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CONTENTS

Editorial

Have glitazones lost their sparkle?

Gillian M Shenfield, Clinical Pharmacologist, Sydney

Key words: adverse effects, cardiovascular disease, diabetes, osteoporosis, thiazolidinediones.

(Aust Prescr 2008;31:58–9)

'All that glitters is not gold' (proverb)

The safety of new drugs has never been as well established as pharmaceutical company promotions may suggest. Health professionals and consumers have become more aware of this with the removal of widely used drugs such as rofecoxib from the market. Now the thiazolidinediones, better known as 'glitazones', are under suspicion of causing serious, previously unsuspected adverse effects. Given these concerns, what can be said about the role of thiazolidinediones in third-line therapy of poorly controlled type 2 diabetes?

There are several reasons why previously undescribed adverse effects emerge after a drug is marketed. Before a new drug is registered for use it must undergo a rigorous series of clinical trials, but the total number of patients who have been given the drug rarely exceeds 3000 before it is marketed. Inevitably any adverse effect, for example liver toxicity, occurring in fewer than 1 in 1000 people may not be detected until the drug has been more widely used. Secondly, if the drug induces an increase in a common disease, such as myocardial infarction, the effect will only be detected by appropriately designed large trials or epidemiological studies. Thirdly, the duration of early clinical trials rarely exceeds a few weeks or months and the patients included are often atypical of the population which will take the new drug for many years. Finally and increasingly, many new drugs act on cell receptors which have numerous functions in addition to the one targeted by drug therapy. Altering one function may have unintended effects on others.

All these problems apply to the glitazones which work by stimulating the peroxisome proliferator-activated receptor gamma (PPARγ). These receptors exist in most body tissues, including arteries, and mediate numerous basic functions beyond their useful effects on fat redistribution and glycaemic control. Troglitazone, the first glitazone marketed, was withdrawn from the market because of deaths due to liver failure. A closely related drug, muriglitazar, which stimulates both PPARγ and alpha receptors, increased adverse cardiovascular events. It was withdrawn by its manufacturer after rejection by the US Food and Drug Administration (FDA). Pioglitazone and rosiglitazone, the two PPARγ agonists available in Australia, do not cause serious liver damage, but do induce weight gain, fluid retention and heart failure. One study found that over 40 months the incidence of heart failure was 8.2% in patients taking thiazolidinediones compared with 5.3% in a control group.[1] The drugs are therefore contraindicated in patients with heart failure (New York Heart Association class III or IV).

Recent data suggest further associations between glitazones, cardiovascular events[2] and peripheral limb fractures.[3] Pioglitazone and rosiglitazone have been associated with an increase in peripheral fractures in postmenopausal women, particularly in the humerus, hands and feet. There is also a study suggesting that rosiglitazone may reduce bone formation and density.[4]

A meta-analysis reported a significant increase in the risk of myocardial infarction with rosiglitazone and a trend towards increased risk of death from cardiovascular causes. (Compared with other treatments, the odds ratio with rosiglitazone was 1.43 for myocardial infarction and 1.64 for death from cardiovascular causes.[2]) These findings have been challenged on methodological grounds[5], but there is sufficient doubt to warrant caution with prescribing the drug for a vulnerable diabetic population already at high risk of having cardiovascular disease.[6] Current data suggest that pioglitazone may not

In this issue…

Often the excitement around the launch of a new drug is soon tempered by the emergence of problems in practice. Mark Boyd and Sarah Pett inform us that the uptake of enfuvirtide has been limited, and Gillian Shenfield considers the adverse effects of thiazolidinediones.

Sometimes a patient has to take a drug despite its serious adverse effects. Cecilie Lander tells us that this is a particular problem for pregnant women who need treatment for epilepsy.

Antiepileptic drugs are also used in bipolar disorders, but Ajeet Singh and Michael Berk say that lithium still has an important role.

Paracetamol and ibuprofen are also old drugs which remain widely used. Sean Beggs reviews how they compare when used to relieve pain in children.

increase cardiovascular events, but the reasons for this difference are unknown.

What are the implications of these findings for managing patients with poorly controlled type 2 diabetes? Firstly, all patients should be assessed for osteoporosis and fracture risk and managed appropriately. It would be wise not to start a glitazone in anyone known to have a history of fracture or significant osteoporosis.

In Australia, patients being considered for treatment with a glitazone will already be taking metformin, a sulfonylurea or both, and will have poor glycaemic control with or without symptoms. The aim of further lowering of blood glucose concentrations is to reduce the incidence of both macro- and microvascular disease. Even better outcomes can be achieved by additionally improving the control of blood pressure.[7] These goals should have a high priority in all patients, but are the glitazones the best way to achieve them? They have been shown to slow the progression of type 2 diabetes over four years[8], but this is only a surrogate measure for long-term outcomes.

The alternative therapy in these patients is insulin. This is as effective as the glitazones on surrogate measures such as glycaemic control and has been used in long-term studies showing a reduction in cardiovascular events. All patients eligible to start a glitazone should therefore be given the choice of taking insulin. Most are scared of injections and many doctors find the thought of starting insulin therapy daunting. Once persuaded to try, it is my experience that the majority of patients admit that insulin is much easier to use than they had feared.

In patients already taking one of the glitazones the first action should be to review how successful it has been. As 25–30% of patients have no significant improvement in glycaemic control after eight weeks, they should stop the glitazone and start insulin. Patients who have had a very good improvement in glycaemic control, and have no overt heart disease, could stay on the glitazone, but be advised about the problems and have strict management for other risk factors. The patients with an intermediate response need to have the pros and cons discussed, but should be advised of the known, long-term efficacy of insulin.

These evolving problems with thiazolidinediones reinforce the fact that new is not always better. We do not have all the answers so it will be necessary to modify prescribing as more information becomes available.

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Professor Shenfield is a member of the National Prescribing Service New Drugs Working Group which oversees the writing of NPS RADAR.

Medicine Update

Medicine Update, the consumer version of RADAR, is a new publication from the National Prescribing Service about medicines listed on the Pharmaceutical Benefits Scheme. While RADAR is written for health professionals, *Medicine Update* is written for consumers to help them ask the right questions about new medicines. Health professionals can use *Medicine Update* as a patient counselling resource when discussing or prescribing a new drug.

Consumers can find out how well a medicine works, its side effects, how it compares with other treatments, and who is likely to benefit most. *Medicine Update* is available online at www.nps.org.au/consumers

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.

Treatment of myasthenia gravis

Editor, – The article on myasthenia gravis (Aust Prescr 2007;30:156–60) made no mention of the role of pseudoephedrine (and perhaps other sympathomimetics), which are most useful in addressing ocular ptosis, when cholinesterase blockers fail.

Although the practice is 'off label', knowing about it can be quite eye-opening, especially for those who rely heavily on the official product information. Non-clinical pharmacists conducting home medication reviews will often query the drug, having no idea why it is being used.

Andrew Montanari
General practitioner
Tamworth, NSW

Dr Stephen Reddel, author of the article, comments:

Dr Montanari is quite correct that sympathomimetics including pseudoephedrine offer a mild improvement in myasthenic syndromes, just as adrenergic blockers such as beta blockers have a mildly deleterious effect.

The benefit is rarely enough to be used as monotherapy other than for a cosmetic degree of ptosis, and tends to be short-lived due to tachyphylaxis. Additionally later withdrawal of pseudoephedrine is difficult because of 'fatigue' experienced upon withdrawal, which I think is usually habituation to the central stimulant effects of the drugs, but is easily confused by the patient as a myasthenic symptom. Long-term consequences of pseudoephedrine use, including hypertension, are not insignificant. In my personal practice I reserve the short-term benefit of these drugs for severely ill patients admitted in crisis, when combined with a neostigmine infusion in the intensive care unit, while awaiting the patient's response to other treatments.

Editor, – I would like to congratulate Dr Stephen Reddel on such a well written article (Aust Prescr 2007;30:156–60), probably the most useful piece I have seen on this little known and often overlooked condition.

Readers may be interested to know that in addition to the New South Wales patient support group, there is also a group in Western Australia, which has recently produced the pamphlet outlining which drugs can worsen myasthenia gravis. As some of these drugs can cause potentially life-threatening exacerbations, the pamphlet has been designed to be easy to use in a hurry, so that the treating doctor or dentist can quickly gauge which drugs to use in a particular clinical setting. Copies can be obtained from the association, and the information will soon be available on the website as well (Myasthenia Friends and Support Group, www.myastheniawa.info or telephone (08) 9459 7168). Another Western Australian publication, 'A Handbook for Myasthenics', is available from the association.

Queensland also has a support group: Myasthenia Gravis Association of Queensland (www.mg-qld.gil.com.au).

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Varenicline

Editor, – A recent comment about the drug varenicline (Aust Prescr 2008;31:25–6) carries the statement that 'although many smokers try to stop, very few succeed without assistance'. This statement is not true.

There are now more ex-smokers than smokers in Australia. About 30% of adults, or about 4.5 million people, once smoked and smoke no longer.[1] Most people who attempt to quit do so.

Self-quitting – quitting without the aid of clinical interventions – has not been well studied. About 20 years ago, it was estimated that 90% of Americans who quit did so on their own.[2]

A recent Australian study showed that things have not changed all that much. Quitting cold turkey was the overwhelming method of choice used in their previous quit attempt by former smokers (88% of attempts) and current smokers (62% of attempts). In contrast, nicotine patches had been used by 7% of former smokers and 28% of current smokers.[3]

Pharmacological aids help some smokers quit. But the great majority of smokers continue to quit on their own.

Mark Ragg
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Tumour necrosis factor inhibitors

Editor, – Since the article on tumour necrosis factor inhibitors was published (Aust Prescr 2006;29:67–70), further evidence has emerged about the risk of malignancy associated with these drugs. A meta-analysis of nine published randomised placebo-controlled clinical trials of adalimumab and infliximab in rheumatoid arthritis showed a 3.3-fold (95% CI* 1.2–9.1) increased risk of malignancy.[1] Patients with prior malignancy were excluded from these trials. Malignancies were significantly more common in those taking high doses compared to low doses of tumour necrosis factor inhibitors.

A US observational study of 6597 patients with rheumatoid arthritis treated with tumour necrosis factor inhibitors showed that their use was associated with an increased risk of non-melanotic skin cancer (odds ratio 1.5, 95% CI 1.2–1.8) and melanoma (odds ratio 2.3, 95% CI 0.9–5.4).[2] However, no other malignancy was associated and the overall risk of any cancer was 1.0 (95% CI 0.8–1.2).

There is no current evidence for the safety of tumour necrosis factor inhibitors in patients with a history of malignancy. Hence, both the UK guidelines and the current product information for these products recommend that tumour necrosis factor inhibitors should be used with caution in patients with previous malignancy.[3] We suggest that until more long-term safety data are available, patients with recent malignancy should not be required to 'fail' a tumour necrosis factor inhibitor before being eligible for an alternative biological disease-modifying antirheumatic drug therapy under the Pharmaceutical Benefits Scheme.

*CI = confidence interval

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Relationships between health professionals and industry

Editor, – In a recent article (Aust Prescr 2007;30:150–3), Professor Paul Komesaroff mentions the Pharmaceutical Society of Australia's policy on gifts from pharmaceutical companies. The Society (PSA) also has a more comprehensive document entitled 'Guidelines for pharmacists' relationship with the pharmaceutical industry' which covers a broad range of issues including the promotion of healthcare products, conduct of meetings with medical representatives, gifts and inducements, loyalty schemes and support of educational activities.

While access to the guidelines is restricted to members of the PSA, we would be very happy to share the document with the author or other potential writers and researchers in this field.

Kerry Deans
Chief Executive Officer
Pharmaceutical Society of Australia
Canberra

(Editorial note: Ms Deans is no longer with the PSA)

Editor, – I refer to Professor Komesaroff's article (Aust Prescr 2007;30:150–3) whereby he understandably expresses concern about the influence that the pharmaceutical industry potentially exerts over prescribing clinicians. It must however be stated that few practising clinicians owe their livelihood to any one pharmaceutical company or product. This is in stark contrast to the involvement of other third party providers that exist within the healthcare system. The obvious example that comes to mind is medical practitioners whose work is predominately or entirely devoted to providing medicolegal reports for insurance companies. In this situation, there is more than a pharmaceutical company notepad, biro, or dinner on the line. Despite all this, it would seem evident that the majority of medical practitioners do practise ethically and appropriately.

