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Editorial

How low to go with glucose control

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Key words: cardiovascular risk, hypoglycaemia.

(Aust Prescr 2009;32:30–1)

The Diabetes Control and Complications Trial[1] in type 1 diabetes and the UK Prospective Diabetes Study (UKPDS)[2] in type 2 diabetes showed that a strategy aimed at intensified control of blood glucose reduced the risk of microvascular complications of diabetes. These results advanced the management of hyperglycaemia and led to the current recommendation that all patients with diabetes aim for a glycated haemoglobin (HbA1c) target below 7%.

There has been a general acceptance that tight glycaemic control will reduce cardiovascular disease, but there is a lack of definitive evidence that outcomes will improve. The studies involved relatively young patients who were therefore at lower cardiovascular risk. In particular, the UKPDS recruited people with type 2 diabetes at the time of diagnosis and the study may have been too short for a cardiovascular benefit to emerge. The failure to show a benefit may also relate to the fact that the initial reductions in HbA1c were not sustained.

Post-study follow-up (observational) of the UKPDS cohort[3] over 10 years did, however, show continued reduction in not only microvascular (24%, p = 0.001) but also cardiovascular outcomes (15% in myocardial infarction, p = 0.01) and in death from any cause (13%, p = 0.007). This benefit – a so-called 'legacy effect' – persisted despite early loss (within a year) of within-study differences in glycaemic control between the intensive and standard groups.

In 2008, two major cardiovascular-outcome trials reported their results.[4,5] These trials involved people with long-standing type 2 diabetes with high vascular risk.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD)[4] study randomised 10 251 people with poorly controlled type 2 diabetes (mean age 62 years, mean duration 10 years, median HbA1c 8.1%). There was an intensive glucose lowering arm aiming for normoglycaemia (HbA1c less than 6%) and an arm with a standard glucose target (HbA1c of 7–7.9%). The primary outcomes were cardiovascular events including cardiovascular death, stroke or non-fatal myocardial infarct. Both groups used almost all of the available drug therapies in different combinations and doses.

The Action in Diabetes and Vascular Disease (ADVANCE)[5] study involved 11 140 patients with similar age and diabetes duration (mean age 66 years, mean duration 8 years). However, these patients had significantly better glycaemic control at baseline (median HbA1c of 7.2%) compared to the ACCORD groups. They were randomised to either an intensive glucose lowering arm (aiming for HbA1c under 6.5%) or to a standard glucose lowering arm. Multiple drug therapies were used, but the oral hypoglycaemic drug taken by everyone in the intensive arm was modified-release gliclazide. The primary outcomes for the ADVANCE study also differed in that they included not only cardiovascular events, but also major microvascular events.

The intensive glucose lowering arms in both ACCORD and ADVANCE achieved a median HbA1c of 6.4%. This was, respectively, 1.1% and 0.6% lower than the HbA1c in the standard treatment arms. During the ADVANCE study, intensive glucose lowering yielded a 21% (p = 0.006) relative reduction in microvascular events (in nephropathy), but no significant effect on major cardiovascular events. Unexpectedly, the ACCORD

In this issue…

Many drugs are metabolised by the liver, so their clearance will be affected by liver disease. Andrew Sloss and Paul Kubler tell us what should be considered when prescribing for a patient with reduced liver function.

An increased concentration of a single hepatic enzyme does not mean that the patient has liver disease. Pat Phillips explains how healthy people may have abnormal test results, and suggests how errors can be reduced.

Laboratory measurements are sometimes used as an indication of the patient's prognosis. Scott Twaddell cautions us that such surrogate markers may not always be directly linked to clinical outcomes. It is important to manage the patient and not just the surrogate marker.

Glycated haemoglobin (HbA1c) is a surrogate marker in diabetes. Kris Park warns us that intensive treatment to reduce HbA1c may not improve cardiovascular outcomes in patients with diabetes.

The outcomes of an injection of botulinum toxin are usually quick to appear. Although there is great interest in the cosmetic use of this drug, Adam Scheinberg describes some of its clinical applications.

study showed a 22% (p = 0.04) relative increase in total mortality in the intensive glucose lowering arm. Although non-fatal myocardial infarctions reduced, there were more deaths from cardiovascular causes. As a result of safety concerns, the intensive treatment arm of the ACCORD study was stopped 18 months early, at three and a half years into the study.

Neither study has shown that intensive glucose lowering (HbA1c less than 6.5%) reduces macrovascular events when compared to standard glucose lowering (HbA1c of 7–7.5%) in older individuals with a long history of diabetes. Rapid and intensive glucose lowering could be harmful in this high-risk group. To date, there is no clear explanation for the higher mortality in ACCORD. No specific drugs (including thiazolidinediones) have been implicated, however drug therapy was not randomised in the trials. In ACCORD, severe hypoglycaemia requiring medical assistance was three times more common in the intensive group (10.5% and 3.5% respectively). It is plausible that severe hypoglycaemia may possibly have triggered fatal cardiac events such as ventricular arrhythmias particularly in those with compromised cardiac function and established autonomic neuropathy. An adverse cardiovascular outcome was not seen in the ADVANCE group who had generally better glycaemic control at the start of the study and who had a more gradual lowering of glucose during the study. Severe hypoglycaemia was less frequent than in ACCORD.

Given the rather unexpected and conflicting findings in these studies, how aggressive should we be in managing hyperglycaemia in people with type 2 diabetes? The findings from ACCORD and ADVANCE are important and should not be dismissed, however they do not change the treatment goal for most patients with type 2 diabetes. The HbA1c target should remain at or less than 7% because there is clear and consistent evidence of considerable benefit in microvascular outcomes.[1,2,3,5] In younger patients with a recent diagnosis of type 2 diabetes and no history of cardiovascular disease, a lower HbA1c target, even below 6.5%, should be considered if it can be reached with relative ease without the need for multiple drugs and with a low risk of severe hypoglycaemia. The 'legacy effect' seen in the UKPDS post-trial period certainly supports this strategy. However, in patients with a long duration of diabetes and established vascular disease, tight glycaemic control may not improve the cardiovascular outcomes. Rapid correction of hyperglycaemia and excessively tight glycaemic control appears harmful and should be avoided. In these high-risk individuals, an HbA1c target of 7–7.5% would be appropriate. The target can be adjusted for each patient with regular assessment for severe hypoglycaemic episodes and hypoglycaemia unawareness. Finally, optimal therapy for people with diabetes includes addressing not only glycaemic control, but also other coexisting vascular risk factors such as hypertension, lipid abnormalities and platelet dysfunction.

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Dr Park was a principal investigator for the ADVANCE Study.

Letters

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

Sulfur allergy

Regarding my previous correspondence (Aust Prescr 2008;31:88–9), I suppose one has to accept the Americanism 'sulfur', but this applies to chemical 'sulphur' as used in dandruff preparations. When sulphonamide preparations first came on the market they were conveniently referred to as 'sulfa' drugs and therefore allergy to these drugs is 'sulfa' allergy and not 'sulfur allergy' as your article stated.

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Prescribing in liver disease

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Summary

As the liver is responsible for the metabolism of many compounds, knowledge of a patient's hepatic function is required for the safe prescribing of many drugs. Assessing liver function by way of a patient history, examination and blood tests such as serum albumin and bilirubin, as well as prothrombin time, is recommended before prescribing some medications. Liver enzyme concentrations may be useful indicators of hepatocellular damage or enzyme induction. For drugs dependent on hepatic elimination, careful choice of compounds and their dose is prudent if liver function is significantly compromised. Drug interactions must also be considered if a common metabolic pathway exists.

Key words: drug prescribing, hepatic metabolism.

(Aust Prescr 2009;32:32–5)

Introduction

The metabolism of many drugs depends on adequate hepatic function. Drugs with a narrow therapeutic range (that is, with little difference between toxic and therapeutic doses) run the risk of accumulating and causing toxicity in patients with hepatic disease.

The liver receives a dual blood supply with about 20% of blood coming from the hepatic artery and 80% from the portal circulation. The blood flow to the liver is around 20–25% of the total cardiac output. Toxins, infectious agents, medications and serum inflammatory mediators may result in a diverse range of disease processes leading to loss of normal histological architecture, reduced cell mass and loss of blood flow. Consequently, functional liver capacity may be lost.

Assessing hepatic function is necessary so that appropriate adjustment of drug dose can be made. However, this is not always straightforward as there is no single test that reliably measures liver function.

Drug metabolism in the liver

The liver is the principal organ of metabolism in the body although other sites are involved such as the gut wall, kidney, skin and lungs. Drug metabolism, by means of enzyme reactions in the liver, is the body's main method of deactivating drugs. Drug molecules are converted into more polar compounds, which aids their elimination. Generally, metabolism results in the loss of pharmacological activity because transport to the site of action is limited due to reduced lipid solubility, or because the molecule is no longer able to attach to its receptor site. However, in some circumstances drugs are metabolised to more active forms, for example the conversion of codeine to morphine, primidone to phenobarbitone and amitriptyline to nortriptyline.

Concentrations of enzymes involved in both phase I and II reactions vary significantly between individuals with normal hepatic function and even more so between the healthy population and those with hepatic impairment.

Phase I reactions

Most drugs are lipophilic and therefore readily cross the cell membrane of the enterocyte. In the process of liver metabolism these substances are converted into more hydrophilic compounds. Hydrolysis, oxidation and reduction are the three types of phase I reactions that do this in the liver. These mainly involve a subset of mono-oxygenase enzymes called the cytochrome P450 system. The most common reaction is hydrolysis which involves the addition of a molecular oxygen atom to form a hydroxyl group, with the other oxygen atom being converted to water (for example, the conversion of aspirin to salicylic acid). Other types of phase I reactions include oxidation via soluble enzymes such as alcohol dehydrogenase, and reduction (for example nitrazepam).

Phase II reactions

These reactions involve conjugation which is the attachment of molecules naturally present in the body to a suitable link in the drug molecule. Most compounds will have undergone a phase I reaction (for example, addition of a hydroxyl group) before the conjugation step can occur. The main conjugation reaction involves glucuronidation (for example with morphine), but other conjugation mechanisms include acetylation (sulfonamides) or the addition of glycine (nicotinic acid) and sulfate (morphine). Natural substances such as bilirubin and thyroxine may be metabolised by the same pathways. The resulting conjugate molecule is usually pharmacologically inactive and substantially less lipophilic than its precursor so it is more readily excreted in the bile or urine.

In some circumstances the parent compound is a prodrug so the metabolite is active (for example, codeine is converted to morphine). A common cause of capacity limited hepatic metabolism is the amount of the conjugate available. Paracetamol overdose is an example of this situation. With normal prescribed doses of paracetamol, the toxic metabolite (N-acetyl-p-benzoquinone imine or NAPQI) is efficiently detoxified by conjugation with glutathione as a phase II reaction. However, when a large amount of NAPQI is generated, the total quantity of available glutathione may be consumed and the detoxifying process becomes overwhelmed. Phenytoin and warfarin are other drugs where capacity limited hepatic metabolism can occur.

