)</td>
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<tr>
<td>olanzapine</td>
<td>valproate decreases olanzapine concentration</td>
</tr>
<tr>
<td>phenobarbitone</td>
<td>reduces valproate concentration</td>
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<tr>
<td>valproate increases phenobarbitone concentration</td>
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<tr>
<td>phenytoin</td>
<td>reduces valproate concentration</td>
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<tr>
<td>valproate increases phenytoin concentration (initially free, later total)</td>
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<tr>
<td>topiramate</td>
<td>increases the risk of valproate-associated adverse effects (e.g. hyperammonaemia)</td>
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<tr>
<td>zidovudine</td>
<td>valproate increases zidovudine concentration</td>
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</table>
Valproate has been prescribed widely for decades. Given that new indications continue to emerge, it is increasingly important for clinicians to remain cognisant of the drug’s adverse effects. A key component of safe valproate use involves the provision of tailored counselling and education to each patient before starting therapy. 

Conflict of interest: none declared

REFERENCES

Health professionals are reminded that, to minimise the risk of fever and febrile convulsion, measles, mumps, rubella, varicella vaccine should not be administered as the first dose of measles-containing vaccine to children younger than four years.

Measles, mumps, rubella, varicella (MMRV) vaccine is a combination live virus vaccine for immunisation against these four common childhood illnesses. While MMRV vaccine is approved for use in children from nine months of age, on 1 July 2013 it was added to the National Immunisation Program (NIP) schedule to be given at 18 months after an initial dose of measles, mumps, rubella (MMR) vaccine at 12 months of age.

Minimising risk
Like most vaccines, MMRV vaccine can cause some mild adverse events. In rare cases, fever after vaccination can lead to febrile convulsions in young children.

MMRV vaccine is only recommended for use as a second dose of measles-containing vaccine. This is because MMRV vaccine administered as a first dose in children aged 9–30 months is associated with an increased rate of fever and febrile convulsions, compared to separate MMR and varicella vaccination.

As described in the postmarketing data section of the Product Information (PI), the attributable risk of febrile convulsions 5–12 days following MMRV vaccination as a first dose of measles-containing vaccine is 3.64/10 000 (95% CI: –6.11;8.30). This equates to one additional case of febrile convulsion per 2747 young children, when compared to MMR or concomitant MMR and varicella vaccination.

When used as the second measles-containing vaccination, there is no indication of an increased risk. The overall risk of fever and subsequent febrile convulsion in children is greatly reduced by following the NIP schedule of the initial dose of MMR vaccine at 12 months and the second vaccine dose, as MMRV, at 18 months.

Dosage instructions in the PI recommend an interval of six weeks to three months between the first and second vaccine doses. As with other live virus vaccines, under no circumstances should the interval be less than four weeks.

Further information for health professionals is available on the Immunise Australia website.

Adverse events
The TGA continues to receive adverse event reports that suggest MMRV vaccine has been administered as the first dose of measles-containing vaccine in children aged 12 months or younger. In the 12 months to 1 May 2014, the TGA received seven such reports. There were also two reports of MMRV vaccine being given at the same time as other vaccines that contain either MMR or varicella.

Adverse events following immunisation at any age should be reported through the usual reporting mechanisms in your State or Territory or to the TGA.
Health professionals are reminded of the risks of accidental exposure to or ingestion of fentanyl patches, especially for children.

Fentanyl is an opioid analgesic, interacting predominantly with mu-opioid receptors. Various strengths of fentanyl transdermal delivery system products (patches) are funded under the Pharmaceutical Benefits Scheme as a restricted benefit for ‘chronic severe disabling pain not responding to non-narcotic analgesics’.

Like other opioids, at lower doses fentanyl may cause constipation, nausea and vomiting, hypotension, dysphoria and euphoria, urinary retention, blurred vision, impaired cognition and sedation. As the dose increases, it can also cause:

- convulsions
- extreme somnolence progressing to coma
- respiratory depression with the potential for respiratory arrest
- cardiac arrhythmias, circulatory collapse and cardiac arrest.

Non-users who are opiate naïve, and especially children, are at greater risk of very serious adverse events if they are inadvertently exposed to or ingest fentanyl patches, whether they be used or unused. The Product Information (PI) for fentanyl patches includes instructions to keep the products out of reach of children before, during and after use, as well as other precautionary information. The PI also provides instructions for the safe disposal of patches. The opiate dose delivered through fentanyl patches is high, with 12 microgram considered approximately equivalent to 45 mg per day of oral morphine. Even used patches can retain high residual levels of the active ingredient (about 60% of the intended dose).1

Adverse events

To 1 May 2014, the TGA has received two reports involving fentanyl patches and accidental exposure in children.

The children in these two cases suffered somnolence and loss of consciousness respectively. Both of the children were hospitalised as a result of the incidents.

The TGA is also aware of reports made to the NSW Poisons Information Centre involving accidental exposure to fentanyl patches in children aged younger than five years.

In 2012, the US Food and Drug Administration evaluated a series of 26 cases of accidental exposures to fentanyl patches in children reported over a 15-year period. Of those 26 cases, 10 resulted in death and 12 in hospitalisation. Sixteen of the 26 cases occurred in children two years old or younger.2

Information for health professionals

Ensure patients are aware of the risks of accidental exposure to fentanyl patches for non-users and in particular children.