Other circumstances involving third party healthcare stakeholders may have the potential to compromise a doctor's livelihood while raising considerable concern about the possible adverse impact on medical ethics and patient care. Recently, I heard of a situation where a young medical specialist who has a rather large practice and hires consulting rooms from a well-known private hospital, was told by hospital management that if he did not admit more inpatients, he would be told to vacate the consulting rooms

on short notice, and this would be 'a pure business decision'. Seemingly, the conduct of pharmaceutical companies would appear to be just one dimension of potentially scurrilous interference in medical management.

Ian Katz
Consultant psychiatrist
Caulfield, Vic.

Professor Komesaroff, author of the article, comments:

This letter makes a single, but important, point that the influence of the 'for profit' sector is not limited to the pharmaceutical industry. While this does not reflect on any of the specific content of my article, it is nonetheless worth drawing attention to the fact that many of the arguments and concerns do apply more widely to include other influences such as those from the biotechnology industry, the private healthcare industry and the contract research organisation sector.

New drugs – sitagliptin

Editor, –The monograph about sitagliptin (Aust Prescr 2008;31:49–55) states that 'while patients with liver disease may be able to take sitagliptin, it is not recommended for patients with renal impairment'. This is presumably because just over 70% of the drug is excreted unchanged in the urine. There are, however, facts – both in the monograph itself and elsewhere – to refute the quoted statement.

First, as noted in the monograph, the drug is presented in three strengths, 25, 50 and 100 mg tablets; this is solely due to the fact that sitagliptin can be safely given to patients with renal impairment (in doses commensurate with the severity of the renal impairment). Second, both the Australian[1] and US[2] product information for sitagliptin state that, 'for patients with moderate renal insufficiency, the recommended dose is 50 mg daily, while 25 mg daily is recommended and safe for patients with severe or end-stage renal disease (including those on renal replacement therapy)'.

Use of the general phrase 'patients with renal impairment' suggests that this is a distinct and perhaps minor group of patients. It is therefore not only misleading, but clearly inaccurate. Patients with type 2 diabetes who were enrolled in the UK Prospective Diabetes Study were followed for a median of 15 years as part of one of its many sub-studies (UKPDS 74).[3] At the end of this period, about 40% developed albuminuria and 30% developed 'renal impairment' (with some overlap between the two groups).

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The Editor comments:

The safety of using sitagliptin in patients with renal insufficiency was no doubt considered in the evaluation of the drug by the Therapeutic Goods Administration (TGA). Unfortunately, the TGA does not publish these evaluations and sometimes there can be delays in finalising the Australian product information.

It is therefore necessary to consider overseas evaluations when preparing a comment about a new drug.

Dr Lowy is correct that the product information in the USA includes doses for use in renal insufficiency, however the European Medicines Agency (EMEA) took a more cautious approach. Its evaluation found that the data were too limited to confirm the safety of sitagliptin in patients with moderate to severe renal insufficiency.[1]

Clearly, the European, USA and Australian regulatory agencies have assessed the data in different ways. Without more transparency in the Australian system we will not know how the TGA interpreted the evidence.

To try and overcome this problem the Editor wrote to the manufacturer seeking more information about sitagliptin, before the new drug comment was published. There was no reply.

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Paediatric analgesia

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Summary

Three main analgesics are routinely used for treating pain in children – paracetamol, ibuprofen and codeine. Paracetamol and ibuprofen are equally effective when used in recommended doses. Codeine has high inter-individual variation in its effectiveness, particularly in children, which significantly limits its routine use in paediatrics. Paracetamol is associated with fewer adverse effects than ibuprofen and so generally remains the first-line analgesic drug in children. However, paracetamol may not be the most appropriate choice in all patients depending on the type of pain being treated and the presence of comorbid illnesses. Paracetamol has unpredictable absorption with rectal administration so this route is no longer recommended. The combined use of paracetamol with non-steroidal anti-inflammatory drugs may be of benefit for some postoperative and musculoskeletal pain.

Key words: codeine, ibuprofen, NSAIDs, paracetamol.

(Aust Prescr 2008;31:63–5)

Introduction

In Australia, the main analgesic medications used in children in an ambulatory setting are paracetamol, ibuprofen and codeine. There has been significant debate in the literature recently as to which of these is the safest and most effective drug to use in children. In general these drugs are safe and effective when used at their recommended doses (Table 1). There are however a number of situations where one may be more appropriate than the other. Factors that need to be considered include the type of pain being treated, comorbidities and concomitant medication use. There are also situations when non-pharmacological methods may be the most appropriate form of intervention, either in isolation or in combination with drugs. This is often the situation in cases of chronic or recurrent pain.

Paracetamol

Paracetamol was discovered over 100 years ago and came into routine over-the-counter use approximately 40 years ago. Its popularity increased significantly in the 1980s when aspirin went out of favour due to its association with Reye's syndrome. Paracetamol is now the most widely used over-the-counter analgesic in children and is approved for use from one month of age. It is available over the counter in multiple paediatric dosage forms including liquids, chewable tablets and suppositories.

Mechanism of action

Despite being used so extensively, paracetamol's exact mechanism of action is still being debated. It has recently been postulated that it works through the inhibition of an isoenzyme of cyclo-oxygenase (COX)-3 that is only found in the brain and the spinal cord.[1] An alternative theory is that it works through the indirect activation of cannabinoid CB(1) receptors.[2] Regardless of this debate, the primary clinical outcome is that paracetamol increases pain tolerance via an effect in the central nervous system. Paracetamol is not an effective anti-inflammatory drug as it does not inhibit prostaglandin production outside the central nervous system, unlike non-steroidal anti-inflammatory drugs (NSAIDs).

Table 1

Recommended doses of paediatric paracetamol, ibuprofen and codeine [10]

Paracetamol	Ibuprofen	Codeine
Community setting		
15 mg/kg every 4–6 hours Maximum 4 doses (60 mg/kg) per day for up to 48 hours	5–10 mg/kg 3 or 4 times a day	0.5–1 mg/kg every 4–6 hours
Other settings		
Up to 90 mg/kg per day can be used under medical supervision with review after 48 hours Single doses of 30 mg/kg may be used for night-time dosing (do not exceed 60 mg/kg per 24 hours)	For juvenile rheumatoid arthritis 10 mg/kg 3 or 4 times a day	

Pharmacokinetics

Although paracetamol is available for administration via the oral, rectal and intravenous route, the oral route is preferred. The oral availability of paracetamol is approximately 90%. Its onset of action is approximately 30 minutes and duration of action is four hours. The rectal route is not recommended as absorption is highly variable and unpredictable, with the reported bioavailability ranging from 24% to 98%. The intravenous route is only used when the oral and rectal routes are not available, as may be the case in some inpatients postoperatively.

Efficacy

Paracetamol has repeatedly been shown in placebo-controlled clinical trials to be an effective analgesic in children with mild to moderate pain. It is effective for minor musculoskeletal pain, headaches including migraines, pain associated with infections such as otitis media and pharyngitis, and for postoperative pain after minor procedures such as adenotonsillectomies and insertion of ventilation tubes. It is not the most appropriate choice for pain that is associated with a significant inflammatory process, such as juvenile arthritis, when an NSAID is more suitable.

Safety

Paracetamol is a safe medication when used in the recommended doses. The main potential harm is liver toxicity (see box), which is caused by the accumulation of a toxic metabolite produced when the liver is depleted of glutathione. Relative to adults, children are less susceptible to acute toxic effects, but may be more susceptible to chronic exposure to paracetamol.

Malnutrition, starvation and intercurrent (febrile) illness increase the risk of liver toxicity. Acute toxicity occurs with paracetamol doses greater than 150 mg/kg. There have been reported cases of children developing liver toxicity who were said to be receiving therapeutic doses. These have tended to be overweight children who had prolonged courses, and were being dosed according to their actual weight, rather than their lean body weight. Children who are more than 20% above their ideal body weight should be dosed according to their lean body weight.[3] A quick conservative estimate of this can be obtained by determining their predicted weight for height (see Case example: Calculating lean body weight in obese children, on pages i and ii at the end of this issue).

Drugs that induce cytochrome P450, such as phenobarbitone, phenytoin and rifampicin, increase the risk of liver toxicity.

Risk factors for acute toxicity with paracetamol

- Paracetamol doses greater than 150 mg/kg
- Incorrect dosing in overweight children
- Intercurrent (febrile) illness
- Malnutrition, starvation
- Drugs that induce cytochrome P450 (such as phenobarbitone, phenytoin, rifampicin)

The dose of paracetamol for obese children should be based on lean body mass

Ibuprofen

Ibuprofen is the most widely used NSAID in Australian children as it has been freely available over the counter since 1998. The approved minimum age has recently been reduced from six to three months of age. NSAIDs work by inhibiting COX and thus limiting the production of numerous prostaglandins involved in the inflammatory response.

Safety

NSAID-related adverse effects that occur in children are the same as those that occur in adults, but they seem to occur less often. These include increased gastrointestinal bleeding, reduced renal blood flow, reduced platelet function and bronchospasm in susceptible individuals. Compared to paracetamol, NSAIDs are associated with more frequent adverse events in children.[4]

The risk of renal toxicity is increased with situations that are associated with decreased renal perfusion, namely dehydration, hypovolaemia and hypotension. Pre-existing renal disease or the concomitant use of other nephrotoxic drugs, such as frusemide, aminoglycosides or ACE inhibitors, will also increase the risk of renal toxicity.

Another special group that is at increased risk of NSAID adverse effects are children with aspirin (or NSAID)-induced asthma. Again this entity is rarer in children than adults, however a recent study estimated the prevalence of ibuprofen sensitivity to be 2% in children with asthma.[5]

Codeine

Codeine has previously been recommended as an analgesic for mild to moderate pain in children.[6] It can be and has been given to children orally, rectally and by intramuscular or subcutaneous injection. In Australia, it is most often given in combination with a simple analgesic as part of an oral fixed-dose combination. Codeine is a weak opioid, with one-tenth the potency of morphine. It has its primary analgesic effects through being metabolised to morphine by the cytochrome P450 enzyme CYP 2D6. The popularity of codeine has been largely related to its perceived lower rate of toxicity compared with other opiates, despite there being relatively few studies of codeine's efficacy in children.

Safety

There is considerable inter-individual variation in the activity of CYP 2D6, with a significant and unpredictable number of individuals being poor metabolisers (7–30% depending on ethnicity) who are unable to benefit from codeine.[7] There is also a proportion of the population who are extensive metabolisers who produce significant amounts of morphine and are thus at increased risk of opioid adverse effects.

The activity of cytochrome P450 enzymes is very low at birth then increases with age. In the very young, CYP 2D6 activity is less than 1% of that in adults and is still less than 25% in children under five years of age.

The wide variation in individual metabolism and the unpredictable influence of age on the effectiveness and safety of codeine means that its routine use in children is not recommended. It can be argued that the use of a small dose of morphine is preferable to codeine as it is more effective and predictable.

Comparative studies

Numerous studies have compared paracetamol and ibuprofen in children. When the current recommended doses of both drugs were used (Table 1), efficacy was essentially the same.[8] A recent study in children with musculoskeletal injuries compared ibuprofen 10 mg/kg, paracetamol 15 mg/kg and codeine 1 mg/kg. Ibuprofen showed a statistically significant benefit over the other two drugs in children with fracture, but not in children with other minor soft tissue injury.[9] However, a significant weakness of the study was that 48% of the children in the paracetamol group received less than the standard dose of 15 mg/kg (as the maximum dose allowed was 650 mg), whereas only 22% of the patients in the ibuprofen group received less than the standard dose of 10 mg/kg (as the maximum dose allowed was 600 mg).