Excretion

Following metabolism, compounds are then either excreted directly into the bile, or re-enter the systemic circulation and are excreted as polar metabolites or conjugates by the kidney.

If excreted in the bile (mainly glucuronidated drugs), the compound enters the biliary duct system and is secreted into the upper small intestine. Then throughout the ileum, these conjugated bile salts (some of which have drugs attached to them) are reabsorbed and transported back to the liver via the portal circulation. This is known as enterohepatic circulation. Each bile salt is reused approximately 20 times and often repeatedly in the same digestive phase. The implications of this process are that compounds may reach high hepatic concentrations resulting in significant hepatotoxicity. Some drugs that undergo enterohepatic cycling to a significant extent include colchicine, phenytoin, leflunomide and tetracycline antibiotics.

Systemic drug availability

After drugs are absorbed from the gut, a proportion of the dose may be eliminated by the liver before reaching the systemic circulation. This pre-systemic or first pass elimination is determined by the hepatic clearance or extraction for the compound. Hepatic clearance depends on three factors:

- extent of drug binding to blood components such as albumin
- blood flow to active metabolic cells, which is dependent on the architecture in the liver
- functional hepatocytes.

The hepatic extraction ratio of a drug will indicate if its elimination is dependent on blood flow and hepatocyte function (highly extracted) or hepatocyte function alone (poorly extracted). Some examples of high and low extraction drugs are listed in Table 1.

Hepatic conditions

Chronic liver disease is more predictably associated with impaired metabolism of drugs than acute liver dysfunction. However, in cases of severe acute liver failure, the capacity to metabolise the drug may be significantly impaired.

In the chronic state, cirrhosis of any aetiology, viral hepatitis and hepatoma can decrease drug metabolism. In moderate to severe liver dysfunction, rates of drug metabolism may be reduced by as much as 50%. The mechanism is thought to be due to spatial separation of blood from the hepatocyte by fibrosis along the hepatic sinusoids.

The use of certain drugs in patients with cirrhosis occasionally increases the risk of hepatic decompensation. An example of this is the increased risk of hepatic encephalopathy in some patients who receive pegylated interferon alfa-2a in combination with ribavirin for the treatment of chronic active hepatitis related to the hepatitis C virus. In addition, co-infection with hepatitis B or C virus, even in the absence of cirrhosis, increases the risk of hepatotoxicity from antiretroviral therapy in patients with coexistent HIV infection.

In the presence of chronic liver disease, there is potential for changing the systemic availability of high extraction drugs, thereby affecting plasma concentrations. A potential consequence of liver disease is the development of portosystemic shunts that may carry a drug absorbed from the gut through the mesenteric veins directly into the systemic circulation. As such, oral treatment with high hepatic clearance drugs such as morphine or propranolol can lead to high plasma concentrations and an increased risk of adverse effects.

Liver damage can also affect drugs with low hepatic clearance. For instance, the effect of warfarin, which has a low extraction ratio, is increased due to the reduced production of vitamin K-dependent clotting factors.

The pharmacokinetic interaction between alcohol and drugs is more complex. An acute ingestion of alcohol may inhibit a drug's metabolism by competing with the drug for the same set of metabolising enzymes. Conversely, hepatic enzyme induction may occur with chronic excessive alcohol ingestion via CYP2E1 resulting in increased clearance of certain drugs (for example phenytoin, benzodiazepines). After these enzymes have been induced, they remain so in the absence of alcohol for several

Table 1

Some examples of drugs with high and low hepatic extraction

High extraction ratio	Low extraction ratio
Antidepressants	Non-steroidal anti-inflammatory drugs
Chlorpromazine/haloperidol	Diazepam
Calcium channel blockers	Carbamazepine
Morphine	Phenytoin
Glyceryl trinitrates	Warfarin
Levodopa	
Propranolol	

weeks after cessation of drinking. In addition, some enzymes induced by chronic alcohol consumption transform some drugs (for example paracetamol) into toxic compounds that can damage the liver.

In the presence of cholestatic jaundice, drugs and their active metabolites that are dependent on biliary excretion for clearance will have impaired elimination. Further impairment will occur if the compound is excreted as a glucuronide and is subject to enterohepatic circulation.

Evaluating hepatic function

A clear patient history with respect to alcohol, illicit drug use and toxic industrial exposure must be recorded. The medication list including supplements such as iron, vitamin A and herbal remedies is vital. A family history of diseases such as alpha-1 antitrypsin deficiency, iron storage diseases, porphyrias and diabetes mellitus may alert the physician to the potential for liver impairment.

It is also important to look for signs of acute or chronic liver disease such as the presence of jaundice, spider naevi, palmar erythema, ascites, abdominal distention, hepatomegaly, splenomegaly and caput medusa. If there is clinical evidence of liver disease, further investigation is required. This includes liver function tests and an ultrasound of the abdomen. A portal vein Doppler study is also recommended to assess for the presence of portal hypertension. A slowing or reversal of portal vein blood flow indicates portal hypertension which may be related to either liver cirrhosis or portal vein thrombosis.

In renal disease, serum creatinine concentration and the glomerular filtration rate provide a reasonable guide to drug dosage requirements. In contrast, there is no single test that measures liver function so a reliable prediction of pharmacokinetics is not possible. Some evaluation of hepatic function is possible by assessing serum albumin and bilirubin, and prothrombin time. However, these parameters are not directly related to drug clearance. Although not directly correlated with liver dysfunction, elevated liver enzymes may raise the suspicion of hepatic impairment requiring further investigation.

The Child-Turcotte score was designed to estimate the operative risk of an alcoholic patient with cirrhosis. The parameters used include serum concentrations of bilirubin and albumin, prothrombin time, nutritional status and ascites. These parameters were modified to substitute degree of encephalopathy for nutritional status and then became known as the Child-Pugh classification (see Table 2).[1] The grades A, B and C may also be a useful indicator of an individual's ability to effectively metabolise a drug. An alternative method for assessing liver dysfunction is the Model for End-Stage Liver Disease (MELD) score (www.unos.org/resources/MeldPeldCalculator.asp).[2] This may be a more accurate method but is less accessible to most clinicians because it involves calculating the score.

Evaluating the drug in question

If a drug is dependent on hepatic elimination, there are several factors to consider when prescribing for patients with liver disease (see box). Determining the hepatic contribution to elimination is paramount and the following general rules should be considered.

Drugs with a narrow therapeutic range that are extensively metabolised by the liver (that is, greater than 20% of their total elimination) should either be avoided altogether (e.g. pethidine) or used with extreme caution (e.g. morphine, theophylline) in patients with significant liver disease.

Drugs with a wide therapeutic range which also undergo extensive hepatic metabolism should be used with caution. In particular, the dosing interval should be increased or the total dose reduced (e.g. carvedilol).

Table 2

Child-Pugh classification [1]

Parameter	Points assigned = 1	Points assigned = 2	Points assigned = 3
Ascites	Absent	Slight	Moderate
Bilirubin, micromol/L	<11	11–45	>45
Albumin, g/L	>35	28–35	<28
Prothrombin time – seconds over control or INR	<4 <1.7	4–6 1.7–2.3	>6 >2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

Total score of 5–6 is grade A or well compensated disease (1 and 2 year survivals are 100% and 85%)

Total score of 7–9 is grade B or disease with significant functional compromise (1 and 2 year survivals are 80% and 60%)

Total score of 10–15 is grade C or decompensated liver disease (1 and 2 year survivals are 45% and 35%)

Depending on hepatic clearance and the therapeutic index of the drug, dose adjustments or drug avoidance may be required in grades B or C chronic liver disease.

Factors to consider when prescribing drugs dependent on hepatic elimination

- Ascertain how much the drug depends on hepatic metabolism for its elimination from the body.
- Determine the degree of hepatic impairment using the Child-Pugh classification (Table 2), hepatic enzyme levels and possibly an ultrasound of the liver with portal vein Doppler study.
- If there is doubt about the degree of hepatic impairment or the drug has a narrow therapeutic index (that is, the upper dose range for efficacy is close to the lower concentration range of toxicity), then lower the recommended starting dose by approximately 50%, and titrate to effect under careful supervision – 'start low and go slow'.
- Determine possible interactions between the new drug and any drugs the patient is already taking.

If hepatic elimination is limited (that is, accounting for less than 20% of total elimination), then the therapeutic range of the compound should be reviewed. If the drug has a wide therapeutic index, then the likelihood of an adverse effect related to hepatic impairment is low. However, if the drug has a narrow therapeutic index, then caution should be exercised as significant hepatic impairment may have a clinically relevant effect on the pharmacokinetics (e.g. lamotrigine).

If greater than 90% of the compound is excreted unchanged in the urine, then hepatic impairment is unlikely to play a significant role in the accumulation of the drug and therefore toxicity.

Conclusion

Prescribing in hepatic impairment is less well defined when compared to guidelines for prescribing in renal failure. Hepatic dysfunction is less overt and may not be apparent until much of the functioning liver is lost. Knowledge of the metabolism of drugs eliminated by the liver is useful along with close monitoring of the patient for unwanted adverse effects related to possible toxicity. When introducing long-term treatment with a drug with high hepatic clearance or a narrow therapeutic index, assess liver function (clinically and with baseline liver function tests). However, once the drug is commenced routine monitoring is costly and its role unclear in most cases of prescribing in patients with hepatic dysfunction.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 55)

1. Liver function tests are unreliable for calculating drug dosing in liver disease.
2. As warfarin has a low extraction ratio, liver damage does not increase its effects.

NPS RADAR April 2009

The latest edition of *NPS RADAR* reviews:

- desvenlafaxine for major depressive disorder
- pramipexole for restless legs syndrome
- valsartan and combinations of valsartan with hydrochlorothiazide or amlodipine for hypertension
- zoledronic acid once-yearly infusion for osteoporosis.

In Brief items cover new and revised Pharmaceutical Benefits Scheme listings for clopidogrel for acute coronary syndrome, ziprasidone for acute mania in bipolar disorder, sublingual desmopressin for primary nocturnal enuresis, and risedronate for corticosteroid-induced osteoporosis.

NPS RADAR is available at www.npsradar.org.au

Managing pertussis in adults

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Summary

Pertussis or whooping cough is typically characterised by paroxysms of coughing with a whooping sound during inhalation. It is thought to be under-diagnosed generally. Whooping cough is caused by *Bordetella pertussis* and is highly contagious. Although childhood immunisation has been effective in preventing the disease, outbreaks in Australia have been associated with waning immunity in older children and adolescents. The peak incidence of infection now occurs in people aged 15 or older. When given early in the illness, antibiotics can decrease the infectious period, but have no effect on the duration or severity of disease. Symptomatic treatment of cough has shown no clear benefit. Antibiotic prophylaxis of contacts is recommended for certain high-risk groups, but there is limited evidence of its effectiveness. Although infants remain the most at risk for severe, life-threatening disease, it is adolescent and adult booster immunisation which remains critical for prevention programs.

Key words: antibiotics, vaccination, whooping cough.