Advise patients to keep fentanyl patches out of reach of children before, during and after use, and to appropriately dispose of patches that have been used or are no longer needed. Specifically, used patches should be folded so that the adhesive side adheres to itself, before being wrapped and disposed of carefully. Unused patches should be returned to the pharmacy for safe disposal.

Fentanyl patches being worn by patients can come into contact with non-users in situations of close contact, and there have been recorded cases of patches being transferred to another person while sharing a bed with a patch wearer.

If a fentanyl patch adheres to a non-user, it should be removed immediately.

Advise patients to contact a doctor immediately in any case of suspected exposure to or ingestion of fentanyl patches.

Toxicological advice is available from the Poisons Information Centre’s 24-hour phone line on 131 126.

REFERENCES

Zolpidem (Stilnox) and next-day impairment

Following completion of a safety review, the TGA reminds health professionals treating patients with zolpidem of the risk of next-day impairment.

Zolpidem (Stilnox) is an imidazopyridine with relative selectivity for the type 1 benzodiazepine receptor subtype. It has been registered in Australia for the short-term treatment of insomnia in adults since 1999.

Currently marketed presentations for Stilnox and Stilnox CR are:
- Stilnox 5 mg tablets
- Stilnox 10 mg tablets
- Stilnox CR 6.25 mg modified-release tablets
- Stilnox CR 12.5 mg modified-release tablets

There are also generic brands of zolpidem 5 mg and 10 mg marketed in Australia.

The Product Information (PI) for zolpidem includes a precaution regarding the drug's effect on the patient's ability to drive and use machinery. It warns that patients should not drive or operate machinery for eight hours after taking the drug and that drowsiness may continue the following day.

The PI also includes a black box warning that, among other things, advises health professionals to use caution when this drug is used with other central nervous system (CNS) depressant drugs.

Minimising risk

The benefit–risk profile for zolpidem remains positive. However, based on the findings of its safety review, the TGA recommends that patients being treated with zolpidem-containing products should take the lowest effective dose. Zolpidem should be taken in a single dose just before bedtime and should not be taken again during the same night.

The daily dose of zolpidem for adults must not exceed 10 mg, or 12.5 mg for the modified-release tablet, while elderly and debilitated patients, who may be particularly sensitive to the effects of zolpidem, should not exceed 5 mg, or 6.5 mg for the modified-release tablet.

Adverse events

As at 1 May 2014, the TGA had received 1360 adverse event reports relating to zolpidem-containing products.

Some of these adverse events were indicative of next-day impairment or the potential for next-day impairment in patients taking therapeutic doses of zolpidem.

Information for health professionals

Discuss the risk of next-day impairment, as well as other risks, with patients before prescribing zolpidem. Ensure that patients understand the importance of not exceeding the recommended daily dose. Advise them to take zolpidem just before going to bed and not to re-administer during the same night.

Advise patients to avoid driving or any other activity requiring mental alertness, such as operating machinery, for at least eight hours after taking zolpidem and explain that drowsiness may continue the following day.

Please report to the TGA all adverse events involving zolpidem. This will assist in the continued monitoring of this drug.

The TGA is working closely with the sponsor to update the PI with further information about the risk of next-day impairment.

FURTHER READING

European Medicines Agency. CMDh endorses new advice to minimise risk of next-morning impaired driving ability and mental alertness with zolpidem. 2014 Apr 25.
Diclofenac and arteriothrombotic events

The Product Information documents for prescription-only diclofenac have been updated to provide further information about the increased risk of arteriothrombotic events.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). Prescription-only products are available in oral and rectal forms.

Information regarding arteriothrombotic events was previously included in the precaution and adverse reaction sections of the Product Information (PI). However, the updated PI includes details from meta-analyses of individual participant data from randomised trials by the Coxib and traditional NSAID Trialists’ Collaboration that estimated, in comparison with placebo, use of diclofenac caused about three additional major vascular events per 1000 patients per year. This information was derived from trials involving long-term (more than 28 days) treatment with high-dose diclofenac (150 mg/day).

You should discuss with patients the benefits and risks associated with this drug before prescribing it. Educate patients regarding the signs and symptoms of arteriothrombotic events.

To minimise risks, the lowest effective daily dose should be used for the shortest duration necessary to control symptoms. Patients with cardiovascular disease or other risk factors may be at greater risk. The TGA is undertaking a review of all NSAIDs with regard to their association with cardiovascular risks.

REFERENCE

Quality use of blood products

SUMMARY
Blood products are a valuable resource, derived from altruistic donations. They undergo high-cost screening and modification to decrease the risk of transfusion-transmitted infection.

Although blood products have achieved a high level of safety, significant risks associated with transfusion remain.

To avoid unnecessary transfusions, patient blood management involves optimising red cell mass, minimising blood loss, and optimising physiological tolerance of anaemia.

A circumspect approach to prescribing blood products is recommended. Regular patient assessment in conjunction with judicious laboratory testing are the primary considerations in the decision to transfuse.