Multimodal analgesia

The evidence for combining paracetamol and NSAIDs in children for analgesia is conflicting. However, it appears that in a significant number of postoperative patients the combination can lead to a decreased need for morphine or other opioid analgesics. The combination of codeine with paracetamol or ibuprofen has not been well studied in children. There is evidence in adults that codeine can add significantly to the analgesic effects of paracetamol, NSAIDs and aspirin.[7] However, given the unpredictable and often poor efficacy of codeine in children, it is unlikely to add to the analgesic effects of paracetamol and NSAIDs.

Conclusion

Paracetamol and ibuprofen are safe and effective forms of analgesia in children. Paracetamol is generally the preferred first-line drug due to fewer adverse effects, however this will not be the case in all individuals, depending on the pain being treated and comorbidities. Codeine has a relatively unpredictable efficacy in children and is thus not routinely recommended. It should also be remembered that in some situations non-pharmacological methods may be the most appropriate treatment.

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Conflict of interest: none declared

Note: To calculate lean body weight, see case example and growth charts on pages i and ii at the end of this issue.

Self-test questions

The following statements are either true or false (answers on page 83)

1. The dose of paracetamol for obese children should be based on lean body mass.
2. Paracetamol is the most effective analgesia for juvenile arthritis.

HIV fusion inhibitors: a review

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Summary

Combination antiretroviral therapy has revolutionised the management of HIV infection. A life expectancy of more than 35 years is now realistic for a young person diagnosed with HIV infection in Australia. Despite this success, antiretroviral regimens predictably fail in a proportion of patients. There is therefore a continuing research effort to discover, develop and deliver new antiretroviral drugs. HIV fusion inhibitors represent a novel class of antiretroviral drugs and enfuvirtide is the first drug within this class to be approved for use in Australia.

Key words: antiretroviral drugs, enfuvirtide, HIV/AIDS.

(Aust Prescr 2008;31:66–9)

Introduction

There are several classes of antiretroviral drugs, each with a different site of action in the HIV life cycle.[1] Combination antiretroviral therapy for treating HIV infection has provided potent and durable reductions in HIV plasma viral load.[2] The resultant immune reconstitution has led to a return to health for many HIV-infected individuals.

Despite its success, sequential combination antiretroviral therapy fails in a proportion of patients who develop multidrug resistant virus. Such patients are at increased risk of HIV disease progression. As a consequence, there is an ongoing need to find new drugs that can be added to the therapeutic armamentarium and provide 'salvage therapy' for those who have failed previous regimens. One such example is enfuvirtide, the first available and only licensed HIV fusion inhibitor.

HIV fusion

The scientific investigation of the life cycle of HIV has been an area of intense research since the first description of the virus in 1983. In order to gain entry to the intracellular human machinery, which all viruses require for replication, the virus must fuse with the human cell membrane. This occurs in a complex sequence of events following attachment of the HIV-1 surface glycoprotein 120 (gp120) binding site to human cells expressing CD4 receptor molecules (for example T-lymphocytes). After binding, gp120 changes shape to allow the viral glycoprotein 41 (gp41) to form a pore in the membrane through which the virus can enter (Fig. 1).

How enfuvirtide was developed

Enfuvirtide is a synthetic 36-amino acid peptide analogue. It binds to the first heptad repeat region of gp41, disrupting interactions with the second heptad repeat region of gp41, thereby interrupting the fusion reaction and preventing the virus from infecting the host cell.

Interestingly, the development of enfuvirtide emerged from a serendipitous observation made during epitope-mapping experiments for HIV vaccine development. Synthetic peptides derived from the HIV envelope gp41 produced an antiviral effect when incubated with HIV virus and human T cells. Subsequent understanding of the fusion process, and how envelope glycoproteins interact, led to an appreciation of how these peptides inhibit the fusion of HIV with the human cell membrane, and interrupt the HIV life cycle.[3]

Pharmacology

Early studies of enfuvirtide showed predictable pharmacokinetics as well as plasma concentrations *in vivo*. However, enfuvirtide cannot be administered orally as it is a large peptide which is broken down in the digestive tract before absorption. It is therefore given twice daily by subcutaneous injection. As a peptide it is catabolised and does not rely on hepatic metabolism so has little potential for clinically meaningful drug-drug interactions.

Clinical studies

The pivotal phase III studies of enfuvirtide (TORO 1 and TORO 2) were conducted in two separate international multicentre randomised controlled trials.[4,5] These studies had almost identical designs, and differed only in the minimum length

Fig. 1

Simplified diagram of HIV fusion and entry into CD4 cells

HIV entry can be divided into several discrete steps: (A) Attachment of the viral glycoprotein 120 (gp120) to the CD4 receptor. (B) Conformational changes of gp120 which expose structural elements on the V3 loop that bind to the chemokine receptors (e.g. CCR5). (C) A structural rearrangement in glycoprotein 41 (gp41) is induced which inserts a hydrophobic fusion peptide region into the target cell membrane bringing the virus and cell membrane in close apposition to initiate fusion. (D) The virus can then enter the host cell. Enfuvirtide inhibits fusion by binding to gp41 and preventing the formation of a pore in the CD4 membrane.

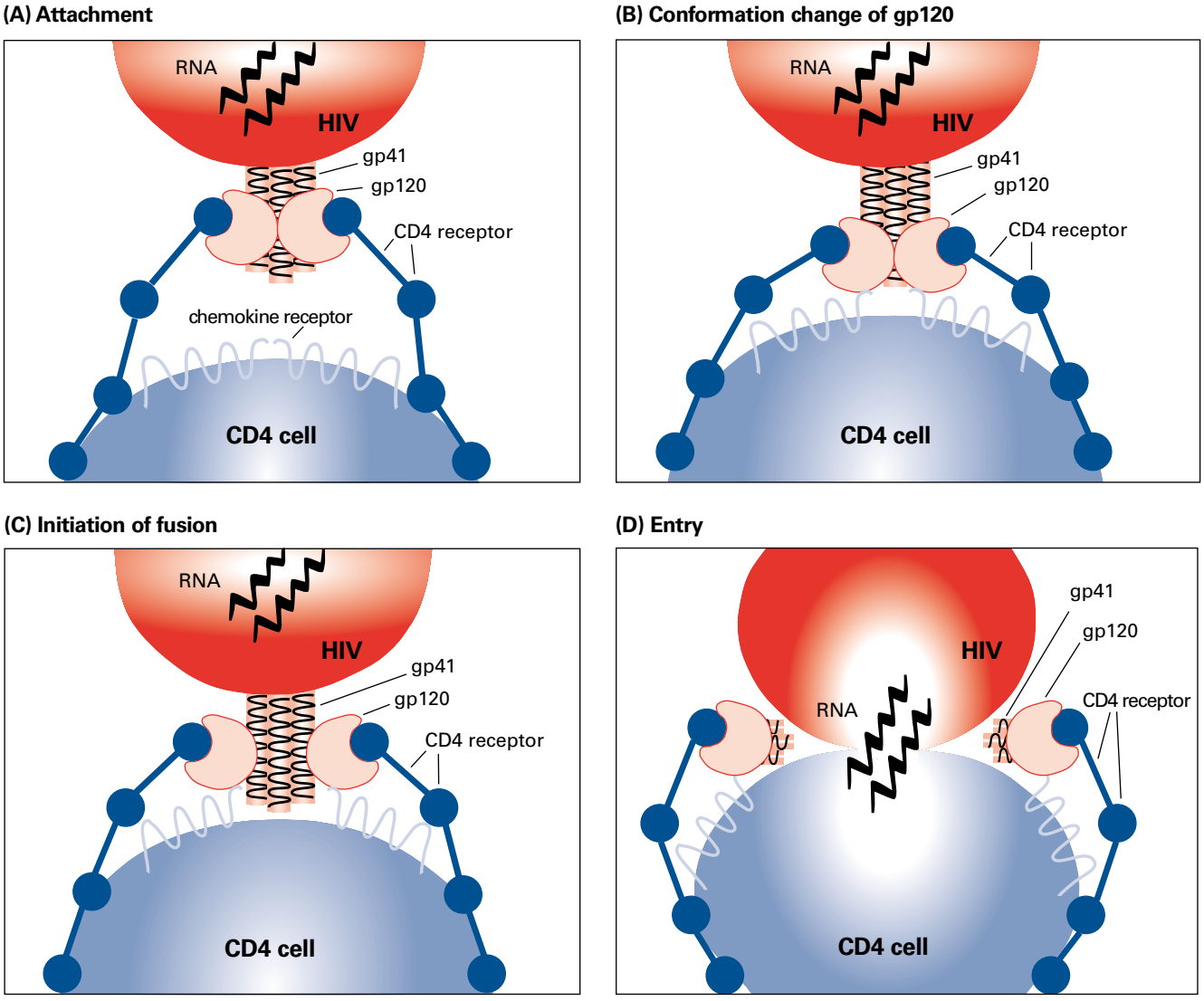

Figure adapted with permission from Hardy H, Skolnik PR. Enfuvirtide, a new fusion inhibitor for therapy of human immunodeficiency virus infection. Pharmacotherapy 2004;24:198-211.

of previous exposure to antiretroviral therapy (six and three months for TORO 1 and 2 respectively). The patient population had been exposed to, and/or had documented resistance to, at least one drug within the three available antiretroviral therapy classes at the time of enrolment. These classes were the protease inhibitors, nucleoside/nucleotide reverse transcriptase inhibitors and the non-nucleoside reverse transcriptase inhibitors. Patients were randomised 1:2 to receive either an 'optimised background regimen' consisting of 3–5 drugs selected on the basis of the patient's history and viral drug resistance testing, or the optimised background regimen plus enfuvirtide.

In both studies the patients on enfuvirtide did significantly better than those who received only the optimised background

regimen, with combined viral load reductions of –1.48 versus – 0.63 $\log_{10}$ copies/mL and CD4+ T cell gains of 91 versus 45 cells/mm^3 after 24 weeks of therapy. Licensing approval was based on these studies. Prolonged follow-up showed that optimised background regimen plus enfuvirtide provided a durable response in 24-week responders out to 48 weeks. The week 12 response predicts durable virological suppression at weeks 24, 48 and 96.[6]

Sub-group analyses of the combined TORO databases suggested that the predictors of better response to optimum background regimen plus enfuvirtide were higher baseline CD4+ T cell count (more than 100 cells per mm^3), baseline viral load of less than 100 000 copies/mL, exposure to less than 10 antiretrovirals and finally, the combination of enfuvirtide with at least two other active antiretrovirals.[6] These findings emphasised the critical importance of using enfuvirtide in combination with other active drugs, and has been reinforced by subsequent experience.[7]

Safety and tolerability

Hypersensitivity reactions manifesting as rash, fever, chills, nausea and vomiting which re-emerge on challenge have been described, albeit rarely. Enfuvirtide appears not to have any overlapping long-term toxicities with other commonly used antiretrovirals (including the HIV lipodystrophy syndrome).

There was an association with an increased risk of bacterial pneumonia reported in the TORO studies in those receiving enfuvirtide compared to those who did not (4.7 vs 0.6 bacterial pneumonia events per 100 person years). However, an analysis of the patients remaining in the study at 96 weeks (that is, patients originally randomised to receive enfuvirtide with continuing follow-up and patients initially randomised to placebo who accessed enfuvirtide after week 48) showed no increase in the incidence of pneumonia (< 2%), which remained unchanged over time. From this the authors suggest that the risk of pneumonia was independent of receiving enfuvirtide.[8]

Injection site reactions

The commonest adverse effect of enfuvirtide is injection site reaction which is experienced by more than 90% of those injecting enfuvirtide. Reactions are generally characterised by one or more of the following, such as local pain, erythema, pruritis, induration, ecchymosis, nodules and cysts. Excisional biopsy studies have shown inflammatory infiltrates consistent with a localised reaction. We have observed in our unit scleroderma-like skin changes with chronic use of enfuvirtide (more than one year exposure).