(Aust Prescr 2009;32:36–8)

Introduction

Pertussis, also known as whooping cough, is a highly contagious disease caused by the bacterium *Bordetella pertussis*. It is generally thought to be under-diagnosed and remains the least well controlled of all the vaccine preventable diseases targeted by the Australian National Immunisation Program.[1] Epidemics occur every 3–4 years. This is despite immunisation continuing to increase, with more than 90% of one-year-olds being fully vaccinated.

The literature suggests that epidemics result from waning immunity in later childhood and adolescence. The peak incidence of whooping cough in Australia occurs in adolescents and adults with more than 70% of pertussis notifications occurring in people older than 15 years in 2004–05. Data suggest that 10–35% of subacute coughing illnesses in adults are due to pertussis infection.[2] Death in individuals older than 10 years of age is rare and non-immunised infants remain the most likely group to have severe life-threatening disease requiring hospitalisation.[1]

Clinical presentation

The classic presentation of pertussis is one of spasms of coughing with a characteristic inspiratory whoop. However, this is less common in older children and adults. The first 1–2 weeks of illness with *B. pertussis* resembles other upper respiratory tract infections, with runny nose and mild cough. This is followed by the paroxysmal coughing phase in the second and third weeks.

Diagnosis

As classic symptoms of whooping cough do not usually exist in adults, exposure to others with prolonged cough is used by some as an indicator of pertussis infection. Although less frequent in adults, post-tussive vomiting may also indicate pertussis. It is therefore important to remember *B. pertussis* when reviewing all adolescents and adults with a chronic cough.

A number of investigations can be performed to support the diagnosis of pertussis. These include:

- bacterial culture, polymerase chain reaction (PCR) or immunofluorescence assays of nasopharyngeal swab or aspirate samples
- serological testing to detect rises in immunoglobulin (Ig) A or IgG titres to *B. pertussis* antigens
- lymphocyte count (raised counts are a non-specific indicator of infection).

For patients presenting early (within the first three weeks) and before the start of antibiotic therapy, PCR, immunofluorescence and culture may be useful. For patients who present later, serological testing – which is reliant on an immune response – is often more helpful.[3] Pertussis-specific IgA is only produced after natural infection, whereas IgG rises with vaccination and natural infection. While a positive IgA test confirms the diagnosis of pertussis, a negative result does not exclude the

possibility of infection. (It is important to remember that a small proportion of the population has an IgA deficiency.) Paired samples showing rising titres of specific IgA or IgG are a more reliable indication that the patient has pertussis.

PCR-based testing is the most sensitive and specific of all investigations, particularly early in the illness. It is sensitive for longer than culture and is less likely to be affected by antibiotic treatment (0% detection via culture after seven days antibiotics).[3] Although direct immunofluorescence is highly specific, it has limited sensitivity. Its main advantage is speed.

Antibiotic treatment

Antibiotics are recommended in the initial catarrhal phase of infection when they are effective in eliminating *B. pertussis* from the nasopharynx and reducing the infectious period. However, after three weeks of coughing, antibiotics have no measurable effect on reducing the infectious period and are not recommended. Patients should avoid contact with susceptible individuals until at least five days of antibiotics have been taken.

Table 1 lists the proven antimicrobial therapies in nasopharyngeal eradication of *B. pertussis*. Erythromycin has been commonly regarded as the treatment of choice for pertussis infections. A 14-day erythromycin course is often recommended, although studies have shown similar efficacy with a seven-day regimen.[4]

The newer macrolides, such as clarithromycin and azithromycin, have replaced erythromycin as the standard treatment. (However, there is not enough clinical evidence to recommend roxithromycin for pertussis infection.) The newer macrolides have fewer gastrointestinal adverse effects and reach higher concentrations in respiratory secretions. This improved safety profile is of particular importance in a therapeutic regimen aimed at eradication of organisms rather than improvement of symptoms. Studies have shown that patients are more compliant when taking the newer macrolides compared with erythromycin. Trimethoprim with sulfamethoxazole can be used as an alternative to macrolides if necessary, but is not the first choice of therapy.

Symptomatic treatment

A Cochrane review found that some symptomatic treatments for the cough associated with pertussis had no clear benefits.[5] The treatments reviewed included antihistamines, dexamethasone, salbutamol and pertussis immunoglobulin. It is possible that immunoglobulin offers some improvement in mean number of whoops, but further well-designed good quality trials need to be developed to determine this.

Managing household contacts

B. pertussis is highly contagious and a significant proportion of contacts become infected (70–100% of household members). The incubation period is typically 7–10 days (range of 4–21 days). Although there is insufficient evidence that antibiotic prophylaxis of close contacts reduces the number of new cases or improves clinical symptoms[4], it is recommended primarily because of the high risks of morbidity and mortality in non-immunised infants (see box).

It is suggested that prophylaxis be given as soon as possible, but within three weeks of symptom onset in the infected contact. The dose and duration of antibiotics for prophylaxis are the same as for treatment (see Table 1).

As three or more injections are required to confer protection, infant vaccination is not helpful in controlling a pertussis outbreak.[1] However, unvaccinated contacts aged eight years or older can be offered a diphtheria, tetanus and acellular pertussis vaccine and younger contacts can be given a catch-up course.

Table 1

Effective antibiotic treatment for pertussis

Drug	Adult dose	Daily frequency	Duration
clarithromycin*	500 mg (7.5 mg/kg up to 500 mg)	twice	7 days
erythromycin	250 mg (10 mg/kg up to 250 mg)	four times	7 days
azithromycin*†	10 mg/kg (up to 500 mg)	once	3 days
azithromycin*	day 1: 500 mg first day (10 mg/kg up to 500 mg) days 2–5: 250 mg (5 mg/kg up to 250 mg)	once	5 days
trimethoprim with sulfamethoxazole	160 + 800 mg (4 + 20 mg/kg up to 160 + 800 mg)	twice	7 days

* best regimens for microbiological clearance with fewer adverse effects[4]
† this regimen is documented in a Cochrane systematic review[4] although not in Australian antibiotic guidelines[6]

Antibiotic prophylaxis for 'high-risk' contacts of pertussis cases [1]

- Women in their last month of pregnancy, irrespective of vaccination status
- Members of a household which includes a child less than 2 years who is not fully vaccinated*
- Children and adults who attend a childcare facility where children under 2 years are not fully vaccinated
- Healthcare workers and babies (if exposed for >1 hour) in a maternity ward or newborn nursery

* Fully vaccinated = three effective doses of pertussis vaccine given at least four weeks apart[1]

Important role of immunisation in adults

Immunisation remains the mainstay of prevention of *B. pertussis* infection. The current Australian immunisation schedule[1] recommends that a child formulation of a diphtheria, tetanus and acellular pertussis vaccine is given at two, four and six months of age with a booster at four years. Another booster is recommended at 12–17 years of age using the adolescent/adult formulation which has a lower concentration of pertussis antigens than childhood vaccinations. It is vital to remember that adult and adolescent vaccination is an effective means of controlling *B. pertussis* and will have positive health ramifications within the community.[1] There are no data on the duration of immunity following vaccination in teenagers, but this is unlikely to be required at intervals less than 10 years. A single booster dose is recommended for adults planning a pregnancy or for parents of a new infant, preferably before hospital discharge. Other household members such as grandparents or carers should also be vaccinated. Likewise, adults working in health care or childcare should be given a booster vaccination. Pertussis booster vaccination can also be considered along with a routine diphtheria and tetanus booster at age 50.

Conclusion

When *B. pertussis* is diagnosed early in the illness, antibiotics can decrease the infectious period, but have no effect on the duration or severity of disease. Antibiotic prophylaxis with macrolides, such as clarithromycin and azithromycin, is recommended for certain high-risk contacts. Symptomatic treatment of cough has not been proven to be significantly helpful in decreasing *B. pertussis* cough. Adolescent and adult booster immunisation remains critical for preventing disease outbreaks.

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Self-test questions

The following statements are either true or false (answers on page 55)

3. PCR testing is the most sensitive method to detect *Bordetella pertussis* in nasopharyngeal samples.
4. Macrolides are recommended for pertussis infection if the patient has had a chronic cough for more than four weeks.

Your questions to the PBAC

Australian Prescriber readers are invited to write in with their questions about decisions of the Pharmaceutical Benefits Advisory Committee. The segment 'Your questions to the PBAC' publishes selected questions from readers, and answers from the Committee itself. Questions may address issues such as regulatory decisions, pharmaceutical benefits listings, withdrawal of a drug from the market and Authority prescriptions. Letters and responses may be edited before publication.

Clinical use of botulinum toxin

***Adam Scheinberg**, Statewide Medical Director, Victorian Paediatric Rehabilitation Service, Royal Children's Hospital, Melbourne*

Summary

Botulinum neurotoxin type A inhibits the release of acetylcholine from cholinergic motor and autonomic nerves. Intramuscular injection leads to muscle relaxation, and intradermal injection reduces sweat gland secretion. The recommended dose depends on which preparation of botulinum toxin type A is used and its dilution, the size of the muscle or gland being injected, and the method used to localise the injection site. Repeat doses are usually required as the effect of the toxin wears off after 3–4 months. Therapy including stretching, splinting and strengthening may prolong the effect of muscle relaxation. Realistic goal setting before treatment is vital.

Key words: muscle spasticity, neurotoxins.

(Aust Prescr 2009;32:39–42)

Introduction

Botulinum neurotoxin was first identified in 1897 and is a product of *Clostridium botulinum*, an anaerobic bacterium which causes botulism food poisoning. During the 1940s, botulinum toxin type A was purified and isolated in a crystalline form. In 1989 the US Food and Drug Administration (FDA) approved botulinum toxin type A for the treatment of strabismus, blepharospasm and hemifacial spasm. It has since been approved for cervical dystonia, hyperhidrosis and cosmetic use. There are now over 30 conditions in which botulinum toxin type A has been reported to be of benefit.

Mechanism of action

Botulinum neurotoxin type A blocks neuromuscular conduction by inhibiting the release of acetylcholine from motor or autonomic nerve terminals. Injected intramuscularly, it produces a localised chemical denervation of the muscle, resulting in localised muscle weakness or paralysis. When injected intradermally, the toxin produces chemical denervation of sweat glands and reduces local sweating. The denervation is reversible. Nerve endings recover over three or more months during which muscle tone increases and glandular secretion recommences.

Botulinum toxin products

There are two different preparations of the type A toxin commercially available in Australia; these are a purified neurotoxin complex (Botox) and a haemagglutinin complex (Dysport). They are dispensed in vials as a vacuum dried powder which is reconstituted with sterile normal saline. Once opened, vials should be stored in the refrigerator and used within 24 hours. The potencies of both preparations are expressed as units of activity, which relate to the median lethal dose in mice. The biological activity for each preparation is unique, so one unit of the neurotoxin complex is not equal to one unit of the haemagglutinin complex. As the potency and safety of these products differ, dose finding on a case by case basis may be necessary if both products are used in the same patient.