Evidence-based guidelines for the appropriate use of blood products have been released by the National Blood Authority.

Introduction
Providing a safe, reliable and economically viable source of blood products is a key role of the National Blood Authority, a statutory agency within the Australian Government Department of Health. The national blood supply is jointly funded by federal, state and territory governments. It costs over $1000 million annually and patients bear no direct costs for these products.

Derived from altruistic donations, blood components are subjected to a series of processes to optimise their safety. These include:

- donor screening
- mandatory testing for ABO and RhD blood type
- antibody screening
- screening for transfusion transmissible infections by serological and molecular methods
- universal leucodepletion of products (by the filtration of white blood cells from all donor units)
- bacterial contamination screening of all platelet units.

These processes are expensive and the Australian Red Cross Blood Service now includes the unit cost on the product label (Table). Further costs are incurred for administering blood products, taking into account pretransfusion testing, dedicated resources during administration, and the cost of investigating and treating adverse transfusion effects. These may be 3–5 times the cost of the actual blood product.

Evidence-based prescribing of blood products is essential. However, wide variability in transfusion practice reflects the relative lack of high quality data on which to base transfusion decisions. Transfusion practice is also undoubtedly influenced by institutional protocols, unit policies and personal experiences.

Blood supply
The ageing population and the development of more intensive and specialised therapies requiring blood support have increased the demand for blood products. The majority of transfusion recipients in Australia are aged over 65 years. This proportion of the population is growing in relation to the pool of donors so there is the potential for a shortfall in the blood supply.

Safety
Comprehensive regulations covering all aspects of blood donation and processing of blood products mean Australian blood supplies are among the safest in the world. Governance for prescribing and clinical use have been formalised in the National Safety and Quality Health Service Standards.

Risks associated with blood transfusion range from transfusion-associated circulatory overload, which

<table>
<thead>
<tr>
<th>Table</th>
<th>Price indications for commonly used blood products 2012–13</th>
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<tbody>
<tr>
<td>Product</td>
<td>Cost per unit</td>
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<tr>
<td>Red cells</td>
<td>$345.14</td>
</tr>
<tr>
<td>Pooled platelets</td>
<td>$356.62</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>$279.29</td>
</tr>
</tbody>
</table>
Red cells

Red cells are used to improve the oxygen-carrying capacity of blood in cases of clinically significant, symptomatic anaemia. A third of red cell transfusions in Australia are used in support of surgery (elective and emergency), a third in haematology and oncology patients, and a third in medical and other contexts. Faced with the situation whereby both anaemia and its treatment with transfusion are associated with unfavourable outcomes, early and adequate investigation for anaemia is important to identify the underlying cause and consider alternatives to transfusion. This is particularly the case in patients who need elective surgery, as timely identification and treatment of anaemia could obviate the need for transfusion in the perioperative period.

Therapy could include iron supplementation (oral or intravenous) in the case of iron deficiency anaemia. Reticulocyte counts improve in as little as three days and haemoglobin should increase appreciably within two to three weeks. Correction of anaemia and repletion of iron stores can take 3–6 months with oral iron supplements, but can occur more rapidly with intravenous preparations. Less commonly vitamin B12 or folate need to be replaced.

Erythropoiesis-stimulating drugs increase haemoglobin concentration in many anaemic patients, but supraphysiological doses are required outside the context of renal failure. However, there is an increase in the risk of thromboembolic disease in the short and long term and these drugs have a trophic effect.

Blood products

Blood products comprise three broad categories: fresh blood products, plasma products and recombinant products (see Fig.).

Fresh components

These are manufactured by separation of blood into its components by centrifugation.

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Fig. Blood and recombinant products

- **Red cells**
- **Clinical plasma**
  - Fresh frozen plasma
  - Cryoprecipitate
  - Cryodeplete plasma
- **Plasma**
  - **Plasma for fractionation**
  - Immunoglobulins
  - Albumin
  - Factor concentrates
- **Platelets**
- **Recombinant products**
  - factor VIIa
  - factor VIII
  - factor IX
Blood products

coagulation tests such as prothrombin time or activated partial thromboplastin time are poorly predictive of bleeding, and prophylactic use to correct laboratory abnormalities is not recommended. Cryoprecipitate and cryodepleted plasma are derived from fresh frozen plasma. Cryoprecipitate contains most of the factor VIII, factor XIII, von Willebrand factor, and fibrinogen. Cryodepleted plasma contains all the other coagulation factors. These products have limited indications. Cryoprecipitate is used for hypofibrinogenaemia, and cryodepleted plasma is used in plasma exchange for thrombotic thrombocytopenic purpura.

Plasma products

These are fractionated from plasma and are classified into three groups: immunoglobulins, coagulation factor concentrates and albumin preparations. The main indication for these products is to replace reduced or dysfunctional plasma proteins. Immunoglobulin preparations and RhD immunoglobulin are used to elicit an immunomodulatory response.

Immunoglobulins

Immunoglobulins can be divided into two groups – normal immunoglobulin and hyperimmune immunoglobulin.