The need for twice-daily injections has proven a substantial barrier to the acceptance of enfuvirtide by prescribers and patients. In those who do access the therapy, the occurrence of local injection site reactions, while infrequently treatment limiting, is associated with a degree of treatment fatigue.[9] Recently a gas-powered, needle-free injector device has been trialled as an alternative drug delivery mechanism. Early experience in observational studies suggest that the needle-free injection system might be associated with less severe injection site reactions and that the pharmacokinetics are similar to those achieved by needle delivery.[10] However, a recent randomised controlled trial conducted in enfuvirtide-experienced patients found that the needle-free injector device made no major impact on injection site reactions compared to delivery through a standard 27-gauge needle.[11] In October 2007, Roche/Trimeris announced that it was withdrawing its application with drug regulators to market enfuvirtide in tandem with the device.

Discontinuations due to adverse effects

Surveillance of the 997 patients entered into the TORO trials through the first 24 weeks showed that 8.9% of patients in the enfuvirtide group discontinued antiretroviral therapy due to adverse events as opposed to 3.6% receiving the optimum background regimen alone. Enfuvirtide injection site reactions accounted for approximately half of the discontinuations.

Resistance to enfuvirtide

As with all antiretroviral therapy, resistance to enfuvirtide may develop, particularly when viral suppression is not optimal. Resistance to enfuvirtide is mediated by amino acid substitutions within the first heptad repeat region of gp41 at amino acids 36 to 45. The mutations confer significantly reduced binding of enfuvirtide to this region and result in decreased antiviral activity *in vitro*.

Resistance emerges fairly rapidly in patients experiencing virological failure with an enfuvirtide-containing antiretroviral regimen, and is associated with the return of the plasma HIV load toward baseline within a few weeks. It seems therefore that enfuvirtide has a relatively low genetic barrier to the development of resistance.

The degree to which enfuvirtide exerts continued antiviral activity in the presence of incomplete viral suppression and drug-resistance mutations has been investigated. In a small study of 25 patients, enfuvirtide interruption was associated with an immediate but limited increase in plasma viral load, suggesting that despite resistance enfuvirtide may still exert partial antiviral activity. The clinical significance of these observations remains undefined.[12]

The future of fusion inhibitors

The use of enfuvirtide has been hindered by a limited acceptance of the twice-daily injection regimen. Unfortunately, a study of the use of once-daily enfuvirtide showed a trend towards a weaker antiviral effect compared with the twice-daily regimen. Hence, there have been renewed efforts to develop the next generation of fusion inhibitor peptides.

Until recently a candidate peptide (TRI-1144) was being advanced as a pre-clinical product in another collaboration between Trimeris and Roche. However, in mid-March 2007 Roche announced that they had returned all rights to joint patents and intellectual property for next-generation fusion inhibitors, including TRI-1144, back to Trimeris. This action inevitably calls into question the future development of the class.

The chemokine (C-C motif) receptor 5 (CCR5) antagonists are a new class of HIV entry inhibitors now in phase III trials, with an expanded access program currently available. Registration in Australia is expected in the near future. These drugs inhibit viral entry by blocking the interaction between the co-receptor CCR5 and HIV. Unlike the fusion inhibitors, they are host-directed not viral-directed drugs. There is interest in the potential synergistic effect of administering an HIV fusion inhibitor with a CCR5 antagonist, and this is currently under investigation.

Conclusion

While the use of enfuvirtide is associated with substantial improvements in virological, immunological and clinical outcomes in treatment-experienced patients, particularly when combined with antiretroviral drugs, its uptake has been limited because of the need for delivery by twice-daily subcutaneous injection. However, there is no doubt that the drug offers potent antiretroviral activity and its use should be strongly considered in patients with multiple regimen failures as a component of a new regimen aimed to effect full and durable virological suppression.

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Dr Boyd has received funding from Roche for attendance at an international conference, and has acted as a paid adviser. Dr Pett has attended a weekend conference funded by Roche.

Self-test questions

The following statements are either true or false (answers on page 83)

3. Resistance to enfuvirtide has not yet been reported.
4. Most patients have a local inflammatory reaction to enfuvirtide injections.

Therapeutic Guidelines: Emergency

The latest update of eTG complete contains the new Emergency guidelines. Topics covered include toxicology, toxinology, resuscitation, anaphylaxis, burns, trauma, ocular emergencies, obstetric emergencies and environmental medicine. eTG complete is available from Therapeutic Guidelines at www.tg.com.au or by phoning (03) 9329 1566.

Antiepileptic drugs in pregnancy and lactation

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Summary

No antiepileptic drug is completely safe to use in pregnancy as the risk of fetal abnormality is increased. Valproate should be avoided if possible because of the risk of major malformations. Ideally a plan for managing the woman's epilepsy during pregnancy should be prepared before conception. The occurrence of an unexpected pregnancy should not trigger sudden cessation or alteration of antiepileptic drug treatment without medical advice. The smallest effective dose of a drug with a low risk of teratogenicity should be used. Doses may need adjustment as the pharmacokinetics of some drugs change during pregnancy. Data are limited, but most antiepileptic drugs seem to have little effect on full-term breastfed babies.

Key words: birth defects, folate, valproate, vitamin K.

(Aust Prescr 2008;31:70–2)

Introduction

Uncontrolled epilepsy in a pregnant woman is a serious and potentially life-threatening condition for both mother and child. Most pregnant women with epilepsy will need to take at least one antiepileptic drug. The goal for all concerned is a healthy, seizure-free mother and an undamaged child. The following somewhat contradictory issues need to be considered concurrently.

- The optimum treatment of the mother's epilepsy requires that the most appropriate antiepileptic drug be used in effective doses throughout pregnancy. This requires knowledge of specific epileptic syndromes and also antiepileptic drug pharmacokinetics before, during and after pregnancy.
- Any adverse effect that the antiepileptic drug could have on the developing child needs to be avoided or minimised during pregnancy and lactation.

Fetal abnormality

Women with epilepsy taking antiepileptic drugs have a greater (2–3 times) risk than other women of having a baby with a fetal abnormality. Taking more than one antiepileptic drug carries a higher risk than monotherapy. Major malformations, such as congenital heart disease, neural tube defects, urogenital defects and cleft lips or palates, occur in about 3–7% of women with epilepsy who take antiepileptic drugs, although a substantially higher risk is attributed to high doses of valproate (greater than 1400 mg/day).

For more than 30 years, a gradually increasing body of literature has attributed a 'fetal anticonvulsant syndrome' and increased malformation rate to all the 'old' antiepileptic drugs – barbiturates, phenytoin, carbamazepine and valproate. Some data are now available for lamotrigine, but very little is known of the risk of the 'new' antiepileptic drugs such as levetiracetam, topiramate, oxcarbazepine, gabapentin, pregabalin, tiagabine and zonisamide.

Problems may emerge in childhood. Numerous small studies have suggested cognitive and language impairment and an increase in autistic spectrum disorder in children who have been exposed to antiepileptic drugs *in utero*.[1] Recent reports suggest that these problems may be highest in children who have been exposed to valproate.

In order to better understand the extent of the teratogenic risks of all antiepileptic drugs, observational pregnancy registers have been established around the world including Australia.* These registers contain useful information about the most commonly used antiepileptic drugs. From these registers, consistent warnings about the increased risk of structural birth defects have been issued for valproate. The North American Pregnancy Register has published specific concerns with respect to phenobarbitone and lamotrigine.

Management of women with epilepsy

Before conception, a comprehensive management plan is desirable. The diagnosis of epilepsy needs to be validated, the epilepsy syndrome elucidated, 'optimal' antiepileptic drug treatment established and folate supplements given. Potential parents should understand that there are no 'safe' antiepileptic drugs in pregnancy. The balance of risks, as presently known, should be explained to them. All risk of harm cannot be eliminated.

Women with epilepsy who are considering pregnancy should be treated with the least teratogenic but most efficacious

* Australian Pregnancy Register for women on anti-epileptic medication. Phone 1800 069 722.

antiepileptic drug for their particular type of epilepsy at the lowest effective dose. Pregnancy counselling and planning are strongly advised. When an unexpected pregnancy happens and embryogenesis has already occurred, there is usually little to gain and there may be substantial risk in stopping or changing antiepileptic drugs. Early monitoring for an adverse fetal outcome and appropriate counselling are advisable.

Folate and vitamin K_1

All women are recommended to take folate supplements before pregnancy. It is reasonable practice to recommend routine folate supplementation, 0.5–1.0 mg/day, to all potentially reproductive women with epilepsy taking antiepileptic drugs even if they are not contemplating pregnancy. It is currently recommended that a woman with epilepsy takes folate 5 mg/day for three months before conception and for at least the duration of the first trimester. There is good evidence that folate supplementation reduces the risks of spina bifida and other malformations in large population studies, but there is no documented evidence that it further reduces teratogenic risk in women taking antiepileptic drugs.

National Health and Medical Research Council Guidelines (2000) recommend that all babies at birth are given 1 mg intramuscular vitamin K_1 or a course of oral vitamin K_1. Maternal oral vitamin K_1, for example 10 mg/day for one month prepartum, has been recommended when enzyme-inducing antiepileptic drugs are prescribed because the drugs may potentially predispose the baby to haemorrhagic disease of the newborn. However, reports suggest that this risk is practically negligible.[2]

Specific epilepsy syndromes

Two major groups of epilepsies need to be distinguished because they typically respond differently to different drugs. Localisation-related or partial epilepsies respond to most antiepileptic drugs. For idiopathic generalised epilepsy valproate is usually the most effective drug. Often, especially in juvenile myoclonic epilepsy, seizures can be controlled with a reasonably low valproate dose, for example 800 mg/day or less. Lamotrigine may be helpful but often is not as effective as valproate and sometimes worsens the myoclonic seizures of juvenile myoclonic epilepsy. Topiramate and levetiracetam may be effective in idiopathic generalised epilepsy while carbamazepine, tiagabine, oxcarbazepine, phenytoin and gabapentin may worsen some seizure types, especially myoclonic and absence seizures. For some women with idiopathic generalised epilepsy syndromes, there may be no effective alternative to valproate.

Drug exposure and effects

The pharmacokinetics of antiepileptic drugs may change in pregnancy. Doses have to balance the risk of seizures with minimising the risk of harming the fetus.

Valproate

Four pregnancy registers and numerous smaller studies have warned that there is a substantial risk of major malformations including spina bifida when valproate is used as monotherapy or with other drugs. The Australian Pregnancy Register[3] has reported the risk to be as high as 16% for first trimester fetal exposure to valproate at doses above 1400 mg/day, compared with 6% at doses below 1400 mg/day. Others have reported higher risk when plasma valproate concentrations are consistently high (more than 70 mg/L). Valproate should therefore be avoided in reproductive women wherever possible. When it is unavoidable, the lowest effective dose should be used. It should not exceed 1000 mg/day in divided doses. The woman needs to be warned of the risk of seizures and she should avoid seizure triggers such as sleep deprivation. While she is taking a reduced dose she may have to restrict her driving.

If the valproate dose has been reduced to a minimum during pregnancy in order to reduce teratogenesis, the prepartum effective dose may need to be re-established before the onset of labour. This is a time of increased seizure risk especially in patients with idiopathic generalised epilepsy who are very sensitive to sleep deprivation.

Breastfeeding is considered compatible with valproate therapy. Valproate concentrations in breastfed babies are low.

Lamotrigine

The North American Pregnancy Register has reported that exposure to lamotrigine in the first trimester may cause an increased risk of oral clefts (a rate of 8.9 per 1000, as compared to 0.37 per 1000 in the reference population).[4] Significant dose-related teratogenesis with lamotrigine exceeding 200 mg/day has been reported.[5]

Lamotrigine clearance increases steadily through to 32 weeks of pregnancy. Plasma concentrations of lamotrigine fall early in pregnancy so dose increases may be necessary to control seizures. A trough plasma lamotrigine concentration before pregnancy, at the onset of the second trimester of pregnancy and every two months during pregnancy may help to guide any necessary increase in lamotrigine dose. Postpartum, the lamotrigine concentration rises within a few days and prompt dose reduction may be required to prevent toxicity.[6]

Lamotrigine is excreted in considerable amounts into breast milk. Early reports show that most full-term babies seem to have little problem with breastfeeding, but close monitoring for toxicity, especially in small or preterm babies, is advised.