Another botulinum toxin type A product (Xeomin) is formulated without complexing proteins and has been approved for use in several European countries but not in Australia. It has recently been shown to be of benefit for focal dystonia and spasticity.

Botulinum toxin type B (Myobloc) is rarely used in Australia. It has been reported to be beneficial in adults with cervical dystonia who have developed resistance to botulinum toxin type A.[1]

Clinical indications

Considering whether to start a patient on botulinum toxin depends on balancing the risks of treatment against the potential improvements in active and passive function, level of pain, secondary effects of unwanted muscle overactivity and quality of life. In Australia, specialist medical practitioners such as ophthalmologists, neurologists, surgeons, rehabilitation specialists and paediatricians may access the government's Section 100 scheme. This provides reimbursement for the cost of botulinum toxin type A for the following conditions:

- blepharospasm
- spasmodic torticollis
- dynamic equinus foot deformity associated with cerebral palsy in children two years or over
- spasticity following stroke.

Botox is also approved for the treatment of strabismus in children and adults, focal spasticity of the limbs, primary hyperhidrosis of the axillae, and spasmodic dysphonia. Botox and Dysport are both approved for the treatment of glabellar forehead lines.

Blepharospasm

In blepharospasm and hemifacial spasm, botulinum toxin type A is administered by subcutaneous injection medially and laterally into the junction between the preseptal and orbital parts of the

upper and lower orbicularis occuli muscles of the eyes. Risks include corneal exposure due to reduced blinking and acute angle closure glaucoma due to the anticholinergic effect.[2]

Cervical dystonia (spasmodic torticollis) [3]

Patients with cervical dystonia have abnormal twisting or sustained postures of the head, neck and shoulders. Botulinum toxin type A is injected into the neck muscles to reduce pain and head rotation. Depending on the head position, a combination of the sternocleidomastoid, splenius, paravertebral, scalene and trapezius muscles may be injected. More than 50% of patients will have significant improvements in symptoms. Dysphagia is the most commonly reported adverse event, which in severe cases may lead to aspiration pneumonia.

Focal hand dystonia (writer's cramp) [4]

Focal hand dystonia is a task-specific dystonia that may affect people who perform repetitive movements for sustained periods. The goal of treatment is to reduce the dystonic posture and improve function. The effect may not be as good when the goal is improvement of complex fine motor tasks, such as occurs with musicians. Electromyography or electrical stimulation is used to guide injections, and correct muscle selection is vital for a good outcome.

Hyperhidrosis [5]

Hyperhidrosis is a condition of excessive sweating of the axillae, palms and soles of the feet. Causes of secondary hyperhidrosis such as hyperthyroidism should be excluded before starting treatment. Botulinum toxin type A is injected intradermally and adverse events are rare.

Spasmodic dysphonia (focal laryngeal dystonia) [6]

Vocal cord spasm, typically adductor muscle spasm, may interfere with communication, and responds to botulinum toxin type A injections. Spasm of the abductor muscle also occurs but may be less responsive to botulinum toxin type A treatment. Laryngoscopy and electromyography are needed for diagnostic evaluation and injection. Injection of laryngeal muscles should be avoided in patients requiring a general anaesthetic for elective surgery.

Focal spasticity

Spasticity is one component of the upper motor neurone syndrome and is defined as a velocity dependent increase in muscle tone. Botulinum toxin type A is often used for managing hypertonicity in conjunction with other treatments such as splinting, stretching and strengthening antagonist muscles.

Children

Ideally, children receiving treatment should have access to a multidisciplinary clinic where other interventions for spasticity can be considered. The largest group of children receiving botulinum toxin type A for spasticity are those with cerebral palsy. Treatment has been shown to be effective in reducing equinus gait pattern in these children (injections to calf, hamstring and hip flexor muscles), improving upper limb function (injections to shoulder, elbow, wrist and finger flexor muscles), reducing pain (injections to hip adductors) and reducing the need for orthopaedic surgery.[7,8,9,10] Children with dystonia may also improve with botulinum toxin type A treatment, although muscle selection and dosing is clinically challenging.

Children with spasticity and minimal contracture, who have functional or care goals, may benefit from treatment as early as 12–18 months. In general, botulinum toxin type A is less effective, particularly in the lower limbs, beyond the first decade.

Adults

Spasticity in adults is seen most commonly after acquired brain injury, stroke, multiple sclerosis and spinal cord injury. Setting goals before treatment, along with the pattern of affected muscle groups and the tone abnormality, determines muscle selection. Early treatment with botulinum toxin type A after stroke has been shown to reduce disability and carer burden.[11,12]

Cosmetic use

Botulinum toxin type A is used for treating glabellar lines (corrugator or procerus muscles), crow's feet (lateral fibres of orbicularis oculi muscle), and forehead lines (frontalis muscle).

Other uses

Botulinum toxin type A has also been shown to be of clinical benefit for patients with Parkinson's disease by reducing jaw tremor and excess salivation.[13] It has been used to relieve sensory and motor symptoms associated with tics, Tourette's syndrome and restless legs syndrome, and for patients with migraine, drooling or neurogenic bladder.

Administration

Before injection the toxin is diluted, usually with 0.5–5 mL of saline per vial. The extent of dilution affects the spread of the toxin once injected and will vary depending on a number of factors including:

- the condition being treated
- the size of the muscle being injected
- the risk of spread beyond the muscle
- the effect of previous injection courses
- the methods used to determine the injection site.

There are several ways to localise the muscle or gland to be injected. Palpation and anatomical landmarks are no longer considered best practice for treatment of focal spasticity.

Electrical stimulation, electromyography, ultrasound or a combination of all three, are generally used for localisation of the muscle and neuromuscular receptors.

During the procedure, which may involve multiple injections, the patient needs to remain relatively still. Children should receive analgesia and sedation. In Australia, several centres perform injections when the child is under general anaesthesia, while others use conscious sedation (either inhaled nitrous oxide or intranasal fentanyl). Topical anaesthetic gel may be sufficient for adolescent and adult patients.

Research has suggested that specific uptake of botulinum toxin type A into the nerve terminal, with less systemic spread, may be improved by activating the muscles soon after the injections. This can be achieved by passively moving the injected limb, using electrical stimulation, or by having the patient exercise the limb.

Safety

Adverse events tend to occur 1–2 weeks after injection and are usually transient. Localised pain, tenderness or bruising may be associated with the injection. Rare events include skin rash, pruritus and allergic reaction. Children sometimes experience transient incontinence, local weakness or in rare cases more generalised weakness. Local weakness represents the expected pharmacological action of botulinum toxin type A, but may be in excess to what is desired clinically. Overdose may present with symptoms of botulism, including ptosis, diplopia, deterioration in swallowing and speech, generalised weakness and respiratory failure.

There have been reports of deaths in children and adults following treatment with botulinum toxin type A. Some of the patients had major risk factors including significant swallowing problems, seizures and cardiovascular disease. Caution is recommended in children and adults who are significantly debilitated or have risk factors such as severe dysphagia.

Botulinum toxin type A is contraindicated in patients with known hypersensitivity and in patients with myasthenia gravis, Eaton-Lambert syndrome or who are pregnant (pregnancy category B3). It is also contraindicated if there is infection at the proposed site of injection. Botulinum toxin type A may interact with medications that affect neuromuscular transmission including aminoglycosides or curare-like compounds. The potential for interaction with these drugs may be up to 3–6 months after administration of botulinum toxin. Toxin preparations contain albumin, which carries a theoretical risk for transmission of viral or prion diseases.

Lack of response

Explanations may include inadequate dose, inappropriate muscle selection or injection site, underlying muscle changes (such as contracture), or neutralising antibodies to the toxin. As botulinum toxin type A is derived from foreign proteins, there is potential for the body to mount an immune response which may reduce the therapeutic benefit of treatment. To avoid this, botulinum toxin type A injections should be given at least three months apart.

Conclusion

Botulinum toxin is used for an increasingly wide range of clinical problems, principally related to muscle or sweat gland overactivity. The effect is temporary, lasting 3–6 months. Adjunctive therapies such as stretching or strengthening of antagonist muscles may allow for more sustained functional improvements after the biological effect of the botulinum toxin has ceased. Adverse effects are uncommon and usually temporary, although more serious effects including generalised weakness and dysphagia have been reported.

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Further reading

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Both Allergan and Ipsen have supported research conducted in Dr Scheinberg's department and in which he was a researcher.

Self-test questions

The following statements are either true or false (answers on page 55)

5. The two botulinum toxin type A formulations available in Australia are bioequivalent.
6. Drooping eyelids may indicate an overdose of botulinum toxin.

Book review

Therapeutic Guidelines: Psychotropic. Version 6.

Melbourne: Therapeutic Guidelines Limited; 2008. 325 pages. Price $39, students $30, plus postage. Also available in electronic format as eTG complete.

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Many general practitioners have a full set of Therapeutic Guidelines on their shelf or computer. With a veritable rainbow of useful guides (there are now 14 in the series), the challenge for a generalist is to ensure the pearls of wisdom they contain are used regularly and efficiently. So when a new edition of a guideline arrives, my approach is to scan through the contents and the tables in the appendix, before checking out the chapters on conditions I encounter frequently in my practice.

On reviewing the latest edition of Psychotropic Guidelines, it took me a while to determine which sections had undergone the 'major revision' promised on the Therapeutic Guidelines website. There has been a reorganisation of chapters, with the useful 'Getting to know your psychotropic drugs' still prominent in the guide. The large table in previous editions listing potential drug interactions has been omitted, so one has to look up individual medications for this information. Presumably many interactions listed in the old table were not clinically significant, although it's worth heeding the warning on page 1 that not all interactions are listed and that one should refer to the Australian Medicines Handbook or http://medicine.iupui.edu/flockhart for more information.

The most useful tables in the new edition are the 'switching' table (for checking antidepressant-free intervals when changing antidepressants, pages 112–3) and the table that differentiates features of selective serotonin reuptake inhibitor (SSRI) discontinuation syndrome, adverse effects of SSRIs, symptoms of depression, and serotonin toxicity (pages 4–5). Distinguishing between these conditions can be quite tricky in general practice, where patients often stop their medications without telling their doctor.

A drawback of the Psychotropic Guidelines is that it gives diagnostic advice in some sections, but these comments cannot replace a full mental health assessment in all patients before prescribing. Similarly, while there is advice about medication adherence and duration of therapy, there is limited advice on frequency of follow-up, and no reference to monitoring tools. These are not major omissions for a guide that is predominantly about prescribing medications, but prescribers should not rely on the Therapeutic Guidelines for assessment and management (as opposed to simply prescribing) advice.

Pitfalls in interpreting laboratory results

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Summary

The results of laboratory tests are affected by the collection and handling of the specimen, the particular laboratory and the method of analysis. They are also affected by variability within the individual and within the laboratory. Interpretation at one point in time should consider the position of the measurement within the laboratory reference range appropriate for the sample and the person being tested. Interpreting results over time should consider the likely variability of the measurement and the level of certainty required to identify a true change or absence of change. The more variable the measurement and the higher the required level of certainty, the larger the change between measurements needs to be before it can be considered clinically significant.