Normal immunoglobulin

This is prepared from normal donors and contains normal concentrations of antibodies against prevalent infections. It is available in intramuscular, intravenous and subcutaneous formulations. These immunoglobulins are used in inherited and acquired immunodeficiency syndromes to replace deficient immunoglobulins. They are also used as an immunomodulator in a range of haematological, neurological, dermatological and inflammatory conditions. Approved indications are detailed in the ‘Criteria for the clinical use of intravenous immunoglobulin in Australia’. Intramuscular preparations are used for passive immunisation of susceptible contacts of patients with infections such as measles, rubella, poliomyelitis and hepatitis A to provide immediate protection against infection. Guidance in specific situations is provided in the Australian Immunisation Handbook.

Hyperimmune immunoglobulin

This is prepared from donors who have responded to a specific infection or immunisation and contains high concentrations of specific antibody. These products can be used in the management of exposure to specific infections in susceptible patients.

Platelets

Platelet transfusions are used in actively bleeding patients with severe thrombocytopenia (generally regarded as platelet counts <50 x 10^9/L), platelet dysfunction as a result of inherited or acquired abnormalities, and as prophylaxis in severely thrombocytopenic patients at high risk of bleeding. Platelets are also used in cases of massive transfusion. It is crucial to identify the cause of thrombocytopenia, as platelet transfusion is ineffective in immune-mediated platelet destruction, and may be contraindicated in some thrombocytopenic conditions. The risk of bleeding is also influenced by factors other than platelet count, including infection, concomitant medicines, vascular injury and coagulopathy.

Fresh frozen plasma

Fresh frozen plasma comprises the acellular component of blood and contains all of the coagulation factors. It is used in patients with coagulopathy who are bleeding, or at risk of bleeding, when more specific therapy is not appropriate or available. Fresh frozen plasma is most commonly used in massive transfusion, cardiac bypass, liver disease or acute disseminated intravascular coagulopathy. Abnormalities in
Exposure to rabies and the Australian bat lyssavirus are treated with rabies hyperimmune globulin. Individuals at high risk of these infections should be actively vaccinated. Rabies immunoglobulin is in short supply and is only available from public health units.\textsuperscript{26} RhD immunoglobulin (anti-D) is used to prevent immunisation of RhD negative women to the RhD antigen and consequently RhD haemolytic disease of the newborn. Current recommendations include a routine antenatal schedule for RhD negative mothers after potentially sensitising events such as miscarriage or the birth of an RhD positive baby. Guidelines on the prophylactic use of RhD immunoglobulin are available from the National Blood Authority.\textsuperscript{27}

**Factor concentrates**

These are indicated for patients with specific factor deficiencies and a haematologist would normally be involved. The main exception is warfarin reversal with prothrombin complex concentrate in patients who are bleeding and have an elevated INR. Consensus guidelines for warfarin reversal have recently been updated.\textsuperscript{28} There is currently no evidence to recommend factor concentrates for the treatment of bleeding in patients taking anticoagulants such as dabigatran, rivaroxaban and apixaban.

**Albumin**

Albumin is available in 4% and 20% formulations. The 4% preparation can be used in the management of shock associated with hypoalbuminaemia, or as exchange fluid in therapeutic plasmapheresis. The 20% preparation can be used to treat critically ill patients with severe hypoalbuminaemia or severe burns.

**Recombinant products**

Recombinant products are manufactured from genetically engineered cell lines and are not purified from blood. They are generally coagulation proteins used for inherited bleeding disorders in which there is a deficiency of a specific protein in the coagulation cascade, for example, recombinant factor VIII for haemophilia A and recombinant factor IX for haemophilia B. They may also be used for patients with bleeding disorders who have developed antibodies that interfere with usual therapy. The costs associated with these products are significant, but they are the safest option and are used whenever possible.

**Patient blood management**

Patient blood management refers to the management and preservation of the patient’s own blood with the aim of reducing or avoiding the requirement for the transfusion of blood components.\textsuperscript{29} Evidence-based prescribing of blood products is an essential tenet of this strategy to minimise inappropriate transfusion. The three ‘pillars’ of patient blood management include:\textsuperscript{30,31}

- optimising red cell production
- minimising blood loss
- optimising physiological tolerance of anaemia.

The shift from component-based guidelines emphasises the importance of correlation with the clinical scenario to achieve the best patient outcomes using evidence-based transfusion practice. The National Blood Authority is developing six evidence-based patient blood management guidelines, each focusing on a patient-based clinical approach. The first four modules are available online* and as a free iPad app (BloodDocs, via the App Store). These comprise guidelines for critical bleeding/massive transfusion and perioperative, medical and critical care. Obstetric and paediatric/neonatal modules are currently being developed.

**Conclusion**

The increasingly evidence-based application of therapeutic decision making in transfusion medicine has the potential to improve patient outcomes, reduce healthcare costs, and slow the inevitable deficit in supply. In the alignment of economic and therapeutic considerations, there is the opportunity for widespread adoption of patient blood management principles. The evidence-based patient blood management guidelines released by the National Blood Authority provide scenario-specific, patient-based guidance and can be accessed online. * www.blood.gov.au/pbm-guidelines


**REFERENCES**


Rebecca Adams: no conflict of interest declared

Robert Bird owns ordinary shares in CSL and is on medical/scientific advisory boards for Amgen and Novartis. He has previously accepted honoraria for speaking at overseas meetings sponsored by Amgen and Novartis, and sponsored travel to overseas conferences from Amgen, GSK, Novartis, Novo Nordisk and Roche.