Carbamazepine

For almost 20 years reports have associated carbamazepine with an increased risk of structural birth defects including spina bifida. However, no pregnancy register has yet shown any statistically significant increase in risk relative to the

total population. In the Australian Pregnancy Register, the malformation rate with carbamazepine cannot be distinguished from that of women with epilepsy who are not taking antiepileptic drugs.

Modest pharmacokinetic changes occur during late pregnancy, but dose changes are not usually required. Carbamazepine is compatible with breastfeeding in the full-term infant.

Phenytoin

Phenytoin is now used less frequently in women with epilepsy. It has been reported to produce an increase in major malformations.

A marked increase in the clearance of phenytoin in pregnancy is associated with a fall in plasma concentrations and possible loss of seizure control. Regular monitoring of plasma concentrations throughout pregnancy helps to determine when a higher dose is required. Postpartum monitoring helps prevent phenytoin toxicity. The pharmacokinetic changes of early pregnancy and postpartum occur more slowly with phenytoin than with lamotrigine. Breastfeeding is acceptable with phenytoin.

Levetiracetam

Levetiracetam has been used in few pregnancies. Its teratogenic risk is unknown.

There appears to be a substantial increase in clearance during pregnancy and an associated fall of blood concentrations.[7] It is not yet known if this is associated with a loss of epilepsy control. Serum monitoring is not currently available, but may prove helpful in clinical practice.

Although levetiracetam is secreted into breast milk, recent data suggest that the neonatal concentrations are low. Breastfeeding is probably acceptable in full-term neonates, but close clinical monitoring is advisable.

Clonazepam

Clonazepam is used as an adjunctive antiepileptic drug. No particular pregnancy risks have been associated with it, but it may cause drowsiness in the breastfed neonate. Withdrawal effects can occur if breastfeeding ceases suddenly.

Oxcarbazepine, topiramate, ethosuximide

Only a few pregnancies have been documented, so the teratogenic risks of these drugs are unknown. Oxcarbazepine clearance seems to increase significantly in pregnancy, but the clinical importance of this is uncertain.

These drugs are excreted in breast milk, but the very limited data available suggest that neonatal drug concentrations are usually low. Breastfeeding is probably acceptable with clinical monitoring.

Phenobarbitone

Phenobarbitone is rarely used now in Australia in reproductive women with epilepsy. The North American Pregnancy Register suggests that it may carry a significant teratogenic risk. A marked increase in plasma clearance occurs in pregnancy. Phenobarbitone in breast milk may cause neonatal drowsiness and apathy.

Conclusion

In women with epilepsy treated with antiepileptic drugs, there is a better than 90% chance that the child will be normal. The most specific therapeutic dilemma and the highest risk is in women who need to take valproate to control their epilepsy. Most infants whose mothers are taking antiepileptic drugs can be successfully breastfed without complications.

Editorial note: Some antiepileptic drugs are used in the management of bipolar disorders. See: Sved Williams A. Antidepressants in pregnancy and breastfeeding. Aust Prescr 2007;30:125–7.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 83)

5. Valproate increases the risk of spina bifida if taken during pregnancy.
6. The dose of lamotrigine may need to be increased during pregnancy.

Acute management of bipolar disorders

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Summary

Acute bipolar presentations include manic, hypomanic, mixed, and depressive states. Manic presentations cannot be contained in a primary care setting and require psychiatric assessment for hospitalisation. Several drugs that have mood stabilising actions are now available, providing more treatment options for clinicians. Antidepressant use in bipolar depression remains controversial, but if considered clinically appropriate must be administered with a drug that stabilises mood. Psychosocial interventions help patients with recovery and to cope with residual symptoms of illness.

Key words: depression, hypomania, management, mania.

(Aust Prescr 2008;31:73–6)

Introduction

Patients with bipolar disorders face significant risks of morbidity and mortality and present medical practitioners with considerable diagnostic and management challenges. The lifetime prevalence of bipolar disorders is estimated at 1–4% of the general population.[1] Suicide is attempted by 25–50% of sufferers[2], and overall 15% of people with bipolar disorders die by suicide.[3]

Accurate diagnosis depends on recognising often under-reported symptoms of elevated mood. Mixed states (combined depressive and elevated symptoms) and comorbid substance misuse frequently cloud the initial diagnosis. These diagnostic complexities along with often impaired patient insight lead to a third of Australian patients suffering illness for more than ten years before accurate diagnosis is made and appropriate treatment given.[4]

Bipolar disorders

These are characterised by episodic depressions and elevations of mood. Bipolar I involves manic symptoms which last for at least a week and are severe enough to markedly impair functioning or require hospitalisation. In contrast, bipolar II involves hypomania in which elevated symptoms are less severe but still clearly different from usual mood and last for at least four days. In both forms of the illness, depressive episodes tend to be more frequent and disabling than mania. Sufferers spend 32–50% of follow-up in depressive episodes and only 1–9% in elevated states.[5] Most patients have inter-episode periods of recovery, but over 90% relapse without medications.[6]

Risk assessment

It is necessary to determine the most appropriate settings for patient care, and assess for suicidal ideations by examining past history of self-harm, current ideation, substance abuse, and the level of social supports.

In elevated and mixed states, the possibility of risk taking, impulsive behaviours, irritability, violence and misadventure must be considered. Where risks are deemed high, the patient needs more assertive care, and referral to psychiatric inpatient services is appropriate. Application of the relevant state mental health act may be required. Manic episodes cannot be contained in a general practice or community setting.

Given the diagnostic and management challenges of bipolar disorder, psychiatric confirmation of diagnosis and management advice is advisable. For patients with low to moderate risk, their initial care will usually be provided by their general practitioner, who has a pivotal role in assessment, diagnosis, referral and ongoing care.

Treatment

The goal of treatment in bipolar disorder is to stabilise mood. Symptomatic and specific maintenance medications are available for the acute treatment of bipolar disorders. However, maintenance medication remains the cornerstone of management – both for acute episodes and maintenance treatment.[7]

In recent years several new drugs have shown efficacy for the control of manic symptoms and prevention of relapse, but not all are approved for use in bipolar disorders.[8] Trialling medications in the acute phase of the illness – depressed, mixed, hypomanic and manic episodes – helps to find the most effective and tolerable drug or drugs necessary to achieve and maintain euthymic mood in individual patients.

In Australia, several effective drugs for bipolar disorders are

subsidised by the Pharmaceutical Benefits Scheme, but some drugs require private prescriptions for use (see Table 1).

Manic episodes

Drugs recommended for the treatment of manic episodes are listed in Table 1.[8,9] Lithium, certain anticonvulsants[10] and several antipsychotics have mood stabilising properties. They treat and prevent mood elevations and, to a lesser extent, help control and prevent depressive episodes.

Episodes of mania typically require inpatient management. Patients with mania require sedation to reduce psychomotor acceleration. So called 'manic exhaustion' had a very high mortality in the premedication era. Prompt restoration of the sleep-wake cycle assists recovery. Often adjunctive benzodiazepines are used for sedation, but it is preferable if the drug chosen to stabilise mood can also serve this function. Managing mania sometimes requires large doses of antimanic drugs in the acute phase, though lower doses may suffice in the maintenance phase. Tolerability is a key factor for subsequent compliance with medications and long-term illness control.

Resolution of the acute episode takes weeks to months. Approximately 50% of patients with mania will respond to monotherapy with any antimanic drug, and around 70–75% will respond to combination therapy. The longer-term evidence on such combination therapy remains limited, and while monotherapy is preferable from compliance, tolerability and cost perspectives, only a third of patients achieve longer-term mood stability on monotherapy.[11] Combination therapy is pragmatically the norm. In rare treatment-resistant cases of mania, where even multiple medications fail to control mania, electroconvulsive therapy and in some cases clozapine may need to be trialled.[12] Acute treatment is generally the start of maintenance therapy.

Table 1

Drugs for the acute management of manic episodes

First-line	– lithium – valproate – carbamazepine – second generation antipsychotics (olanzapine*, risperidone, quetiapine, aripiprazole*, ziprasidone*)
Second-line	– second generation antipsychotic plus lithium or valproate – lithium plus valproate
Third-line	– electroconvulsive therapy – clozapine†

This list is a composite of recent evidence-based reviews and consensus management guidelines for bipolar mania[8,9]

* indicates no Pharmaceutical Benefits Scheme subsidy for acute mania at time of writing

† the efficacy of clozapine is decreased with smoking

Hypomanic episodes

Due to the shorter duration of hypomanic episodes, and the lack of marked impairment, hypomania is less frequently the presenting symptom of the illness. Patients with hypomania may feel energetic and creative, and may not need much sleep. They are unlikely to present complaining of feeling 'too well'.

In clinical practice, treatments for manic states are effective in hypomania. Importantly, patients with only hypomanic but no manic episodes (bipolar II pattern) do not tend to progress to bipolar I manic states. Nonetheless, hypomanic episodes are a core precipitant of downward mood destabilisations into major depressive episodes, and thus warrant active treatment, even though depression is invariably the reason patients present for treatment in bipolar II disorder.

Mixed episodes

Mixed states are characterised by elevated and depressed mood mixed together and are among the most difficult mood conditions to identify. Elevated symptoms can be brief, and include racing and 'crowded' thoughts, lability of affect, insomnia and restlessness. Specific pharmacotherapy for mixed states is extrapolated from treatments for mania. One crucial factor is to avoid antidepressants during such mixed states, as they will exacerbate and sometimes trigger the episodes. This can be counterintuitive, when patients present with a dysphoric affect. Mixed states are the most under-recognised of the bipolar specific states, and it is likely that many mixed states are triggered by antidepressants. If a patient's agitated depressive symptoms seem to worsen with antidepressants, consider the possibility of a mixed state and bipolar diagnosis.

Depressive episodes

Drugs for the treatment of bipolar depressive episodes are listed in Table 2.[8,9] The best current evidence for efficacy in bipolar depression exists for lithium, quetiapine and lamotrigine.[8]

Antidepressants place patients at risk of switching to elevated phases of the disorder and rapid cycling patterns. Although the results of a recent study do not support the use of adjunctive antidepressant therapy in the acute treatment of bipolar depression[13], this topic remains very controversial. Many patients with bipolar depression will not respond to changes in mood stabilising medicines alone. They may need an antidepressant, but this must be taken with a mood stabilising drug. Frequent regular mental state review is necessary for any patient taking this combination to detect destabilisation, and non-response or loss of response to the antidepressant. Patients should not simply be left on the antidepressant long term without review.

Considerable controversy exists as to how long antidepressants should be continued, and there is no good evidence of efficacy in the maintenance phase. What is clear is the need for

monitoring of the patient's mental state and dose reduction or cessation of the antidepressant if elevated symptoms emerge.

Should an antidepressant be needed, low-dose selective serotonin reuptake inhibitors are usually adequate and may have less propensity to induce elevated phases of the disorder.[14] As fluoxetine has a five-week washout period it is best avoided in bipolar conditions in case a manic, mixed or hypomanic mood switch necessitates cessation.

Psychosocial care

Education, self-monitoring of mood, mood diaries and social rhythm training all assist with better longer-term patient outcomes. Psychosocial care is best implemented as early as possible in the course of illness to help patients with recovery and to cope with residual symptoms of illness. Including family and carers in the management plan is an important aspect of care. Continuity of care with good communication and rapport between doctor and patient is particularly important in fostering compliance with treatment and earlier presentation for acute care in the event of relapse.

Conclusion

Bipolar disorders can present in varying ways. Prompt recognition of the phase of illness and tailoring the patient's therapy accordingly will help optimise outcomes. Consider bipolar disorders in patients with treatment-resistant or recurrent depression. Newer anticonvulsants and antipsychotics offer further treatment options for these diverse and often disabling illnesses. Prescribers should carefully monitor patients with bipolar disorders who require antidepressants, given the risk of destabilising their mood. Integrating education, lifestyle modification and engagement of patients and carers in management augments therapeutic efficacy.