Key words: diagnostic tests.

(Aust Prescr 2009;32:43–6)

Introduction

Health professionals may find it hard to get clinically useful information from the barrage of figures, ranges, stars and comments in laboratory results. Some knowledge about the accuracy of laboratory results can help to sort out important clinical signals from the background 'noise'. The laboratory does not know all the patient's details. Clinicians should consider test results in the context of the clinical presentation and not rely completely on the laboratory's interpretation.

Reference ranges

Quoted reference ranges depend on the method used in the laboratory, and the population from which the reference range was derived. The results from one method may be systematically different from those of another and therefore the reference ranges will be different.

Some laboratories give the range quoted by the manufacturer of the test or derived from an easily accessible population such as blood donors. Others give ranges in terms of age, sex or biological phase. For example, the ranges quoted for female sex hormones are related to pre- and post-menopausal status and the phase of menstrual cycle. Some important biological influences, such as seasonal effects on 25-hydroxyvitamin D, are often not included in the reference ranges. Perhaps this is because users would find it harder to interpret results if the reference ranges were changing all the time and because of the logistics and laboratory workload needed to derive such specific reference ranges.

The ideal reference range would relate to the individual being tested while healthy, at the same age, biological phase and in the same season. Clearly this is not possible, but sometimes one gets insights from looking back through previous results (ideally reported by the same laboratory using the same method).

By tradition, laboratories quote a reference range including 95% of the reference population. If results are normally distributed, this includes results within approximately two standard deviations above and two standard deviations below the mean value. The reference range therefore covers four standard deviations. Some results vary so much within the population that the laboratory may quote a reference range that includes a smaller proportion of the population. For example, the reference range commonly quoted for serum insulin may only include results within one standard deviation above and one standard deviation below the mean value. This includes 68% of the reference population. In this case, 16% of normal people will have 'abnormal' high insulin and 16% will have 'abnormal' low insulin according to the quoted reference range. Serum insulin is therefore not a useful test for assessing 'insulin resistance'.

Results have to be interpreted in terms of the particular laboratory reference range. When monitoring results over time, clinicians also need to be aware that different laboratories will have different reference ranges.

As reference ranges are population-based, a patient might have a result near the top or bottom of the normal range. Clinically significant changes could then occur, without the results moving out of the population reference range. For example, if an elderly patient's plasma creatinine concentration is usually near the bottom of the reference range but then rises to the upper end of that range, the patient may have had a significant deterioration in renal function. Similar considerations apply to a haemoglobin concentration falling from a high normal to a low normal value.

Table 1

Abnormal laboratory results caused by incorrect collection and handling †

Step	Mechanism	Result	Measurement affected
Sample	Incorrect sample	Incorrect results	For example, random spot urine calcium:creatinine ratio instead of first voided
Venepuncture	Prolonged venostasis	Plasma filtration and concentration	Protein concentrations – globulins, albumins and lipoproteins and measurements affected by them (e.g. calcium)
	Difficult venepuncture	Haemolysis	Red cell leakage with high potassium, phosphate and lactate dehydrogenase
Specimen tube	Incorrect collection tube	Incorrect results	
		Assay added analyte	Lithium heparin anticoagulant – lithium assay
			If potassium EDTA used for chemistry – potassium assay
		Assay interference	If potassium EDTA used for chemistry – assays for calcium and enzymes (calcium binding and enzyme inhibition)
Specimen handling	Delay in transport	Red cell use of glucose and leakage of contents	Blood glucose (if fluoride tube not used). Potassium, phosphate, lactate dehydrogenase
Laboratory	Specimen mislabelling	Incorrect results	Virtually everything
	Machine malfunction		
	Transcription error		

† Derived from reference 1

Specimen collection and handling

Laboratory results can be affected by the procedures for specimen collection and handling (Table 1).[1] If a result is a surprise, check the patient's name and date of birth on the result report. You can also contact the laboratory and ask if the specimen looked normal and consider repeating the test.

Why normal people often have abnormal results

A multiple biochemical analysis can be performed by one machine and produce 20 results. Assuming these results were all independent of each other (which they are not) and that results from the reference population are normally distributed (which they may not be), only 36% of normal people will have all 20 results in the reference range. There will be 64% with at least one abnormal result (Box 1). However, the more abnormal the result and the more related tests are abnormal, the more likely the abnormality is clinically significant.

If you consider the 99% reference range (approx. ± 2.6 standard deviations) and the 99.9% reference range (approx. ± 3.3 standard deviations), 82% and 98% of people will have all 20 tests within the reference range (0.99^{20} and 0.999^{20} respectively). These facts can be useful when interpreting an isolated abnormal result.

For example, the reference range of alkaline phosphatase is 30–110 U/L. This covers two standard deviations below the mean and two above the mean. One standard deviation is therefore 20 U/L [(110–30) ÷ 4]. A result of 150 U/L is two standard deviations above the upper limit of the reference range and therefore four standard deviations above the mean. This is very unlikely to occur in a normal individual. However, the result may be normal if the quoted reference range is inappropriate. For example, in pregnancy and growing children alkaline phosphatase is produced by the placenta and bone. These are good examples of why it is important to consider whether the population reference range is appropriate for the individual being tested.

Box 1

Normal results in normal people

If the reference range covers 95% of results for a normal population, the chance of a healthy individual having a certain number of normal tests is:

- Two out of two tests 90% (0.95 x 0.95 = 0.90)
- All 20 of 20 tests 36% (0.95^{20})

When deciding if a result is abnormal, look at related tests. Alkaline phosphatase is one of the 'liver function tests' (others are bilirubin, gamma glutamyl transferase, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase). Abnormalities in the other tests would suggest that the abnormal alkaline phosphatase could be the result of liver disease. An elevated alkaline phosphatase in isolation may indicate another problem, such as bone disease.

Laboratory accuracy

We often know the within-laboratory, within-method variability as this is usually quoted by the laboratory. Modern laboratories provide remarkably consistent results for many analytes – typical coefficients of variation (see Box 2) are 1–6% for the components of multiple biochemical analysis, electrolytes, calcium and phosphorus, and renal and liver function tests.

Box 2

Coefficient of variation

The coefficient of variation (CV) is calculated as:

$$CV = \frac{\text{standard deviation of the measured value}}{\text{mean value}} \times 100$$

Variability is different at different absolute values of the measurement and is usually quoted at a specific clinically relevant value. For example:

CV for plasma sodium	0.8% at 139 mmol/L
CV for plasma bilirubin	6.1% at 10 micromol/L

The coefficient of variation is one way of expressing the variability of biological measurements. Laboratories sometimes also refer to the imprecision of a measurement.

National quality control programs monitor the accuracy and imprecision of different methods used in different laboratories. One result has been that the differences between laboratories for individual methods are now usually a small component of the overall variability of measurements.

Why values vary within one individual

In addition to the variations caused by specimen collection and handling and the differences within and between laboratories and their methods, there is intra-individual variation. Assuming specimen collection and processing errors do not occur, the largest source of variability is within the individual. Values vary by age, sex and within the menstrual, diurnal and seasonal cycles. Intra-individual biological variability for different analytes can range from very large to moderate, for example, 8% for total cholesterol[2] versus 40% for microalbuminuria[3] assessed by the albumin:creatinine ratio. In addition, the longer the interval between tests, the greater the total intra-individual variability of the measure.

It is much more difficult for laboratories to provide information on the total intra-individual variability than for the within-laboratory, within-method variability which is automatically generated by their quality control programs. However, it is the total variability within an individual which is important when interpreting results.

Are changes in results caused by intra-individual variability or the effects of treatment?

One trap is the phenomenon of 'regression to the mean'.[4] Results within an apparently homogeneous group of patients are likely to lie within the 95% reference range for that measurement. If the same patients are retested at a different time, the pattern of the overall results will look much the same. In a normal distribution, values are bunched around the group mean and progressively 'thin out' further from the mean. However, individual results are likely to have changed, particularly those at the extremes.

Box 3

Least significant change

1. The overall variability of the difference between two measurements is greater than the variability of the individual measurements: $\sqrt{2}\ CV_i$ *
2. The more confident one wishes to be that the change in a measurement is a signal rather than noise, the greater the change needs to be relative to this: $\sqrt{2}\ CV_i \times z$

   The z value is used to refer to normally distributed values and describes the distance of a particular value from the mean in numbers of standard deviations (SD). The greater the distance from the mean (the z value) the less likely a result has occurred by chance.

   z varies from 1.28 for 80% confidence to 2.6 for 99% confidence.
3. Generally 80% confidence is used (z = 1.28):

   Least significant change = $\sqrt{2}\ CV_i \times 1.28 = 1.8\ CV_i$
   This approximates to $2CV_i$

CV_i Intra-individual coefficient of variation

* For explanation of the variability of the difference between two measurements, see extended Box 3 in this article online at www.australianprescriber.com/magazine/32/2/43/6.

The initial results at the extremes are the result of extreme random variability in one direction or the other. The same amount and direction of variability is unlikely to occur on the second measurement in the same individual. Subsequent measurements will therefore move closer to the middle (or 'regress to the mean'). Results from other individuals who initially were closer to the mean may now lie closer to the extremes of the distribution.

This phenomenon can be exploited intentionally or unintentionally in trials that select and treat individuals with high values of a measurement to demonstrate that a treatment is effective. 'Regression to the mean' is one reason why randomised placebo-controlled prospective trials are the gold standard for assessing treatments.

A large difference between two measurements is more likely to be a signal of a true change than the result of the background noise of measurement variability. Similarly, the smaller the total intra-individual variability, the more likely a specific absolute change is a signal. The less likely the observed change is caused by variability, the surer one can be that the change is real.

These three elements are brought together in the concept of the least significant change. To be 80% confident the observed change is real, the change should exceed approximately twice the intra-individual coefficient of variation (CV_i) (Box 3). For example:

- A total cholesterol which decreases from 7.0 to 5.6 mmol/L, after starting a statin, is a 20% fall from the initial value. The CV_i for total cholesterol is 8% so the least significant change

is approximately 16% ($2CV_i$). You can be 80% sure that the 20% change is real rather than apparent.

- A decrease in microalbuminuria from an albumin:creatinine ratio of 5.0 to 2.0 mg/mmol, after starting an ACE inhibitor, is a 60% fall. The total CV_i of the albumin:creatinine ratio is 40% so the least significant change is approximately 80% ($2CV_i$). It is likely that this 60% change is apparent rather than real.

The effects of treatment on measurements may be delayed

Laboratory results may take a long time to change after starting treatment. This may reflect pharmacokinetics, biology or a combination of the two.

The half-life of thyroxine in the body is approximately seven days. Testing after one week will only show half the expected total effect. (This may sometimes still be useful information.) By six weeks (six half-lives in this case) 98.4% of the effect will have occurred [$1 - (½)^6$].