Full text free online at www.australianprescriber.com
ARTICLE


FURTHER READING


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P-glycoprotein and its role in drug-drug interactions

SUMMARY

Efflux transporters such as P-glycoprotein play an important role in drug transport in many organs. In the gut, P-glycoprotein pumps drugs back into the lumen, decreasing their absorption. Drugs which induce P-glycoprotein, such as rifampicin, can reduce the bioavailability of some other drugs. Inhibitors of P-glycoprotein, such as verapamil, increase the bioavailability of susceptible drugs.

Many, but not all, of the drugs which are transported by P-glycoprotein are also metabolised by cytochrome P450 3A4.

Important substrates of P-glycoprotein include calcium channel blockers, cyclosporin, dabigatran etexilate, digoxin, erythromycin, loperamide, protease inhibitors and tacrolimus. Predicting clinically important interactions is difficult because of interindividual differences in drug transport.

Introduction

P-glycoprotein is one of the drug transporters that determine the uptake and efflux of a range of drugs. This process affects their plasma and tissue concentrations and ultimately their final effects. P-glycoprotein functions as a transmembrane efflux pump, pumping its substrates from inside to outside the cell. Drugs which induce or inhibit P-glycoprotein can interact with other drugs handled by the pump.

Pharmacology

P-glycoprotein was first described in tumour cells. These cells had over-expression of P-glycoprotein which reduced the access of cytotoxic drugs. As this made the tumours resistant to various anticancer drugs, P-glycoprotein was also known as multidrug resistance protein 1. P-glycoprotein is also expressed in a variety of normal, non-tumorous tissues with excretory functions (small intestine, liver and kidney) and at blood-tissue barriers (blood-brain barrier, blood-testis barrier and placenta).

Along with the cytochrome P450 (CYP) family of enzymes, concomitant expression of P-glycoprotein is believed to be an important evolutionary adaptation against potentially toxic substances. As an efflux transporter it limits the bioavailability of orally administered drugs by pumping them back into the lumen. This promotes drug elimination into the bile and urine and protects a number of tissues such as the brain, testis, placenta and lymphocytes. The substrates for P-glycoprotein are a broad variety of structurally diverse compounds.

Drug absorption

The epithelial cell lining of the small intestine is not just a site for drug absorption, but also an important barrier to the absorption of xenobiotics. P-glycoprotein is found in the apical (luminal) membrane of the entire intestine from duodenum to rectum, with a high expression in the enterocytes of the small intestine. It reduces the oral availability of drugs that are its substrates.

Like the enzymes involved in drug metabolism, substrates of P-glycoprotein can potentially act as inhibitors or inducers of its function. Inhibition of P-glycoprotein can result in increased bioavailability of the susceptible drug. Induction of P-glycoprotein reduces the bioavailability.

Drug distribution

Once a drug has reached the systemic circulation, P-glycoprotein further limits penetration into a number of sensitive tissues. P-glycoprotein is also important for the blood-brain barrier as a defence against the penetration of toxins and drugs into the central nervous system.

Drug elimination

P-glycoprotein has a modest role in drug elimination. It is expressed in the luminal membrane of proximal tubule cells in the kidneys. P-glycoprotein pumps drugs into the urine.

Drug interactions

P-glycoprotein is an important mediator of drug-drug interactions. The pharmacokinetics of a drug may...
P-glycoprotein and drug-drug interactions

be altered when co-administered with compounds which inhibit or induce P-glycoprotein.\textsuperscript{1,6} Inhibitors include clarithromycin, erythromycin, ritonavir and verapamil. Inducers include rifampicin and St John’s wort.

P-glycoprotein has a very wide substrate spectrum similar to CYP3A4. It is involved in the transport of drugs from different drug classes including:

- antineoplastic drugs e.g. docetaxel, etoposide, vincristine
- calcium channel blockers e.g. amlodipine
- calcineurin inhibitors e.g. cyclosporin, tacrolimus
- digoxin
- macrolide antibiotics e.g. clarithromycin
- protease inhibitors.

The substrates of P-glycoprotein can be further divided into drugs which are not metabolised in humans, such as digoxin, and those which are substrates of both P-glycoprotein and drug-metabolising enzymes, particularly CYP3A4.\textsuperscript{2,3} As many P-glycoprotein substrates are also substrates of CYP3A4 and because P-glycoprotein inhibitors are also inhibitors of CYP3A4, many drug-drug interactions are related to inhibition or induction of both P-glycoprotein and CYP3A4. Drugs which are ‘objects’ of such interactions include cyclosporin, tacrolimus and rivaroxaban.\textsuperscript{3}

Enterocytes, like hepatocytes, simultaneously express the major drug-metabolising enzyme CYP3A4 and the efflux transporter P-glycoprotein.\textsuperscript{7} This creates a drug efflux–metabolism ‘alliance’, which increases the exposure of the drug to metabolism by CYP3A4 through repeated cycles of absorption and efflux.\textsuperscript{2} Modification of this active barrier function by concomitantly administered drugs contributes to altered absorption, increased interindividual differences in systemic drug concentrations and probably an increased risk of toxicity.\textsuperscript{4}