Table 2

Drugs for acute management of bipolar depressive episodes

Optimise current medications or initiate therapy	
First-line	– lithium, quetiapine or lamotrigine monotherapy – lithium or valproate with selective serotonin reuptake inhibitor or bupropion* – olanzapine with selective serotonin reuptake inhibitor – lithium with valproate
Second-line	– add-on or switch to a second mood stabiliser† and/or add a selective serotonin reuptake inhibitor (if patient is not already taking one)
Third-line	– mood stabiliser† with serotonin noradrenaline reuptake inhibitor or tricyclic antidepressant or monoamine oxidase inhibitor – electroconvulsive therapy

This list is a composite of recent evidence-based reviews and local consensus management guidelines for bipolar depression[8,9]

* an antidepressant re-patented in Australia for smoking cessation

† lithium, valproate, carbamazepine, lamotrigine, olanzapine or quetiapine. Keep patient on whichever mood stabilising drugs have worked during elevated phases of illness.

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Self-test questions

The following statements are either true or false (answers on page 83)

7. Patients with mania are best managed in general practice.
8. In bipolar disorders, patients taking a mood stabilising drug combined with an antidepressant should be regularly reviewed for changes in their mental state.

Your questions to the PBAC

Methylphenidate

The management of adolescents who need stimulant medications is complicated by the restrictions of the Pharmaceutical Benefits Scheme (PBS). I have a patient who has benefited from using an extended-release formulation of methylphenidate. She is calmer and more relaxed than she was on intermittent doses of the immediate-release formulation. The problem is that my patient is now over 18 years old so cannot receive the extended-release formulation as a PBS prescription.

There are probably many adolescents with attention deficit hyperactivity disorder who are well managed with the extended-release formulation. Some of them will continue to need treatment after their eighteenth birthday, but the current PBS authority requirements prevent this. To continue treatment, patients will have to switch to another formulation or a different drug without an age restriction. How can this anomaly in the PBS be rectified?

George Blake
Paediatrician
Moana Medical Centre
Adelaide

PBAC response:

In assessing applications and making recommendations for PBS listing, the Pharmaceutical Benefits Advisory Committee (PBAC) is required to take into account a number of criteria, including the indication for which the medicine has been approved for use in Australia. The PBAC cannot make a recommendation on a medicine for use outside its approved indication as registered with the Therapeutic Goods Administration (TGA) as this would go against evidence-based decision making.

In the case of extended-release methylphenidate, the registered TGA indication is for the treatment of attention deficit hyperactivity disorder in children and adolescents aged 6–18 years. Consequently, when considering the application to list the drug on the PBS, the PBAC was limited to making a recommendation that covered the 6–18 year old population only.

For the PBS listing to be extended to include persons over 18 years of age, the drug's sponsor would first need to have the TGA indication changed. This would most likely involve submitting data to the TGA to demonstrate safety and efficacy in this age group. Following a revised indication, the next step would be to provide a submission to the PBAC that includes an evaluation of the cost-effectiveness of extended-release methylphenidate against immediate-release methylphenidate or another appropriate comparator in the treatment of adults.

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' will publish 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.

It may not be possible to reply to all individual questions. Those letters and responses selected by the Editorial Executive Committee will be published in the journal, subject to the usual editorial controls.

Bronchiectasis: a new look at an old adversary

Amy McLean, Respiratory and Sleep Physician, Royal Prince Alfred Hospital, Sydney

Summary

The management of bronchiectasis is finally advancing and patients have new options in terms of diagnostics, antibiotic therapy and physiotherapy. The principles of management have not changed, but with some simple interventions patients can experience improved quality of life and health outcomes. Many treatments developed for cystic fibrosis are now being applied to the management of bronchiectasis due to other causes.

Key words: antibiotics, cystic fibrosis.

(Aust Prescr 2008;31:77–9)

Introduction

For many healthcare professionals, the term 'bronchiectasis' conjures up a bygone era of cold damp houses and coughing children. Today there is a revived interest in this condition among respiratory physicians and after many stagnant years we are able to offer something new.

The management of cystic fibrosis has rapidly improved over the past 20 years with vastly improved life expectancies. Research has flourished, and many treatments developed for the management of cystic fibrosis-related bronchiectasis are already being used in non-cystic fibrosis bronchiectasis sufferers in the clinical setting. Compared to other respiratory disorders such as asthma, evidence for the safety and efficacy of treatments used in bronchiectasis is scarce.

What do general practitioners want to know?

There are a number of commonly asked questions regarding bronchiectasis in general practice.

What monitoring is appropriate and when?

The advent of high resolution CT scans means there is a new gold standard for diagnosis.[1] We are able to assess the anatomy and severity of patients with known disease more accurately as well as diagnosing new patients. High resolution CT chest scanning should be performed at diagnosis and as determined by clinical progress. Chest X-rays are most useful in evaluating complications such as pneumonia.

Functional monitoring with spirometry (and lung volumes where available) is very useful and should be performed both during exacerbations and in stable periods. The frequency of testing will depend on the deterioration and exacerbation rate for the individual patient.

When is the best time to perform sputum cultures?

Sputum cultures should be done when the patient is stable and, ideally, not taking antibiotics. This information can then be used to guide the management of their next exacerbation. Patients on long-term macrolide antibiotics can still be managed along the same lines, as these drugs (in the low doses used) have little effect on actual pathogens isolated and on antibiotic susceptibility profiles.

If no sputum culture is available for a particular patient, collect a sample then treat for the more common pathogens, for example *Haemophilus influenzae*, with drugs such as amoxycillin/clavulanic acid or roxithromycin. If the patient fails to respond, consider treating empirically for pseudomonas pending the results of sputum culture.

Does pseudomonas colonisation matter?

We know a lot more about this pathogen than we used to. We are now aware that it forms three-dimensional structures, referred to as biofilms, which adhere to the respiratory epithelium and resist antibiotic penetration. Patients colonised with pseudomonas have a worse prognosis and more rapid decline in lung function than those who are not.[2] During an exacerbation, patients with pseudomonas should be treated aggressively with antipseudomonal antibiotics. A suitable oral antibiotic would be ciprofloxacin for at least 14 days. Patients who develop resistance to ciprofloxacin should be considered for combination treatment with ciprofloxacin and nebulised aminoglycoside (for example tobramycin). This is usually best administered in consultation with a hospital respiratory outpatient unit. Inpatients are usually treated with ticarcillin/clavulanic acid combined with an inhaled or intravenous aminoglycoside. For chronic colonisation, patients should probably have a trial of long-term macrolide antibiotics.[3]

Is physiotherapy still important and is there anything new?

Physiotherapy is still considered an essential part of bronchiectasis management and research has consistently shown it to be of benefit. For example, patients with cystic fibrosis had a faster decline in lung function when they were non-compliant with chest physiotherapy. Options for physiotherapy are broader than they used to be. Easy to use

hand-held devices such as positive expiratory pressure or flutter devices in addition to active-cycle breathing techniques are an option for many patients. Postural drainage still has a place for heavy sputum producers. Refer your patients to a local respiratory physiotherapist for advice on this important management tool.

Should my patient be on long-term antibiotics?

The cautious answer to this question is, 'We don't know'. There has been a lot of research in this area in cystic fibrosis. Several large clinical trials of macrolide antibiotics in cystic fibrosis have shown improvements in various clinical outcomes including sputum production and quality of life.[3] A lot of bench research has shown that macrolide antibiotics have anti-inflammatory effects and this may be the mechanism by which they help in cystic fibrosis. Many respiratory colleagues now give patients a trial of a low-dose regular macrolide, for example azithromycin 250 mg daily or clarithromycin 125 mg twice a day, for a few months and assess for improvements in sputum production and exacerbation rates. A large randomised controlled trial of this strategy has not yet been done.

Should my patient be on inhaled corticosteroids?

Bronchiectasis is an inflammatory condition in which the ongoing damage of the airways is due to the inflammatory response to pathogens. Inhaled corticosteroids reduce this inflammatory damage. Several randomised controlled trials have shown a benefit of inhaled corticosteroids in patients with bronchiectasis, with the main improvements being reduced sputum production and exacerbations.[4]

Are there any new medications to assist sputum clearance?

Drugs to assist sputum clearance are seeing a revival with research into using two osmotic agents – nebulised hypertonic saline and inhaled mannitol. Both of these agents have been shown to assist sputum clearance predominantly by increasing hydration of the sputum and improving the viscosity. Hypertonic saline has been shown to reduce exacerbation rates in a large cystic fibrosis trial.[5] In non-randomised studies, mannitol improved airway clearance and quality of life in patients with non-cystic fibrosis bronchiectasis. A large randomised controlled trial has just been completed. Neither treatment is available commercially at the time of writing but hypertonic saline is available through public hospital outpatient clinics, and mannitol should be available as a metered-dose inhaler over the next few years.

Is pulmonary rehabilitation of benefit?

All patients with chronic lung disease and dyspnoea warrant some form of pulmonary rehabilitation to prevent the inevitable deconditioning that occurs and exacerbates the dyspnoea. There has not been much research for patients with bronchiectasis, but one study has clearly demonstrated benefit.[6]

What long-term sequelae should I be aware of?

The important long-term sequelae in bronchiectasis are respiratory failure, cor pulmonale, nocturnal hypoventilation, poor nutrition, osteoporosis and haemoptysis.

Respiratory failure can be hypoxic or hypercapnic or both. Hypoxic patients benefit from home oxygen and this can be prescribed by a respiratory physician. Hypercapnic patients may benefit from treatment with non-invasive ventilation, that is bi-level positive airway pressure or variable positive airway pressure.

Cor pulmonale will present with the development of right heart failure symptoms (ankle swelling, often the first thing noticed by the patient) and this should prompt investigation with echocardiography to measure right heart parameters as well as consideration of fluid restriction and diuretics.

Patients with nocturnal hypoventilation will complain of poor sleep, morning headaches and excessive daytime sleepiness. They should be referred to a respiratory/sleep physician for an assessment.

Nutritional deficiency is common in this condition due to the chronic inflammatory state, breathlessness and poor appetite. Patients who are struggling should be weighed each appointment and encouraged to try calorific supplements and see a dietitian.

Osteoporosis is common because patients may have received a lot of prednisone in the past and have nutritional deficiency. Also, a high proportion of patients are postmenopausal women. Broken ribs and vertebral crush fractures can be a problem in patients with lung disease who have become unable to complete physiotherapy and suffer worsening respiratory failure using adequate analgesia. It is best to prevent this with calcium supplementation and bisphosphonates. These patients should probably have an annual bone mineral density scan.

Haemoptysis is dangerous and can occur at any stage of the disease. It requires prompt assessment in a hospital environment. These patients can bleed profusely due to abnormal vasculature, and asphyxiation can develop quickly because of poor gas exchange.

Depending on your local resources, the development of any of these conditions should prompt referral to a specialist centre with multidisciplinary experience in the management of chronic lung disease.

Vaccinations

Patients with bronchiectasis should be considered 'at risk' for serious sequelae from pneumococccal and influenzal illness. They should be given the pneumococcal vaccine and an annual influenza vaccine.

Conclusion

Patients with bronchiectasis experience a lot of morbidity. The management requires attention to a diverse range of concerns, but each intervention is simple and generally easily available. A holistic management strategy will improve health outcomes and quality of life.

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Conflict of interest: none declared

Patient support organisation

The Australian Lung Foundation

Phone 1800 654 301

Website www.lungnet.com.au

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.

Alglucosidase alfa

Myozyme (Genzyme)

vials containing 50 mg powder for reconstitution

Approved indication: Pompe disease

Australian Medicines Handbook Appendix A

Pompe disease is a rare inherited glycogen storage disease caused by a deficiency in the enzyme acid alglucosidase alfa, which breaks down glycogen to glucose. In patients who lack this enzyme, glycogen builds up in various tissues, particularly cardiac and skeletal muscle, leading to cardiomyopathy, progressive muscle weakness and impaired respiratory function. Early-onset disease typically leads to death from cardiorespiratory failure within the first year of life.

