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Editorial

H1N1 immunisation: too much too soon?

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Key words: adverse effects, influenza vaccines, vaccination.

(Aust Prescr 2010;33:30–1)

In April 2009, a new influenza strain – H1N1 'swine flu' – was identified in Mexico with an apparent high case fatality rate (about 5%). As H1N1 spread rapidly throughout the world it caused not only a 'pandemic' but also widespread fear. However, overall, swine flu has been associated with fewer deaths (case fatality rate < 0.01%) than seasonal influenza (case fatality rate < 0.1% approx.),[1] and is of low virulence. While younger people were disproportionately infected by swine flu, it was people aged 50–60 years who had more frequent serious illness in terms of admissions to intensive care units and deaths.[2–4]

In the 2009 Australian winter, swine flu's associated mortality rate was 0.9 per 100 000 people. In those under 40 years with no risk factors, the mortality rate was less than one per million.[3] While there were some differences (for example pregnant women), the overall effects of this virus as judged by absenteeism, hospitalisations and deaths were similar to those of previous seasonal influenza strains.[2–4]

While swine flu is a 'new' virus, it is an H1N1 virus, strains of which have been circulating since 1918. Not surprisingly, many people have pre-existing immunity. Most people over 65 years appear to be immune, as reflected by their low infection rates. In an Australian H1N1 vaccine trial of adults (aged 18–65 years), 27% had protective antibody concentrations and 62% had detectable pre-existing antibodies.[5] Most infections in the 2009 winter occurred in children and younger adults.[2–4] It is likely therefore that more than 50% of the Australian population are already immune because of pre-existing immunity or recent infection. In any mass vaccination campaign, those who are already immune are unlikely to get additional benefits from the vaccine, but remain at risk of adverse effects.

The timing of a mass vaccination program is important. In Australia, our mass vaccination program for this virus started in spring 2009. However, it was very unlikely that the swine flu virus would circulate widely in Australia during the summer. The composition of a trivalent vaccine for next winter's seasonal influenza will include a swine flu component. People already vaccinated against swine flu who need protection for seasonal influenza will still need re-vaccination in autumn with the trivalent vaccine as we cannot necessarily predict which influenza strains will be circulating in winter 2010.

The use of multidose vials in the vaccination program was a needless additional risk. In the past, many infections, such as *Staphylococcus aureus*, hepatitis B and HIV, have been caused by vaccination programs using multidose vials.[2] Even a very low individual risk can translate into hundreds of people with cross-infections when multidose vials are used in large populations. Over eight million doses of trivalent seasonal influenza vaccine are given per year in Australia using single-use preloaded syringes. It is difficult to see why this could not have been done for the swine flu vaccine. Also with multidose vials, large amounts of vaccine may be wasted. The advantages of multidose vaccines are small monetary savings in manufacture and the potential for a more rapid roll-out of a vaccine. However, current technology allows single-dose preloaded syringes to be rapidly manufactured.

We need to learn lessons from the past. In the USA in October 1976 there was a mass immunisation campaign for H1N1 swine flu. Unexpectedly, Guillain-Barré syndrome occurred at a rate of about 1 per 100 000 vaccine recipients. The expected swine

In this issue...

Patients in hospital are at risk of venous thromboembolism, particularly if they have had surgery to their legs. Although heparins have a role in preventing thromboembolism they have to be given by injection. The development of effective oral anticoagulants for prophylaxis is therefore of great interest. Timothy Brighton explains how the new drugs work and Alex Gallus reviews their use in orthopaedic surgery.

Like the control of clotting, the physiology of calcium and phosphate is complicated. Darren Roberts explains how disturbances of this physiology in patients with kidney disease results in bone damage.

flu epidemic did not eventuate. Thus, the complications that occurred were not offset by any meaningful benefits in the general population. It was only after 40 million people had been vaccinated over two and a half months that the association of these rare but serious adverse effects with the vaccine was accepted. The program was stopped in December 1976.[6]

In Australia, we do not have good postmarketing surveillance mechanisms in place and mainly rely on voluntary reporting. This is unlikely to accurately measure the percentage of people who get adverse effects or to identify rare adverse effects in a timely fashion. A more effective way might be to follow a large sample of vaccine recipients for, say, a month. This could be done by practice nurses in a defined number of general practices.

A problem with this vaccine and other influenza vaccines is that there are relatively few well-designed, large randomised studies.[5,7] The efficacy of seasonal inactivated parenteral vaccines in preventing influenza in healthy adults varies from 50% to 80%.[7] The often quoted efficacy for protection from all-cause mortality with seasonal influenza vaccines is around 50%. However, those in vaccinated groups frequently have fewer comorbidities than those in non-vaccinated groups. A recent Californian study looked at over 100 000 deaths over nine years[8] and showed that the decrease in all-cause mortality attributable to seasonal influenza vaccine was 4.6%.