When starting a thiazolidinedione (glitazone) the full effect on blood glucose requires a steady state of the glitazone (pharmacokinetic) but also requires the shift in fat metabolism which in turn causes the reduction in glucose (biologic). Finally, the glycated haemoglobin (HbA1c) reflects the average blood glucose over the preceding 4–6 weeks because of the slow turnover of the red cells (biologic and pharmacokinetic).[5] The combination of these factors means that testing after one week of treatment may show little change in the HbA1c which may take 2–3 months to show the full effect of treatment.

Another glycated protein (albumin, which becomes fructosamine) has a much faster turnover. It therefore reflects the average glucose over a shorter period (2–3 weeks).

One can reduce the variability of the measurement change by reducing the variability of the baseline and final measurements (for example, the mean of two measurements for each). If both initial and final measurements were repeated the variability of the change would be reduced to CV_i (not $\sqrt{2}\ CV_i$).

Using the microalbuminuria example, with two measurements before and after the intervention, the least significant change would be 51% (1.28 x 40%). You could then be 80% sure that the 60% observed change was real and not apparent.

Recommendations

When interpreting laboratory results it is important to know that the sample was collected and handled correctly. The appropriate reference range for the test should be used. Different laboratories may report different results on the same specimen.

When comparing results over time, use the same laboratory and method for testing. Consider the variability of results within the individual and the least significant change. This is the amount of difference between measurements that is likely to be a real biological 'signal' instead of resulting from the noise of biological variability within the individual and within the end measurement variability within the laboratory. As a rough rule, the least significant change is twice the intra-individual coefficient of variation ($2CV_i$).

If an important clinical decision depends on whether a change occurs with a particular treatment, consider making two (or more) measurements before and after starting treatment. This reduces the variability and the possibility of misinterpreting the regression to the mean of an initial high or low value. Monitoring trends with time involves more measurements and gives a more reliable indication of change than a single comparison at two points.

Remember, the more tests you do the more likely you are to get at least one 'false positive' outside the laboratory reference range. Aim to limit the number of tests to those that are relevant to the clinical situation rather than requesting a screening battery.

When assessing the effects of treatment, consider how long the treatment will take before the therapeutic effect reaches a steady state (e.g. 4–6 half-lives of a drug) and how long the biological response will take before the measurement you make reaches a steady state. Trying to assess therapeutic effects before treatment and response have reached a steady state can seriously underestimate the therapeutic effect.

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Conflict of interest: none relevant to this article

Self-test questions

The following statements are either true or false (answers on page 55)

7. A laboratory result which is two standard deviations from the population mean is always abnormal.
8. If treatment reduces a patient's total cholesterol by 5% the change is significant.

Surrogate outcome markers in research and clinical practice

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Summary

A surrogate measure or marker aims to predict a clinical outcome or prognosis. Surrogates are often used in drug or therapeutic intervention trials as they reduce the size, duration and cost of the study. Surrogates are commonly used as trial end points and often become the standard by which new drugs gain regulatory approval for marketing. The surrogate marker should be able to reliably predict an effect of the drug or intervention on the long-term clinical outcome. Surrogate markers should be validated in longer term trials to confirm their association with the clinical outcome. They should not be adopted as true markers of disease in the absence of evidence of their validity. Clinicians should manage the whole patient and not just their surrogate markers.

Key words: clinical trials, drug regulation.

(Aust Prescr 2009;32:47–50)

Introduction

> A surrogate end point, or marker, is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy.
>
> US Food and Drug Administration[1]

The essential feature of this definition is the strong association between the marker and the clinical end point or outcome. The effect of a treatment on a surrogate marker must reflect its effect on the clinical outcome.[2] For example, a drug which reduces intraocular pressure will reduce loss of vision in patients with glaucoma.

The cost and time constraints of large clinical trials make surrogate markers an attractive proposition in research. Many new drugs gain approval by showing positive effects on surrogate measures that have been previously accepted as markers of a particular disease, for example, the concentration of low density lipoprotein (LDL) cholesterol as a marker of cardiovascular disease. While some surrogates achieve acceptance in clinical practice as markers of disease, based on the results of phase III trials[3], others are adopted even though they have little correlation with the progression of disease (Table 1).

Table 1

Surrogate markers often used in clinical practice

Generally accepted as valid		Doubt still exists about validity	
Surrogate marker	**Predicts**	**Surrogate marker**	**Predicts**
HbA1c	Diabetic microvascular complications	HbA1c	Diabetic macrovascular complications
FEV_1	Mortality in chronic obstructive pulmonary disease	Bone mineral density	Fracture risk
Blood pressure	Primary and secondary cardiovascular events	Prostate specific antigen	Prognosis of prostate cancer
Viral load	Survival in HIV infection	Suppression of arrhythmia	Long-term survival
Cholesterol concentration	Primary and secondary cardiovascular events	Carotid intima-media thickness	Coronary artery disease
Intraocular pressure	Visual loss in glaucoma	Albuminuria	Cardiovascular events

HbA1c glycated haemoglobin
FEV_1 forced expiratory volume in one second

Reliable surrogates in clinical practice

Reducing a patient's blood pressure is a well accepted risk reduction strategy for the primary and secondary prevention of cardiovascular events. The relationship between blood pressure (the surrogate marker) and the risk of cardiovascular events is continuous and independent. Drugs that reduce blood pressure significantly more than other drugs consistently show better results in clinical outcome trials. The relationship is considered so strong that we presume a drug will reduce future cardiovascular events if it effectively controls blood pressure.

One of the most reliable of all surrogate measures is the intraocular pressure in glaucoma. There is a strong correlation between increasing intraocular pressure and the clinical end point of visual loss. Any drug which lowers intraocular pressure will reduce the risk of visual loss.[4]

Forced expiratory volume in one second (FEV_1) as a percentage of the predicted volume is used for prognosis in chronic obstructive pulmonary disease (COPD). Interventions that slow the rate of deterioration of FEV_1 are considered the most clinically useful treatments for patients with COPD. There is good long-term evidence to support the utility of this measure.[5,6]

Surrogate markers in clinical trials

In phase II trials[3], surrogate markers provide interim measures of interventions and thereby predict whether longer term, more extensive and costly phase III trials are worthwhile. There is great interest in markers that allow researchers to make predictions of drug effects or disease progression by extrapolating short-term results to long-term clinical end points. Studies frequently make use of these markers rather than clinical outcomes. Surrogate markers can be used to monitor disease control, for example glycated haemoglobin (HbA1c) as a marker of diabetes control. They can also be used to determine disease prognosis, for example increased viral load and decreased CD4 cell count as a predictor of progression to AIDS in patients infected with HIV. Other markers are used to determine the risk of developing a separate outcome, for example, blood pressure and the risk of adverse cardiovascular events.

While surrogate markers are useful for reducing the duration of studies, the translation of results from trials involving one drug to trials of another drug is likely to be invalid unless the marker has been shown to be valid in multiple different trials.[7] However, surrogate markers are frequently used in drug comparison studies. Improvements in surrogate markers may be accepted by drug regulatory authorities as evidence that one drug is more efficacious than another.

Validating surrogate markers

The only way to properly validate potential surrogate markers is through stringent examination in phase III clinical trials. The primary end point then needs to be a relevant clinical event. Final evidence of a strong association is shown through consistent performance of the marker in meta-analyses of multiple phase III trials.

There are criteria which define the validity of surrogate markers.[8] Although these are controversial[7], they provide a useful framework on which to base a model for surrogate markers. The ideal situation is one in which the surrogate lies directly in the causal pathway to the clinical end point and the drug or intervention has a predictable and direct effect on both the surrogate and the clinical end point.

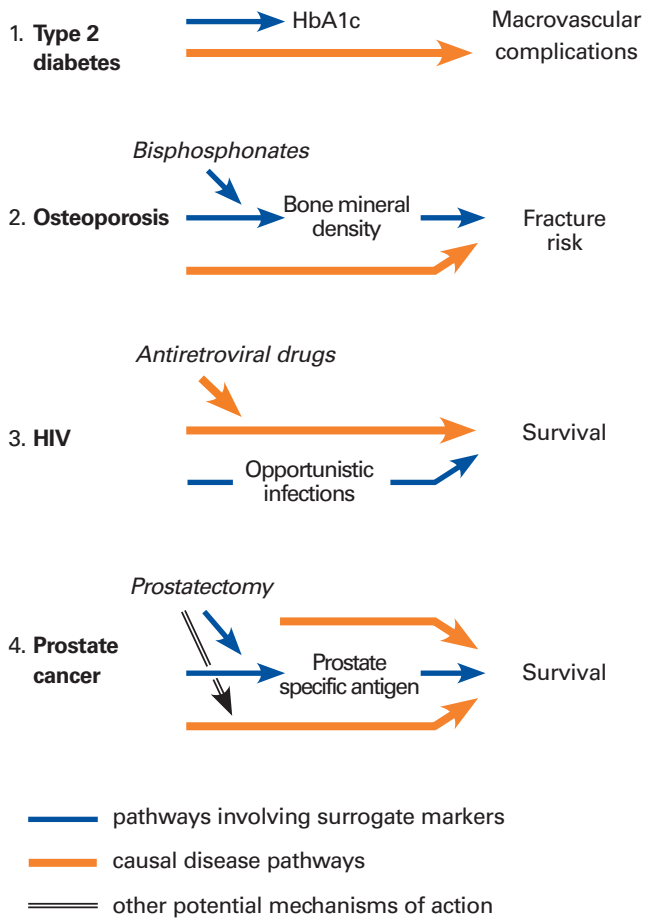
Perhaps more useful is an explanation of how surrogates fail to predict clinical end points. There are four possibilities (see Fig. 1).[2]

1. The surrogate may not be in the causal pathway of the disease, therefore any effect of the drug or intervention on the surrogate has no effect on the clinical end point. For example, the mechanisms leading to the development of macrovascular complications in type 2 diabetes may not involve HbA1c.
2. There may be several causal pathways, of which the surrogate is one, and the drug or intervention may affect only the surrogate without affecting the true clinical end point. For example, improvement in bone mineral density with bisphosphonates may not be a reliable predictor of fracture risk because reduced bone mineral density is not the only reason for the increase in risk.
3. The surrogate may be involved in the causal pathway of the disease but be unaffected by the drug or intervention. In patients with HIV, the incidence of opportunistic infections may not be reduced by a specific antiretroviral drug even though the drug improves prognosis.
4. The drug or intervention has effects independent of the disease and may or may not affect the surrogate or clinical end point. For example, prostatectomy may influence survival in prostate cancer via a pathway for which prostate specific antigen is a marker, but also via mechanisms independent of that effect. This makes the measurement of prostate specific antigen unreliable as a sole prognostic marker.

An example of a surrogate marker which may not be causally related to clinical outcome is the thickness of the walls of the carotid artery. A proven reduction of intima-media thickness seen on ultrasound has been suggested as a surrogate marker for the success of drugs in reducing overall cardiovascular risk. However, concerns have been raised about the reliance on changes in one area of the carotid and the inference that this reflects changes in other vascular areas. Measuring changes in the media may be a poor substitute for a disease process that occurs primarily in the intima. The changes in intima-media thickness induced by 'statins' cannot necessarily be extrapolated to effects produced by other drugs.