This recombinant form of human alglucosidase alfa is produced in Chinese hamster ovary cells. The recommended dose is 20 mg/kg given as an intravenous infusion every two weeks. Its elimination half-life is 2–3 hours.

The efficacy of recombinant alglucosidase alfa (20 mg/kg or 40 mg/kg fortnightly) has been assessed in 18 infants with Pompe disease (aged 7 months or younger) and compared to a historical cohort of 61 untreated infants. All patients given alglucosidase alfa survived until 18 months of age compared with only one of the 61 untreated controls. However, three of the treated infants required invasive ventilatory support during the study. Thirteen of the 18 treated infants had improved motor development by week 52 of treatment with seven of them being able to walk independently. In general, the higher alglucosidase alfa dose (40 mg/kg) did not seem to offer any clear advantage over the lower dose (20 mg/kg).[1]

In a similarly designed trial, 21 infants aged 3–36 months were given alglucosidase alfa 20 mg/kg fortnightly. Of the 16 infants who did not need invasive ventilatory support at enrolment, four had died, two required invasive ventilatory support and ten did not after a year of treatment. Of the five infants who needed ventilatory support at baseline, one had died and four still required ventilation. A historical comparison of the treated infants with 86 untreated infants showed no significant difference in mortality rate. The trial was inconclusive probably due to the heterogeneous study population.

Around half of the children treated with alglucosidase alfa had an infusion-related reaction, which included fever, rash, urticaria, cough, decreased oxygen saturation, vomiting, flushing and tachycardia. These were usually managed by slowing or interrupting the infusion or giving an antipyretic, antihistamine or corticosteriod. Life-threatening anaphylactic reactions have been reported. Pneumonia, respiratory failure or distress, intravenous catheter-related infection, respiratory syncytial virus infection and gastroenteritis have also occurred following treatment.[1]

There is an increased risk of cardiac arrhythmia and sudden death during general anaesthesia for central venous catheter replacement. This has been observed in patients with cardiac hypertrophy. Acute respiratory failure has also occurred in one

infant following an infusion of alglucosidase alfa. This was possibly associated with fluid overload.

Most infants developed antibodies to the recombinant alglucosidase alfa within three months of starting treatment. High antibody titres have been associated with reduced efficacy and an increased incidence of infusion reactions.[1]

Alglucosidase alfa replacement therapy is the only treatment available for improving the short-term survival of infants with Pompe disease. The long-term prognosis of these patients is not known. As there is a potential for serious adverse events, appropriate medical support, including resuscitation equipment, should be available when treating patients. The effectiveness of alglucosidase alfa in late-onset Pompe disease has not yet been established.

X manufacturer did not respond to request for data

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Duloxetine

Cymbalta (Eli Lilly)

30 mg and 60 mg capsules

Approved indication: major depression

Australian Medicines Handbook section 18.1.2

Duloxetine is a new antidepressant which selectively inhibits serotonin and noradrenaline reuptake. It also weakly inhibits dopamine uptake.

After oral administration of duloxetine, maximum plasma concentrations are reached after six hours. Duloxetine is extensively metabolised in the liver and has an overall half-life of about 12 hours. Most of the metabolites are excreted in the urine.

The efficacy of duloxetine (60 mg/day) has been compared to that of escitalopram (10 mg/day) and placebo in a randomised study of 684 patients (randomised in a 2:2:1 ratio). The onset of efficacy was defined as a 20% sustained reduction in the patient's score on the Hamilton Rating Scale for Depression Maier subscale, by the second week of treatment. The probability of meeting these criteria was 42.6% in patients given duloxetine, 35.2% in patients given escitalopram and 21.5% in patients given placebo. After eight weeks, the probability of responding to treatment (defined as a 50% improvement from baseline on the Hamilton Rating Scale for Depression) was not statistically different between patients given active drug or placebo. Response rates were 48.7% for duloxetine, 45.3% for escitalopram and 36.9% for placebo.[1]

In a review analysing efficacy data from nine duloxetine trials, the number needed to treat for a duloxetine dose of 60 mg/day or more was 6 for a response (based on the Hamilton Rating Scale for Depression), 7–9 for remission and 6–7 for a Clinical Global Impression-defined improvement by eight weeks. For fluoxetine or paroxetine (20 mg/day), the number needed to treat was 7 for a response, 11 for remission and 8 for a Clinical Global Impression-defined improvement.[2]

A safety analysis revealed significantly more nausea, dry mouth, vomiting and yawning reported by patients on duloxetine treatment compared to those on escitalopram or placebo. Nausea was the most common adverse event occurring in 23.8% of patients taking duloxetine, 12% of patients taking escitalopram and 8.8% of patients taking placebo. There were considerably more dropouts due to nausea in the duloxetine group than in the escitalopram group. Mean changes in blood pressure and heart rate after treatment were higher for duloxetine than escitalopram.[1]

Fatal cases of liver failure have been reported with duloxetine so it is contraindicated for patients with hepatic impairment and should not be given to patients who are drinking substantial amounts of alcohol. A lower dose of 30 mg/day should be used in patients with end-stage renal disease.

The concomitant use of monoamine oxidase inhibitors with duloxetine is contraindicated. Duloxetine should be started at least 14 days after finishing monoamine oxidase inhibitor treatment.

The metabolism of duloxetine involves cytochrome P450 1A2 and 2D6 therefore concomitant administration of P450 1A2 inhibitors such as ciprofloxacin should be avoided. Caution should be used when giving duloxetine with drugs that are metabolised by P450 2D6. Thioridazine should be avoided.

If tolerability is a concern, patients can be started on a dose of 30 mg/day before increasing to 60 mg/day. If patients do not respond to 60 mg/day, there is little evidence to suggest that they will respond to a higher dose. When discontinuing duloxetine after more than one week of treatment, tapering of the dose is recommended.

The short-term effectiveness of duloxetine is comparable to low-dose escitalopram but its tolerability is less. There appear to be no published studies comparing duloxetine to other drugs that inhibit the reuptake of noradrenaline and serotonin, such as venlafaxine and reboxetine. There are limited data about the long-term use of duloxetine.

T manufacturer provided only the product information

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Ibandronic acid

Bondronat (Hospira)

vials containing 6 mg/6 mL

Approved indications: hypercalcaemia, bony metastases of breast cancer

Australian Medicines Handbook section 10.3.1

Bisphosphonates can reduce the hypercalcaemia of malignant disease by inhibiting the resorption of bone. Clodronate, pamidronate and zoledronic acid are already available for this indication. They are now joined by ibandronic acid which has been approved for patients, with or without metastases, who have tumour-induced hypercalcaemia. It is also approved for the treatment of metastatic bone disease in patients with breast cancer.

When ibandronic acid is given intravenously, it should be diluted and infused over two hours. For hypercalcaemia the dose is determined by the serum calcium, after correction for the albumin concentration. Patients with metastatic breast cancer can be given an intravenous infusion every four weeks or a daily oral dose. Ibandronic acid should not be taken with food as this reduces its bioavailability by 90%. The tablets must be swallowed whole with water and the patient must not lie down for 30 minutes afterwards.

About half of the dose is absorbed by bone. The remainder is excreted unchanged in the urine. No dose adjustment is suggested for hepatic impairment, but the dose should be reduced in patients with severe renal impairment.

A randomised phase II trial studied 174 cancer patients with hypercalcaemia.[1] These patients were given ibandronic acid in one of three different doses. The best response to treatment was seen in the patients given the highest dose (2 mg). In this group of 55 patients, 37 became normocalcaemic. Patients with higher baseline concentrations of calcium also responded better to the highest dose.

The efficacy of intravenous ibandronic acid, given every 3–4 weeks, was assessed in a placebo-controlled trial of 466 women with breast cancer and bony metastases. Their median time in the study was 13 months with placebo and 18 months with ibandronic acid. Although a 2 mg dose was not statistically different from placebo, the rate of skeletal complications was reduced in women given ibandronic acid 6 mg. At that dose there were 2.65 'bone events' per patient compared with 3.64 in the placebo group. (These events included fractures and other bony complications requiring treatment.) The women taking ibandronic acid 6 mg also had less bone pain.[2]

Oral ibandronic acid was assessed in 435 women with bony metastases randomised to take 20 mg, 50 mg or a placebo daily for up to 96 weeks. The mean number of bone events per patient was 1.36 with 20 mg, 1.43 with 50 mg and 2.23 with placebo. Although the two doses of ibandronic acid had similar efficacy the higher dose is recommended for clinical use.[3]

The adverse effects of oral treatment include dyspepsia, oesophagitis, abdominal pain, nausea and hypocalcaemia. Intravenous ibandronic acid is associated with fever or a flu-like illness, asthenia, diarrhoea, vomiting, headache and myalgia. Calcium and renal function should be monitored during treatment. The patient must have an adequate intake of calcium and vitamin D if there is a risk of hypocalcaemia. They should also have a dental check-up before treatment because of the association between bisphosphonates and osteonecrosis of the jaw.

A Cochrane review has concluded that bisphosphonates are effective treatment for the bony metastases of breast cancer, although they have no effect on survival. It did not report if ibandronic acid had a clinical advantage over other bisphosphonates.[4] An analysis in the UK found that oral ibandronic acid is more cost-effective than intravenous pamidronate or zoledronic acid, but this could reflect the cost of infusions rather than greater efficacy.[5] Comparative trials are needed.

T T T manufacturer provided all requested information (provided by Roche)

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Pramipexole

Sifrol (Boehringer Ingelheim)

125 microgram, 250 microgram and 1 mg tablets

Approved indications: Parkinson's disease, restless legs syndrome

Australian Medicines Handbook section 16.2.1

In Parkinson's disease, there is a reduced concentration of dopamine in the nigrostriatal system. Dopamine agonists, such

as bromocriptine, therefore have a role in the treatment of Parkinson's disease. Pramipexole is a non-ergoline dopamine agonist which acts on D_2 and D_3 receptors (see 'Dopamine – clinical applications i. neurology', Aust Prescr 1994;17:21-3).

Levodopa (combined with a decarboxylase inhibitor) remains the first-line drug treatment for Parkinson's disease of moderate severity. In advanced disease, the effect of this therapy starts to wear off. Maintaining the stimulation of dopamine receptors may alleviate this disabling complication.

When pramipexole was added to levodopa treatment, in a double-blind trial of 291 patients with advanced disease, it was more effective than placebo. Pramipexole improved motor function and decreased 'off' time. The patients' self-assessments also suggested that the severity of the 'off' time was reduced by pramipexole. Compared to placebo, the biggest changes were seen in rigidity, resting tremor, hand movements and finger tapping. At the end of the 32-week trial, the dose of levodopa required by the patients taking pramipexole had been significantly reduced.[1]

In the trial, the maximum dose was 4.5 mg a day. Usually pramipexole is given in divided doses, beginning with 125 microgram three times a day. The dose is increased every week if the patient is improving without adverse effects. While the dose is being titrated, the dose of levodopa can be reduced.

After a dose-ranging study in early Parkinson's disease[2], pramipexole was compared with levodopa in a double-blind trial involving 301 patients. Those randomised to receive pramipexole took longer to develop problems with the effect wearing off, on-off fluctuations or dyskinesia.[3]

Pramipexole also has an indication for restless legs syndrome. It was compared with placebo in a 12-week trial involving 344 patients. On a 40-point symptom rating scale, there was a mean improvement of 9.3 points with placebo and a 12.8 point improvement in people taking pramipexole 250 microgram daily. While 75% of patients responded to this dose of pramipexole, the response in the placebo group was 51%.[4]

In Parkinson's disease, lower doses of pramipexole are required if the patient has renal impairment as the drug is mainly excreted unchanged in the urine. The elimination half-life is increased from 8 to 12 hours in elderly patients. Renal clearance is also reduced by cimetidine which is thought to inhibit secretion in the renal tubules. This mechanism also creates the potential for interactions between pramipexole and ranitidine, diltiazem, verapamil, digoxin, triamterene and trimethoprim.