The reason these issues are important is that we do not have robust data on which to make proper decisions on the cost-effectiveness of any mass vaccine programs. In young people without risk factors, the rates of death and complications last winter from swine flu were very low and are similar to the risk of serious vaccine-associated adverse effects such as Guillain-Barré syndrome and anaphylaxis. Around 50% of people who received the H1N1 vaccine in the Australian trial had mild to moderate systemic adverse effects and 1.7% had (solicited) systemic adverse effects recorded as severe.[5] In children, 20% had moderate to severe systemic adverse effects after receiving a single 15 microgram dose of vaccine.[9] It is very important that we make sure we do more good than harm with any vaccine. Thus, we need a large cohort of people (tens of thousands) followed prospectively so that we can accurately know what are the percentages of people with adverse effects in the postmarketing period. We also need a robust system to accurately detect the very rare but serious adverse effects. Otherwise we risk repeating the mistakes made in the 1976
USA swine flu vaccine program.[6]

The disproportionate fear generated by the swine flu virus has caused many decisions to be made that in retrospect were inappropriate. We need to learn from our experiences and more importantly ensure that well-designed, large, prospective long-term studies are done so we can answer basic questions on the true safety and efficacy of influenza vaccines. This is not only in the elderly but also in groups proposed for routine seasonal influenza campaigns such as children and pregnant women. We need these types of data before embarking on further mass immunisation programs, particularly if done during periods with likely low infection rates (that is, summer) using multidose vials.

References

1. Flu.gov (U.S.). Community strategy for pandemic influenza mitigation. 2007 Feb. www.flu.gov/professional/community/mitigation.html [cited 2010 Mar 12]
2. Collignon P. Pandemic influenza: inappropriate fear causes inappropriate responses. In healthcare we need good surveillance data to make the best decisions [editorial]. Healthcare Infect 2009;14:77-9. www.publish.csiro.au/view/journals/dsp_journal_fulltext.cfm?nid=241&f=HI09021 [cited 2010 Mar 12]
3. New South Wales public health network. Progression and impact of the first winter wave of the 2009 pandemic H1N1 influenza in New South Wales, Australia. Euro Surveill 2009;14:pii=19365. www.eurosurveillance.org/ViewArticle. aspx?ArticleId=19365 [cited 2010 Mar 12]
4. Department of Health and Ageing. Australian influenza surveillance summary report. No. 29, 2009, reporting period: 21 November 2009 – 27 November 2009. www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/ozflu2009.htm/$File/ozflu-no29-2009.pdf [cited 2010 Mar 12]
5. Greenberg ME, Lai MH, Hartel GF, Wichems CH, Gittleson C, Bennet J, et al. Response to a monovalent 2009 influenza A (H1N1) vaccine. N Engl J Med 2009;361:2405-13. http://content.nejm.org/cgi/reprint/361/25/2405.pdf [cited 2010 Mar 12]
   For supplementary appendix see http://content.nejm.org/cgi/data/NEJMoa0907413/DC1/1 [cited 2010 Mar 12]
6. Neustadt R, Fineberg H. The swine flu affair. Decision-making on a slippery disease. Washington: U.S. Department of Health, Education, and Welfare; 1978. www.iom.edu/Global/News%20Announcements/~/media/Files/swine%20flu%20affair%20electronic%20edition%20200904web.ashx [cited 2010 Mar 12]
7. Demicheli V, Di Pietrantonj C, Jefferson T, Rivetti A, Rivetti D. Vaccines for preventing influenza in healthy adults. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD001269. DOI: 10.1002/14651858.CD001269.pub3. www.cochrane.org/reviews/en/ab001269.html [cited 2010 Mar 12]
8. Fireman B, Lee J, Lewis N, Bembom O, van der Laan M, Baxter R. Influenza vaccination and mortality: differentiating vaccine effects from bias. Am J Epidemiol 2009;170:650-6.
9. Nolan T, McVernon J, Skeljo M, Richmond P, Wadia U, Lambert S, et al. Immunogenicity of a monovalent 2009 influenza A(H1N1) vaccine in infants and children: a randomized trial. JAMA 2010;303:37-46.

Conflict of interest: none declared

Letters

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. Letters are usually published together with their responses or comments in the same issue. The Editorial Executive Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

Biosimilars are not (bio)generics

Editor, – The Generic Medicines Industry Association wishes to comment on the editorial 'Biosimilars are not (bio)generics' (Aust Prescr 2009;32:146–7) by Professor McKinnon and Dr Lu.

The authors raise several key issues surrounding the important introduction of quality cost-effective 'biosimilars'. Many of the concerns raised are equally pertinent to the originator biologic reference products, and so are neither new nor unique to 'biosimilars'.

Of note, there exists a broad spectrum of 'biosimilar' medicines, ranging from small unglycosylated proteins (for example filgrastim) – which can be extremely well characterised – to much larger molecules (for example monoclonal antibodies) that currently are more difficult to characterise. Therefore, as with all pharmaceuticals, each product should be assessed on a case by case basis, and not be subject to conclusions based on broad generalisations.