Accurate prediction of potential drug–drug interactions through P-glycoprotein is complicated by pronounced interindividual differences in bioavailability. This also affects drugs that are not metabolised in humans (fexofenadine, digoxin).\textsuperscript{2,4} A better knowledge of the role of genetics in transporter expression and function will contribute to a better understanding of interindividual and interethnic differences in drug disposition and effects.\textsuperscript{2}

Loperamide

P-glycoprotein is the most important drug transporter for reducing the entry of drugs into the central nervous system. The over-the-counter antidiarrhoeal medication loperamide is a potent opiate, but does not have opioid effects on the central nervous system at usual doses. This is because P-glycoprotein prevents transport across the blood-brain barrier. Concomitant administration of loperamide and a potent P-glycoprotein inhibitor, such as verapamil, may be associated with respiratory depression. This potentially dangerous central nervous system effect from such a widely used and easily accessible drug is of great interest. It raises safety concerns but suggests that inhibiting P-glycoprotein could be a novel strategy to overcome the blood-brain barrier to increase drug delivery to the brain.\textsuperscript{8}

**Digoxin**

Induction or inhibition of intestinal P-glycoprotein appears to be a major mechanism underlying drug interactions that lead to reduced or elevated digoxin concentrations. Rifampicin and St John’s wort induce P-glycoprotein and thereby decrease concentrations of digoxin.

**HIV-1 protease inhibitors**

The effective treatment of HIV may be hindered by P-glycoprotein located in cell membranes. Potential mechanisms include the following:

- intestinal P-glycoprotein limits the absorption of HIV protease inhibitors
- HIV protease inhibitors are good P-glycoprotein substrates,\textsuperscript{5} so this limits their transfer across the blood-brain barrier, which can contribute to viral persistence and reduced effectiveness
- P-glycoprotein is also expressed in CD4 cells, the major target of anti-HIV drugs.

**Dabigatran**

As dabigatran etexilate is a substrate of P-glycoprotein, there is potential for drug interactions involving drugs acting on P-glycoprotein. Inhibitors of P-glycoprotein such as ketoconazole, amiodarone, verapamil, ticagrelor and clarithromycin may increase the peak plasma concentrations of dabigatran, and subsequently lead to a significantly increased risk of severe haemorrhage.\textsuperscript{10}

**Conclusion**

P-glycoprotein is an efflux transporter pump present in many organs and plays an important role in drug transport. Expression of P-glycoprotein can have important effects on drug absorption, distribution and elimination. Although interactions with drug transporters can be clinically insignificant, an awareness of potential transporter-related drug-drug

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Self-Test Questions

True or false?

5. Inhibitors of P-glycoprotein increase the oral bioavailability of its substrates.

6. P-glycoprotein metabolises dabigatran.

Answers on page 143
interactions is important. Central nervous system depression, untreated HIV infection and transplant rejection are all possible outcomes if these interactions occur. Knowledge of these potential interactions in at-risk patient groups can help ensure the provision of safe and effective treatment.

Conflict of interest: none declared

REFERENCES


FURTHER READING


New drugs

Afatinib

Approved indication: non-small cell lung carcinoma

Giotrif (Boehringer Ingelheim)

10 mg, 30 mg, 40 mg and 50 mg film-coated tablets

Australian Medicines Handbook section 14.2.3

Like erlotinib (Aust Prescr 2006;29:52-5), gefitinib (Aust Prescr 2003;26:94-5) and crizotinib (Aust Prescr, published online 2014 Apr 16), afatinib is a tyrosine kinase inhibitor approved for advanced or metastatic non-small cell lung carcinoma. Afatinib irreversibly binds to the ErbB family of epidermal growth factor receptors – ErbB1 (epidermal growth factor receptor or EGFR), ErbB2 (human epidermal growth factor receptor 2 or HER2), ErbB3 and ErbB4. By blocking signalling from these molecules, afatinib slows down the growth and spread of tumour cells.

About 10% of Australian patients with non-small cell lung carcinoma have mutations in the EGFR gene. These are activating mutations which contribute to the malignant phenotype – the two most common are Del 19 (deletion in exon 19) and L858R (point mutation in exon 21). Afatinib is only approved for patients who have tumours with these mutations.

An open-label phase III comparative trial assessed the efficacy of afatinib (40 mg once a day) as a first-line treatment in 345 patients with an activating mutation in their EGFR gene. A subgroup of 308 patients had the Del 19 or L858R mutation. After a median of 11 months, afatinib significantly prolonged median progression-free survival compared to chemotherapy (see Table). In the afatinib group, progression-free survival was 2.5 months longer in those with Del 19 or L858R mutations. Afatinib did not significantly prolong overall survival compared to chemotherapy.1

In a questionnaire about symptoms, the onset of cough (p=0.007) and dyspnoea (p=0.015) was significantly delayed with afatinib compared to chemotherapy. However, diarrhoea, dysphagia and sore mouth were reported to be worse.2

A phase II trial in lung adenocarcinoma found that median progression-free survival was slightly longer for patients who received afatinib first-line compared...