Some of the adverse effects of pramipexole can be predicted because of its stimulation of dopamine receptors. For example, up to 17% of patients will develop hallucinations. Other common adverse effects include nausea, insomnia, somnolence and dyskinesia. A few patients have fallen asleep suddenly, including when driving, and others have become compulsive gamblers while taking pramipexole.

Pramipexole should be withdrawn gradually over several days. Sudden cessation of antiparkinson drugs can cause neuroleptic malignant syndrome.

There are few published comparative studies of the dopamine agonists. A study in which pramipexole compared favourably with bromocriptine did not have enough power to show a statistical difference.[5] There is limited information about the long-term use of pramipexole. This is important because, for example, retinal degeneration has been seen in long-term studies of rats. Although fewer patients given pramipexole develop dopaminergic motor complications, patients given levodopa have a greater improvement in their early Parkinson's disease. While both drugs cause an initial improvement, after two years the patients' quality of life scores decline significantly less with levodopa.[3]

T T manufacturer provided additional useful information

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Sitaxentan sodium

Thelin (CSL)

100 mg tablets

Approved indication: pulmonary hypertension

Australian Medicines Handbook section 6.7.2

Pulmonary hypertension results from intimal hypertrophy narrowing small pulmonary arteries. The increase in pulmonary vascular resistance leads to right ventricular failure. Primary pulmonary hypertension is less common than the pulmonary hypertension associated with other conditions such as connective tissue diseases. The choice of treatment has expanded over recent years[1] with the approval of drugs such as bosentan, epoprostenol and treprostinil.

Patients with pulmonary arterial hypertension have increased concentrations of endothelin 1. This peptide acts on the endothelin A receptor to cause vasoconstriction and on the endothelin B receptor to cause vasodilation. Sitaxentan antagonises the endothelin A receptor, so the arterial pressure should reduce.

The daily dose of sitaxentan is well absorbed. The molecule is metabolised by cytochrome P450 2C9 and 3A4. As warfarin is also metabolised by P450 2C9, sitaxentan can increase the anticoagulant effect. Sitaxentan's metabolites are excreted in the urine and faeces, with an elimination half-life of eight hours.

There have been three placebo-controlled trials of sitaxentan involving a total of 516 patients. One trial lasted for 12 weeks and the others for 18 weeks. All three trials used changes in the distance patients could walk in six minutes as an outcome measure. At the start of the 12-week study, the patients could walk approximately 400 metres in six minutes. By the end of the study, patients given sitaxentan 100 mg could walk 35 metres further than the placebo group in six minutes. At the start of the18-week studies, the patients could walk 322–361 metres. After treatment, those given sitaxentan 100 mg could walk 25–31 metres further than those in the placebo group. There was an improvement in the severity of the condition in 12–25% of the patients. Although patients with less severe disease were included in the trials, the approval of sitaxentan is limited to patients with class III disease, according to the World Health Organization's classification. The approval also specifies primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.

Peripheral oedema, headache, insomnia, nasal congestion and epistaxis were common adverse events which occurred more frequently with sitaxentan than with placebo. Liver function must be checked before and during treatment with sitaxentan as hepatitis can develop. A rise in liver enzymes may require treatment to be stopped. Sitaxentan may also cause a decline in haemoglobin.

It is not clear if sitaxentan has any advantage over bosentan, another endothelin antagonist. Patients who do not respond to bosentan are unlikely to respond to sitaxentan.

T manufacturer provided only the product information

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

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

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

Answers to self-test questions

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

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Case example: calculating lean body weight in obese children

Lean body weight calculation

Lean body weight (males) = (1.1 x weight) – (0.0128 x BMI x weight)

Lean body weight (females) = (1.017 x weight) – (0.0148 x BMI x weight)

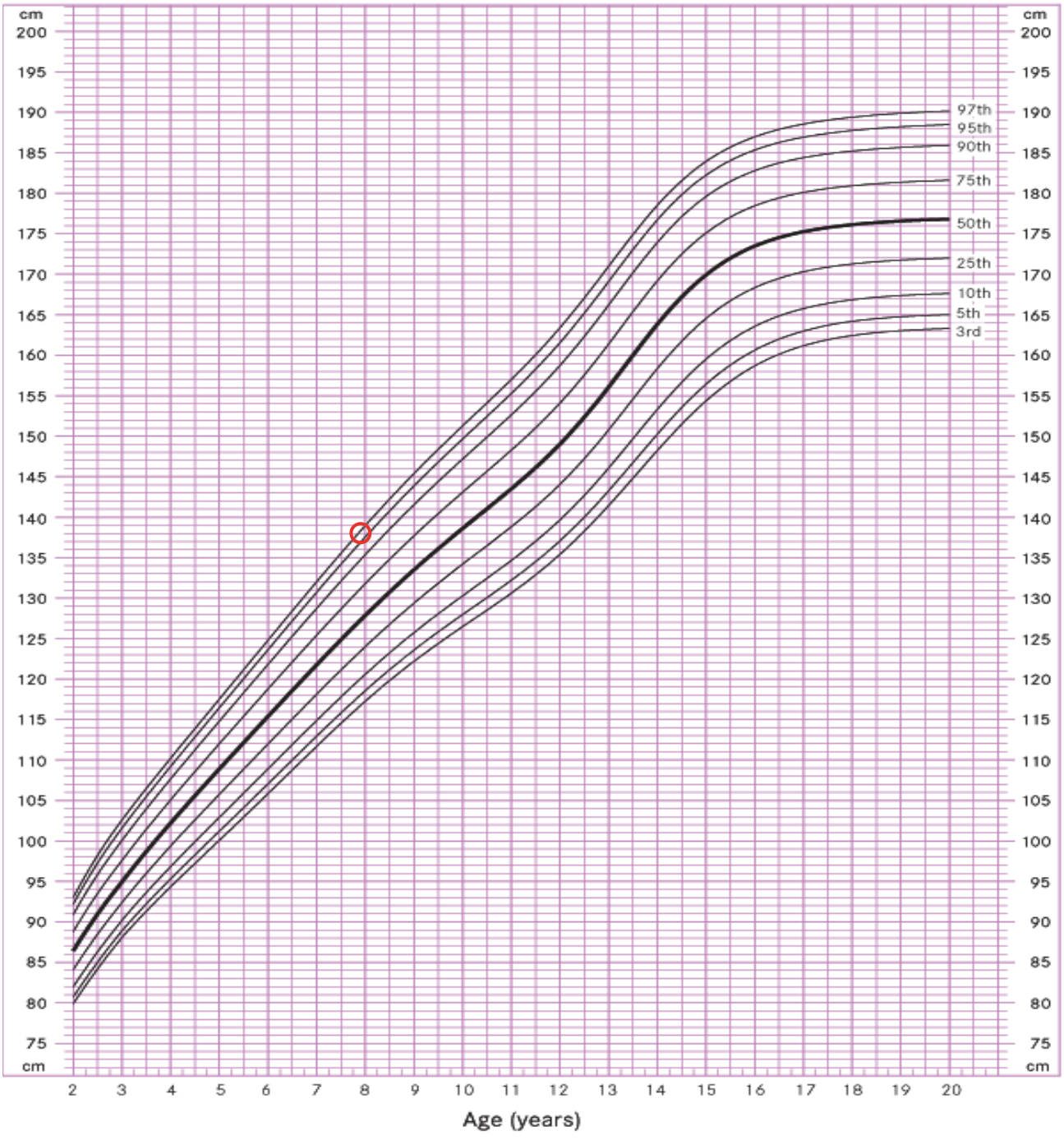
Body mass index (BMI) = weight (kg) / (height (m))^2

Weight for height

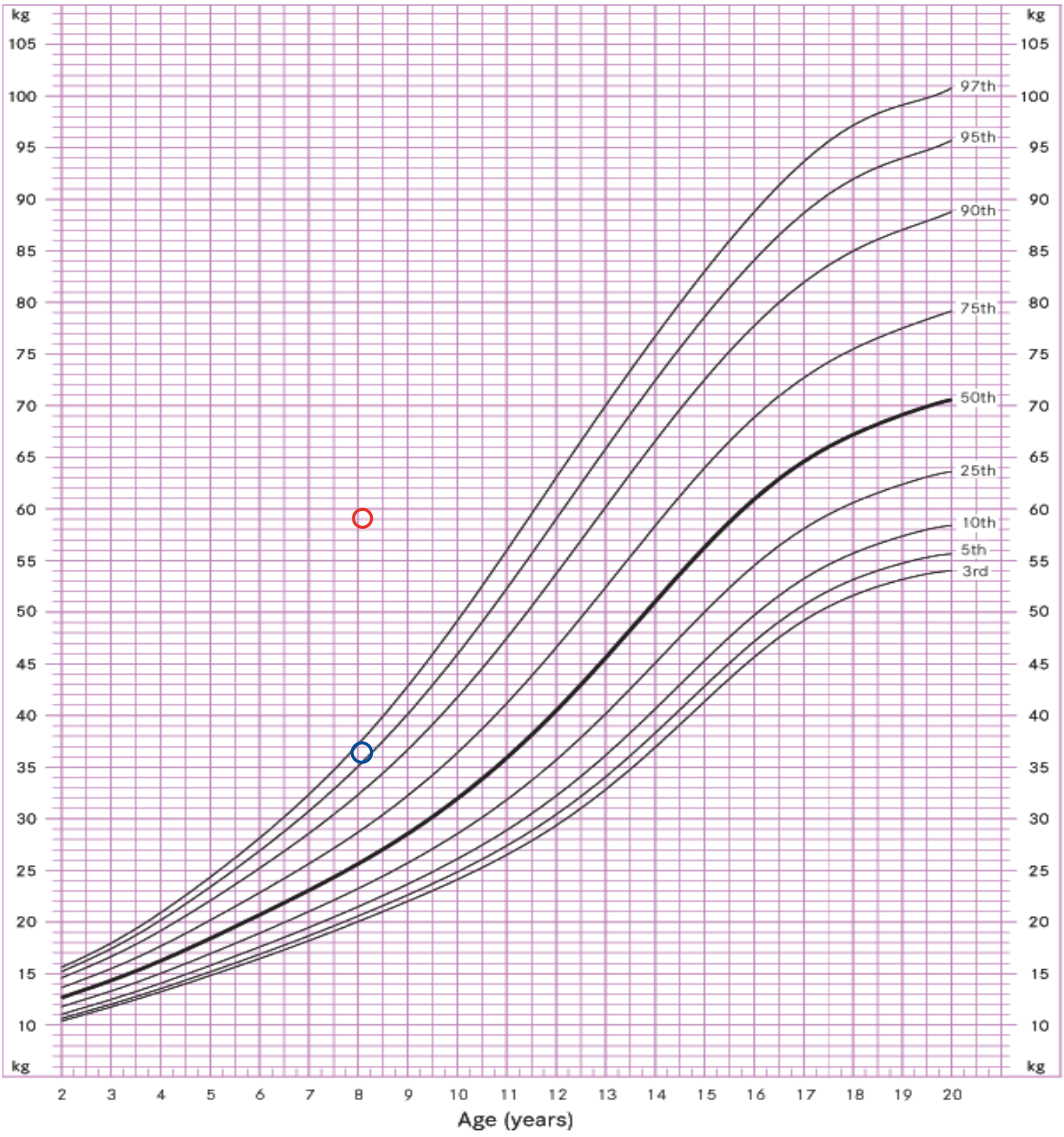
In this example an eight-year-old boy has a weight of 60 kg, and height of 138 cm which is on the 95th percentile for his age, thus his predicted weight for height is obtained by determining what weight corresponds to the 97th percentile for an eight-year-old boy, and here it is 35 kg. Therefore, his doses should be calculated using 35 kg, rather than 60 kg.

○ Actual weight and height ○ Predicted weight for height

Stature-for-age percentiles: Boys, 2 to 20 years



Weight-for-age percentiles: Boys, 2 to 20 years



Growth charts developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). The charts are available at www.health.vic.gov.au/childhealthrecord/growth_details/boys.htm