Fig. 1

Examples of failure of surrogate end points to reliably predict true clinical outcomes [2]



1. Glycated haemoglobin (HbA1c) may not be in the causal pathway of macrovascular disease.
2. Bisphosphonates affect only the bone mineral density but there may be other causal pathways.
3. Antiretroviral drugs alter survival by effects independent of the number of opportunistic infections.
4. Prostatectomy for prostate cancer has mechanisms of action including but also in addition to the pathway affecting prostate specific antigen.

Surrogates and safety

Surrogate markers may have implications for safety because they may be unaffected by the adverse effects of an intervention. The ILLUMINATE trial in cardiovascular disease was stopped because there was higher mortality with the study drug (torcetrapib) even though it was effective at reducing LDL cholesterol.[9]

The use of a surrogate marker in a short-term study using relatively small numbers of patients may not reveal rare adverse effects, whereas a longer, larger phase III trial would be more likely to detect these events. This risk may be further increased if these surrogates move from research to clinical practice. Unless there is a strong correlation between the surrogate and the clinical outcome, clinicians should focus on treating the disease, not just the surrogate marker.

The risk of translating surrogate markers to clinical practice

Even if an intervention has an effect on a surrogate marker and that marker is clearly in the causal pathway of the clinical end point, the effect may not persist long enough for the drug to alter the long-term clinical outcome. The drug may seem to be efficacious because of its short-term effect on the surrogate marker, but have no effect on the clinical outcome.

There is evidence that LDL and total serum cholesterol are valid markers or 'risk factors' for cardiovascular outcomes, based on a number of well validated long-term studies. However, there is doubt about whether a reduction in LDL or total cholesterol over a short period of time will predict the long-term effect and therefore outcome. An example of this would be when a new drug is shown to be more effective than another at lowering LDL cholesterol over 16 weeks and the result is extrapolated to imply a greater reduction in the long-term risk of cardiovascular events.

A recent example is the ENHANCE trial.[10] Although the combination of ezetimibe and simvastatin lowered LDL cholesterol over a two-year period, there was an increase in the carotid intima-media thickness. The trial relied on the combination of one well accepted (LDL cholesterol) and one controversial (intima-media thickness) surrogate marker to show the drug's effect. One of the many questions raised by this study is whether a reduction in intima-media thickness will translate into a reduction in cardiovascular events. This question will remain until the results of larger phase III trials are available.

Questions remain as to the utility of bone mineral density in predicting fracture risk. The major problem seems to be establishing a threshold level for acceptable risk in a condition which has multiple contributing risk factors such as age, sex, smoking history and alcohol intake. The introduction of bisphosphonates and how much benefit can be gained, based solely on changes in bone mineral density, is difficult to determine for an individual.[11,12] The restriction of bisphosphonate use, at least in Australia, to those who have sustained a fracture may seem overly cautious but might be the most reasonable way to attribute individual risk because of the poor individual correlation between bone mineral density and risk of fracture.

Conclusion

Surrogate markers are born of phase II trials and are not necessarily ideal for use in clinical decision making. Phase III trials should be the true testing ground for the validity of

surrogate markers. There are some valid surrogate markers of disease progression which can be reliably used to monitor chronic conditions, and as treatment goals. However, the clinical utility of many surrogates is open to question and their validity is largely untested. Practitioners need to keep in mind that some widely used surrogate markers of disease have not been adequately validated for use in clinical situations. A disease may be associated with a surrogate marker, but this does not mean that treating the marker will improve the outcome of that disease.

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Conflict of interest: none declared

Treatments for severe psoriasis: update

In March 2009 it was announced that efalizumab would be withdrawn from the Australian market. This follows a review of the drug in Europe which found the benefits no longer outweigh the risk of harm. There are reports of progressive multifocal leucoencephalopathy arising in patients who have been treated with efalizumab for more than three years.[1] The drug has also been under review in the USA.[2]

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Comment from Dr JR Sullivan and Dr V Preda, the authors of an article about treating severe psoriasis recently published in Australian Prescriber (Aust Prescr 2009;32:14–18):

For rare side effects it takes a number of years of post-marketing surveillance for a signal to appear. This can take longer for therapies with only a single therapeutic indication such as efalizumab. This drug has only been used in 46 000 patients worldwide.

The tumour necrosis factor-alfa antagonists, infliximab and etanercept, for psoriasis have been used for a number of clinical indications over a much longer period. We have 15 years of patient safety data and over 1.4 million patient years and 630 000 patients with etanercept, and 15 years of patient safety data and 4.3 million patient years and 340 000 patients with infliximab. For these two drugs much more is known about their longer-term safety profiles.

The use of biologicals for the treatment of severe psoriasis needs to be considered in light of the safety profile of each drug and also in the context of the individual patient. Biologicals are not only used in severe psoriasis but also for a number of other disorders. Thus with regard to safety data we can benefit from the experience with these medications used in other specialties such as rheumatology and gastroenterology. From rheumatology we know to screen for tuberculosis before starting therapy to help prevent potentially serious infections. Although adverse effects are often grouped together as a class effect, it is important to consider each biological drug individually as they have their own unique pharmacological profiles.

New drugs

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

Dabigatran etexilate

Pradaxa (Boehringer Ingelheim)

75 mg and 110 mg capsules

Approved indication: prevention of postoperative venous thrombosis

Australian Medicines Handbook section 7.1

Patients who have had major surgery on their legs are at risk of venous thrombosis. This risk can be reduced by anticoagulation with a heparin or an alternative such as fondaparinux. A disadvantage of these drugs is that they have to be given by injection, so patients may not continue them after leaving hospital. An oral anticoagulant, without the disadvantages of warfarin, might improve the effectiveness of prophylaxis.

Dabigatran is a direct inhibitor of thrombin which can be taken orally as a prodrug (dabigatran etexilate). By inhibiting thrombin, it blocks the conversion of fibrinogen to fibrin and thus reduces clot formation. It is given 1–4 hours after surgery.

In healthy people dabigatran etexilate is rapidly absorbed and converted to dabigatran. Absorption is slower initially in postoperative patients, but subsequently peak plasma concentrations of dabigatran are reached two hours after a dose. The half-life, 12–14 hours, is also slightly longer after surgery. Treatment begins with half the ongoing dose. Most of the dose is excreted as dabigatran in the urine. People with reduced renal function, such as some elderly patients, may require a lower dose. If the creatinine clearance is under 30 mL/min, dabigatran is contraindicated.

A double-blind trial has compared dabigatran etexilate (220 mg and 150 mg daily) with a daily dose of subcutaneous enoxaparin 40 mg in 3494 people having total hip replacements. Treatment continued for 28–35 days until the patients had venography. However, many patients did not have venography so efficacy could only be assessed in 2651 patients. Death or venous thromboembolism occurred in 8.6% of the patients taking dabigatran 150 mg, 6% of those taking 220 mg and in 6.7% of the patients injected with enoxaparin.[1]

The same drugs and doses were used in a study of 2076 patients having total knee replacements. Treatment continued for 6–10 days. As some patients did not have venography, efficacy was assessed in 1541 patients. Death or venous thromboembolism occurred in 40.5% of the patients taking dabigatran 150 mg, 36.4% of those taking 220 mg and 37.7% of the enoxaparin group.[2]

Bleeding is a major concern when anticoagulants are used following surgery, and there is no antidote for dabigatran. After hip replacement, significant bleeding occurred in 1.3% of the dabigatran 150 mg group and 2.0% of the 220 mg group. This was fatal for one patient in each group. In the enoxaparin group 1.6% of patients had significant bleeding, but there were no fatalities.[1] After knee replacement the incidence of major bleeding was 1.5% in the dabigatran 220 mg group and 1.3% in the 150 mg and enoxaparin groups.[2] To reduce the risk of a haematoma forming, dabigatran should not be given for at least two hours following the removal of a spinal or epidural catheter.

Common adverse effects include nausea, vomiting, fever and constipation, but they occur irrespective of the treatment used. Routine monitoring is not required, but liver function should be checked before treatment as liver disease is a contraindication to dabigatran. Drugs which act on the P-glycoprotein transporter may alter the plasma concentration of dabigatran. These drugs include amiodarone, verapamil, clarithromycin and St John's wort. Quinidine is contraindicated. Anticoagulants and antiplatelet drugs such as clopidogrel are not recommended while the patient is taking dabigatran. Doses of aspirin above 75 mg daily increase the risk of bleeding. Non-steroidal anti-inflammatory drugs (NSAIDs) can be used for short-term analgesia, but there may be an increased risk of bleeding particularly if the NSAID has a long half-life.

The main studies of dabigatran have shown that it has similar efficacy to enoxaparin, however an American study found inferior efficacy. In the USA prophylaxis can be given as enoxaparin 30 mg twice daily. The study of 1896 patients having knee replacement found venous thromboembolism in 31–34% of the patients taking dabigatran but in only 25% of those given enoxaparin.[3]

The development of the first direct thrombin inhibitor, ximelagatran, was halted because of concerns about adverse effects on the liver. Hepatotoxicity has not yet emerged as a significant problem with the relatively short-term use of dabigatran. If its safety and efficacy are confirmed in more widespread use, oral dabigatran may be a cost-effective alternative to subcutaneous low molecular weight heparins.

 manufacturer declined to supply data

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Daptomycin

Cubicin (Novartis)

lyophilised powder for injection

Approved indications: skin infections, *Staphylococcus aureus* bacteraemia

Australian Medicines Handbook section 5.1

Daptomycin is a cyclic lipopeptide derived from a natural product of *Streptomyces roseosporus*. Its bactericidal effects stem from its ability to rapidly depolarise the membrane potential of Gram-positive bacteria. This causes inhibition of DNA, RNA and protein synthesis, and results in cell death.

It is indicated for adults with complicated skin and skin structure infections who require initial parenteral therapy and who are intolerant of alternative antibiotics (including those with penicillin allergy). It should only be used for infections suspected to be caused by susceptible Gram-positive bacteria.

Steady-state concentrations of daptomycin are reached after the third daily intravenous infusion. It is primarily excreted by the kidneys (mainly as unchanged drug) so dose adjustment is required for patients with severe renal insufficiency. Renal function and creatine kinase should be frequently monitored in these patients. In patients requiring haemodialysis, daptomycin should be administered after the procedure.