Table  Efficacy of afatinib in advanced non-small cell lung carcinoma

<table>
<thead>
<tr>
<th>Phase III trial</th>
<th>afatinib</th>
<th>chemotherapy (cisplatin plus pemetrexed)</th>
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<tr>
<td>Number of patients</td>
<td>229</td>
<td>115</td>
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<tr>
<td>Progression-free survival:</td>
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<tr>
<td>all patients (n=345)</td>
<td>11.1 months</td>
<td>6.9 months</td>
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<tr>
<td>patients with exon 19 deletion or L858R mutation (n=308)</td>
<td>13.6 months</td>
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<td>Response rate (complete or partial)</td>
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<td>23%</td>
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<td>Median overall survival</td>
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<tr>
<td>patients with exon 19 deletion or L858R mutation (n=308)</td>
<td>30.3 months</td>
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<table>
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<td>Number of patients</td>
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<tr>
<td>Progression-free survival</td>
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<tr>
<td>Response rate (complete or partial)</td>
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<tr>
<td>Median overall survival</td>
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<td>23.3 months</td>
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</table>

Referral to an ophthalmologist should be considered for patients who develop eye symptoms such as inflammation, lacrimation, blurred vision, light sensitivity or pain, as ulcerative keratitis can occur. Contact lenses increase the risk of these adverse events. Inhibitors of HER2 have been associated with left ventricular dysfunction so cardiac monitoring should be considered in patients who have risk factors. Women of childbearing age should avoid becoming pregnant while taking afatinib as it has the potential to cause fetal harm. In animal studies, afatinib was excreted in breast milk so breastfeeding is not recommended.

Following oral administration, peak plasma concentrations of afatinib are reached within 2–5 hours. The terminal half-life is 37 hours with the dose being excreted in the faeces (85%) and urine (4%). Exposure to afatinib is increased in women, those with a low body weight and those with renal impairment so closer monitoring for adverse effects is recommended for these patients. Afatinib is not recommended if renal or hepatic impairment is severe. Drug exposure is decreased when afatinib is taken with a high-fat meal so food should be avoided for at least three hours before and one hour after taking a dose. The recommended starting dose of 40 mg a day can be escalated to 50 mg a day. However, there is no extra proven benefit at this dose and adverse events are more common.

Afatinib is a substrate for P-glycoprotein so strong inhibitors and inducers of this transporter may affect
plasma concentrations. Strong inhibitors (such as ketoconazole, erythromycin and verapamil) should only be administered at the same time or after the afatinib dose.

Afatinib adds to the treatment options for patients with non-small cell lung cancer, but patients must have the Del 19 or L858R mutation to qualify for treatment. Afatinib slows disease progression when used first-line or after chemotherapy, but showed little benefit in patients who had previously been treated with erlotinib or gefitinib. As with other drugs in this class, severe, and sometimes fatal, adverse reactions to afatinib can occur and often limit treatment.

REFERENCES


First published online 21 May 2014

Macitentan

Approved indication: pulmonary arterial hypertension

Opsumit (Actelion)

10 mg film-coated tablets

Australian Medicines Handbook section 6.6.2

Pulmonary arterial hypertension can cause dyspnoea on exertion and leads to right heart failure. It can be idiopathic and familial or can be associated with connective tissue diseases and congenital heart disease with repaired shunts.

The available treatments for pulmonary arterial hypertension include calcium channel blockers, endothelin antagonists, phosphodiesterase 5 inhibitors and prostanoids. Some patients require combinations of these drugs and some will not respond and will need a lung transplant.

Macitentan was developed by modifying the structure of the endothelin receptor antagonist bosentan. It stops endothelin from binding to the endothelin A and B receptors. These receptors are associated with vasoconstriction. Although the maximum plasma concentration is reached eight hours after an oral dose, macitentan has a rapid onset of effect. The drug is metabolised, mainly by cytochrome P450 3A4, to form an active metabolite. Macitentan has a half-life of 16 hours and its active metabolite has a half-life of 48 hours. Most of the metabolites are excreted in the urine.

The main trial of macitentan involved 742 patients with an average age of 45.6 years. Most of the patients had idiopathic or heritable pulmonary arterial hypertension or an associated connective tissue disease. They were randomised to start macitentan 3 mg or 10 mg, or a placebo, once daily. Other treatments for pulmonary arterial hypertension could be continued. The primary end point of the study was a composite of clinically worsening pulmonary arterial hypertension, the need for prostanoids, lung transplant or death.1

After a median treatment duration of 115 weeks, one of these events had occurred in 38% of the macitentan 3 mg group, 31.4% of the 10 mg group and 46.4% of the placebo group. Another composite end point of death or hospitalisation for pulmonary arterial hypertension was reached by 26% of the 3 mg group, 20.7% of the 10 mg group and 33.6% of the placebo group. The advantages of macitentan over placebo in these composite end points were statistically significant. There were also improvements in exercise capacity.1

Adverse events led to treatment discontinuation in 13.6% of the 3 mg group, 10.7% of the 10 mg group and 12.4% of the placebo group. Compared with placebo, patients taking macitentan 10 mg (the dose recommended in Australia) more frequently developed respiratory infections, headache and anaemia.1 The blood count should be measured before and during treatment. As liver function can be affected, macitentan is contraindicated in patients with aminotransferase concentrations greater than three times the upper limit of normal. Monthly monitoring of liver function is recommended. Patients with renal impairment may have an increased risk of hypotension or anaemia. Macitentan is teratogenic.

Although exercise tolerance improved with macitentan, the increase was relatively small. At the start of the study the patients could walk an average of 360 metres in six minutes. After six months the patients taking macitentan 10 mg could walk 12.5 metres further.1 As this change may not be a good surrogate for clinical outcomes, it is important that mortality was studied. However, the drug did not have a significant effect on all components of the primary composite outcome. Most of the benefit was due to macitentan 10 mg
NEW DRUGS

Reducing the proportion of patients with worsening pulmonary arterial hypertension. Deaths from any cause and from pulmonary arterial hypertension were not significantly different from placebo.1

REFERENCE


First published online 13 May 2014

Riociguat

Approved indication: pulmonary hypertension

Adempas (Bayer)

0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg film-coated tablets

Australian Medicines Handbook section 6.6

There are several causes of hypertension in the pulmonary circulation. They include pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. In pulmonary hypertension there is an imbalance between vasodilators, such as nitric oxide and vasconstrictors such as endothelin-1. Nitric oxide activates guanylate cyclase which leads to relaxation of smooth muscle. Riociguat is a drug which acts synergistically with nitric oxide and also independently stimulates guanylate cyclase. Riociguat is taken three times a day. It is converted by the cytochrome P450 system to an active metabolite. There are many potential interactions and co-administration with drugs such as ketoconazole and ritonavir is not recommended. The use of nitrates and phosphodiesterase inhibitors, such as sildenafil, is contraindicated. Riociguat and its metabolites are eliminated in bile and urine. It is not recommended for patients with severe hepatic or renal impairment. As smoking reduces plasma concentrations of riociguat, the doses may need to be adjusted in patients who stop or start smoking during treatment.

The effect of riociguat on exercise tolerance was studied in a phase III placebo-controlled trial of 443 patients. These patients had pulmonary arterial hypertension that was mainly idiopathic or associated with connective tissue disease or congenital heart disease. In one group of patients the dose of riociguat was adjusted up to a maximum of 2.5 mg three times daily while another group was limited to a maximum of 1.5 mg three times daily. After 12 weeks the patients in the 2.5 mg group could walk an extra 30 metres and those in the 1.5 mg group could walk an extra 31 metres. In the placebo group the patients walked on average six metres less than they did at the start of the study. Riociguat also improved cardiac output and mean pulmonary arterial pressure. The benefits of treatment were seen irrespective of whether the patients were already taking prostanooids or endothelin-receptor antagonists.1

Riociguat has also been studied in 261 patients with chronic thromboembolic pulmonary hypertension. The 173 patients who took riociguat started at a dose of 1 mg three times a day which was adjusted up to a maximum of 2.5 mg three times a day. After 16 weeks their mean six-minute walking distance had increased from 342 metres to 381 metres. This increase of 39 metres was significantly better than the six metre decrease in the placebo group. Cardiac output and pulmonary arterial pressure also improved.2

Systemic hypotension is a predictable adverse effect of riociguat. Relaxation of smooth muscle could also contribute to complaints of headache, dizziness and dyspepsia. Nausea, vomiting and diarrhoea are also more frequent with riociguat than with placebo.1,2 Approximately 3% of the patients taking riociguat withdrew from the trials because of adverse events.1,2

Riociguat increases the risk of bleeding and anaemia. In the clinical trials serious bleeding affected 2.4% of patients, but none of the placebo group. There was serious haemoptysis in 1% of the patients taking riociguat and one case was fatal.2

In animal studies, riociguat was teratogenic so it is contra-indicated in pregnancy. It is also contra-indicated in lactation.

Extensions of the main clinical trials showed that the increase in walking distance was at least maintained, but the long-term clinical efficacy and safety of riociguat is unknown. Thromboembolic pulmonary hypertension can be treated by pulmonary endarterectomy. Riociguat may be an option for patients who cannot have surgery or who do not improve after surgery. In pulmonary arterial hypertension only 21% of patients have an improvement in their functional class.3 Although riociguat has a dual mechanism of action it is unclear if this gives it any clinical advantage over the phosphodiesterase inhibitors.

A phase II trial involving 201 patients with pulmonary hypertension due to left ventricular dysfunction found that after 16 weeks the effect of riociguat on mean pulmonary artery pressure was not statistically different from placebo.3

REFERENCES


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The Transparency score (1) is explained in ‘New drugs: T-score for transparency’, Aust Prescr 2014;37:27.

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

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

Addendum

Treatment of nausea and vomiting in pregnancy

Box 2 Drug treatments for nausea and vomiting in pregnancy – current guidelines8,9

Additional reference 8 added May 2014

ANSWERS TO SELF-TEST QUESTIONS
1 True 2 False 3 False 4 False 5 True 6 False

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