The efficacy of daptomycin (4 mg/kg intravenously once daily for 7–14 days) has been compared to a penicillin (cloxacillin, nafcillin, oxacillin or flucloxacillin) or vancomycin in two randomised trials with similar designs totalling 1092 participants. These patients were hospitalised mainly with complicated skin infections including wound infections, major abscesses, infected diabetic ulcers or other ulcers. Patients with mixed infections involving Gram-negative or anaerobic organisms were given concomitant aztreonam or metronidazole as appropriate. Among the clinically evaluable patients, treatment success rates for daptomycin were comparable to the comparator (83% vs 84%). However, in both groups success rates for methicillin-resistant *Staphylococcus aureus* infections were lower than for methicillin-sensitive *S. aureus* (75% vs 86% for daptomycin and 69% vs 87% for comparator). Success rates were also lower in patients aged 65 years or older.[1]

In another analysis of the trials looking only at patients with diabetic ulcers (mainly of the foot), 66% (31/47) of clinically evaluable patients benefited from daptomycin treatment compared with 70% (39/56) of patients treated with a penicillin or vancomycin. Methicillin-resistant *S. aureus* was isolated from ten patients; one received daptomycin and the rest received a comparator. After a course of treatment, infection was cleared in three of the comparator-treated patients but not in the daptomycin-treated patient.[2]

Adverse events were similar between groups with gastrointestinal disorders being the most common. Fifteen of the 534 patients (2.8%) receiving daptomycin developed elevated creatine kinase levels compared to ten of the 558 (1.8%) receiving the comparator.[1]

In Australia, daptomycin has also been approved for adults with bacteraemia caused by *S. aureus*, including those with right-sided native valve infective endocarditis caused by methicillin-susceptible or methicillin-resistant isolates. This approval was based on an open label randomised trial of patients with bacteraemia with or without left- or right-sided endocarditis. Daptomycin (6 mg/kg intravenously once daily) was compared to standard treatment consisting of gentamicin plus a penicillin (nafcillin, oxacillin or flucloxacillin) or vancomycin. (Patients in the daptomycin group who had left-sided endocarditis were also given gentamicin for the first four days.) The median duration of therapy was 14 days for daptomycin and 15 days for standard treatment.

Successful outcomes were reported in 53 of 120 (44%) patients receiving daptomycin and 48 of 115 (42%) patients receiving the comparator. In patients infected with methicillin-resistant isolates, success rates were similar for daptomycin but lower with standard treatment (44% vs 32%). Treatment failure was more often associated with persistent or relapsing *S. aureus* infection in the daptomycin group (15.8% of patients), whereas in the comparator group failure was more frequently associated with treatment-limiting adverse events. Therapy failed in all nine patients who had left-sided endocarditis caused by methicillin-resistant *S. aureus*, regardless of which treatment they received.[3]

Creatine kinase elevations were twice as common with daptomycin than with standard treatment (25% vs 12.5%). Adverse events related to the peripheral nervous system were also more common with daptomycin than with standard treatment (9.2% vs 1.7%), whereas renal impairment was more common with standard treatment than with daptomycin (18.1% vs 6.7%).[3]

Patients should be monitored for the development of muscle pain or weakness. Creatine kinase should be monitored weekly and more frequently in patients who have a higher risk of developing myopathy, such as those with severe renal insufficiency or taking other drugs that are associated with myopathy (HMG-CoA reductase inhibitors, fibrates, cyclosporin). Consider temporarily stopping HMG-CoA reductase inhibitors while patients are receiving daptomycin.

In patients taking concomitant warfarin, anticoagulant activity should be monitored during the first week of daptomycin therapy. Caution is urged when co-administering daptomycin with tobramycin.

Daptomycin-resistant bacteria have emerged in patients enrolled in the clinical trials. To reduce the development of daptomycin resistance, this antibiotic should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. Daptomycin does not seem to be effective for infections caused by enterococci, including *Enterococcus faecalis* and *E. faecium*. Susceptibility of bacterial isolates should be monitored during the course of treatment.

Daptomycin provides another option for hospitalised adults with serious infections caused by Gram-positive pathogens. However, its efficacy may be lower in older adults. It can also be used for mixed infections involving Gram-negative or anaerobic bacteria if co-administered with appropriate antibiotics.

This antibiotic is not effective for left-sided endocarditis, or for pneumonia because it binds to surfactant and is inactivated. The efficacy of daptomycin in patients with prosthetic heart valves has not been demonstrated.

T manufacturer provided only the product information

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Etravirine

Intelence (Janssen-Cilag)

100 mg tablets

Approved indication: HIV

Australian Medicines Handbook section 5.4

Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). It binds to reverse transcriptase and blocks the RNA- and DNA-dependent activities of DNA polymerase. Etravirine is indicated for treatment-experienced adults with HIV who have evidence of viral replication and drug resistance to other antiretroviral drugs including NNRTIs.

The approval of etravirine is based on two identically designed randomised placebo-controlled trials (DUET-1 and DUET-2) in patients with advanced disease. These patients were resistant to currently available NNRTIs and had at least three primary mutations to protease inhibitors. All patients received darunavir (a protease inhibitor) boosted with ritonavir, as well as at least two other antiviral drugs. At the beginning of the studies the average viral load in enrolled patients was 70 000 copies/mL blood. The main measure of effectiveness for etravirine was the number of patients with less than 50 viral copies/mL. After 24 weeks of treatment, 59% (353/599) of patients who added etravirine (200 mg twice daily) had less than 50 viral copies/mL compared to 41% (248/604) of patients who added placebo. The mean increase in CD4 cells was 84 cells/microlitre in the etravirine groups and 65 cells/microlitre in the placebo groups. Using other active antiretroviral drugs with etravirine increases the likelihood of treatment response.[1,2]

The trials are ongoing and preliminary results presented at a conference reported that response rates to etravirine were maintained after 48 weeks of treatment (www.retroconference.org/2008/PDFs/790.pdf and www.retroconference.org/2008/PDFs/791.pdf). The total duration of the trials is expected to be 96 weeks.

Resistance to NNRTIs can develop easily. A single mutation in the reverse transcriptase gene of the virus can lead to reductions in susceptibility, often to all currently available inhibitors in the class. This broad cross-resistance limits the sequential use of other NNRTIs after treatment failure. In the DUET trials, decreased susceptibility to etravirine emerged and was associated with a number of different viral mutations. Cross-resistance with etravirine and other NNRTIs was also observed. The majority of viral strains containing two or three mutations conferring NNRTI resistance also had decreased susceptibility to etravirine.

The most common adverse events with etravirine are rash (17%), diarrhoea (15%) and nausea (14%). Rash was the most common adverse event for which patients discontinued treatment in the DUET trials (2% for etravirine, 0% for placebo). Severe and potentially life-threatening skin reactions, including

Stevens-Johnson syndrome, hypersensitivity reactions and erythema multiforme, have occurred in patients taking etravirine. Treatment should be stopped if this occurs. Other common adverse effects of etravirine include abdominal pain, tiredness and high blood pressure. Neuropsychiatric events occurred in 25% of patients taking etravirine. Similar numbers of events were seen in the placebo group.

Patients who also had hepatitis B and/or hepatitis C were included in the DUET trials, providing they were clinically stable. The incidence of hepatic events (such as hepatobiliary disorders) tended to be higher in patients taking etravirine compared to those taking placebo (11% vs 6%).

This drug should be taken after a meal to increase its bioavailability. Following oral administration, the maximum plasma concentration of etravirine is reached by four hours. Although etravirine is primarily metabolised by the liver, no dose adjustment is needed for patients with mild to moderate liver impairment. Etravirine has not been studied in patients with severe liver disease.

As etravirine induces CYP3A4 and inhibits CYP2C9 and CYP2C19, co-administration of drugs that are metabolised by these enzymes may affect the therapeutic or adverse effects of etravirine. Many drugs may interact with etravirine, including combinations of other antivirals. Etravirine should not be co-administered with other NNRTIs and there are specific recommendations about giving etravirine with protease inhibitors. Other drugs which potentially interact with etravirine include antiarrhythmics, anticoagulants, anticonvulsants, antifungals, antibiotics, benzodiazepines, corticosteroids, statins, immunosuppressants, phosphodiesterase type 5 inhibitors and St John's wort. It is therefore important to obtain a full record of the patient's medications before prescribing etravirine.

Etravirine represents another option for patients infected with multi-resistant HIV strains, although decreased susceptibility to this drug has been observed. Long-term data are needed to assess how durable the observed responses are. The patient's treatment history and antiviral resistance testing should guide the use of this drug.

☒ manufacturer declined to supply data

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Nitisinone

Orfadin (Orphan)

2 mg, 5 mg and 10 mg capsules

Approved indication: hereditary tyrosinaemia type 1

Tyrosine is one of the amino acids involved in the synthesis of molecules such as dopamine and noradrenaline. The metabolic pathway for tyrosine includes the enzyme fumarylacetoacetase. In hereditary tyrosinaemia there is a deficiency of this enzyme leading to accumulation of its substrates. This causes liver failure, renal tubular dysfunction and neurological crises. In the acute form of the disease death usually occurs before the child is one year old. Children with chronic forms of the disease are at risk of liver cancer. They need to have a diet with a restricted tyrosine intake.

Nitisinone blocks an earlier step in the metabolism of tyrosine. By competitively inhibiting the enzyme hydroxyphenylpyruvate dioxygenase it is thought to reduce the production of the toxic substrates of fumarylacetoacetase.

As hereditary tyrosinaemia type 1 is a rare disease, one of the early studies of nitisinone only included five children. During 7–9 months of treatment plasma and urinary markers of the toxic metabolites declined and liver function improved.[1]

The approval of nitisinone was based on an international, uncontrolled study of 207 children. They were treated for a median duration of 22 months. The biochemical markers improved and there was some evidence of improved survival. The four-year survival was 93%, but only 35 patients were included in that analysis. (Death or liver transplantation resulted in the withdrawal of 37 patients.) Compared to the treatment of historical controls with diet alone, the probability of surviving for four years increased from 29–60% to 88–94%. The occurrence of liver cancer was reduced, particularly in children who began treatment before their first birthday. Starting treatment before six months of age appears to reduce the need for liver transplantation.

As nitisinone blocks the metabolism of tyrosine, the plasma tyrosine concentration will increase. The patient therefore still needs to follow a diet deficient in tyrosine. High concentrations of tyrosine can have toxic effects on the eyes, skin and nervous system.

Nitisinone was originally developed as a herbicide, but development stopped when animal studies found it had ocular adverse effects. Ophthalmological assessment is needed before treatment and if ocular symptoms develop.

Patients need regular blood counts because leucopenia and thrombocytopenia can occur. These abnormalities may be transient but may require a reduced dose of nitisinone.

The pharmacokinetics of nitisinone have not been studied in detail. There are also no drug interaction studies.

Although it may be a lifelong treatment, much remains unknown about nitisinone. While it improves survival, it may not ameliorate the complications of the disease.[2] At present, the benefits of nitisinone with a low tyrosine diet do appear to outweigh the harms in treating hereditary tyrosinaemia type 1.

[T] [T] manufacturer provided additional useful information

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The T-score ([T]) is explained in 'New drugs: transparency', Aust Prescr 2007;30:26–7.

T-scores are as follows:

[T] [T] [T] manufacturer provided clinical evaluation

[T] [T] manufacturer provided additional useful information

[T] manufacturer provided only the product information

[T] manufacturer declined to provide data

[X] manufacturer did not respond to request for data

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

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

Answers to self-test questions

1. True	3. True	5. False	7. False
2. False	4. False	6. True	8. False

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