It is critical to appreciate that very high levels of data are demanded by regulatory agencies for establishing the quality, safety and efficacy of all 'biosimilars'. These include product characterisation, comparative trials between the 'biosimilar' and the originator, and robust postmarketing surveillance plans.

It is well acknowledged that the Therapeutic Goods Administration is the competent authority to determine on every occasion whether these criteria are met, and there is no reason in the case of 'biosimilars' to believe or suggest otherwise.

Kate Lynch
Chief Executive Officer
Generic Medicines Industry Association

Professor R McKinnon and Dr C Lu, authors of the article, comment:

The comments by the Generic Medicines Industry Association are welcome and we generally endorse the views expressed. We would, however, note that the emphasis of our editorial was deliberately on contrasting biosimilars with generic products based on traditional small chemical entities, rather than on a detailed comparison of biosimilar approval processes with those relating to the approval of the originator biological reference products.

Flying and thromboembolism

Editor, – I refer to the article 'Flying and thromboembolism' (Aust Prescr 2009;32:148–50) and the patient's perspective on the same topic (Aust Prescr 2009;32:150–1).

I recall with relish the media exposure the 'economy class syndrome' had at the turn of the millennium and the impact this had on the airline industry in terms of seating standards and raising consumer awareness. The article revisited the relevance of both mechanical and chemical prophylaxis in different at-risk groups. However, it failed to address the more controversial issues about practical management of patients with treated venous thromboembolism – particularly with advice on mobilisation and flying – which was elegantly illustrated by the patient's perspective article.

Even with available research showing the benefits of early mobilisation in deep vein thrombosis with no significant risk in pulmonary embolism, there is still hesitation in the medical community in recommending continuing mobilisation in massive deep vein thrombosis, particularly those proximal to the femoral veins. Practical advice on flying and other activities after deep vein thrombosis should be addressed early in conjunction with patient handouts.

Ms Hannah Baird should be congratulated for her remarkable ability to manage her deep vein thrombosis in spite of the limited support she received. I wonder what would be the outcome if she was neither well-informed nor motivated to take charge of her condition.

Shyan Lii Goh
Orthopaedic registrar
Dubbo Base Hospital, NSW

Associate Professor Frank Firkin and Associate Professor Harshal Nandurkar, authors of the article, comment:

The purpose of the article was to discuss the relative degrees of risk conferred by in-flight and pre-existing medical factors. Prophylactic measures for patients at high risk, including those with a history of venous thrombosis, were discussed in the article.

The question of management of a patient with newly diagnosed venous thrombosis on therapy in relation to taking flights is a different issue. Dr Goh raises the issue of the extent to which early mobilisation confers risk despite administration of standard therapy for deep vein

thrombosis. Various factors may play a part, including physical limitations imposed by the impact of the thrombus on venous return, sequelae of pulmonary emboli and imaging results that raise concerns about thrombus stability.

More pertinent issues relate to the period in which there is an increased risk of venous thrombosis following the onset of deep vein thrombosis, amounting to many weeks, and thus delayed diagnosis and suboptimal therapy are disadvantageous. This enhanced risk is normally suppressed by appropriate treatment with low molecular weight heparin and warfarin, and regular monitoring to ensure the INR is maintained.

Editor, – In reference to the article 'Flying and thromboembolism' (Aust Prescr 2009;32:148–50), is there any place for rivaroxaban – currently only listed for major orthopaedic surgery – in high-risk long-haul flight patients? If so, at what dosage and for how long? These patients would previously have been offered subcutaneous low molecular weight heparin.

Mick Coward
Medical Adviser
The Travel Doctor – Traveller's Medical and Vaccination Centre
Adelaide

Associate Professor Frank Firkin and Associate Professor Harshal Nandurkar, authors of the article, comment:

There has been no official approval in Australia for low molecular weight heparin for prophylaxis in high-risk subjects on long-haul flights. Its use for this purpose is based on extrapolation from its proven efficacy in thromboembolism prophylaxis in major hip and knee joint surgery, when the venous thromboembolic risk is generally viewed as greater than that posed by a long-haul flight.

Oral rivaroxaban has been shown to be at least as effective as low molecular weight heparin for thromboembolism prophylaxis in major hip and knee joint surgery, and can be viewed as at least as effective for prophylaxis in long-haul flights, with the obvious advantage that it is an oral drug. However, this is a non-approved purpose as is the case with low molecular weight heparin. Prescribers should be aware of the risks associated with using rivaroxaban in patients with renal impairment or liver disease, and that other drugs may affect its metabolism. These issues are addressed in this issue of *Australian Prescriber* and in the August 2009 issue of RADAR (www.nps.org.au/nps_radar/rivaroxaban).

Editor, – I was staggered to read the article on 'Flying and thromboembolism' (Aust Prescr 2009;32:148–50) and not see the word 'pregnancy' mentioned once in the entire article.

I think this glaring omission needs to be corrected as there is too much evidence-based research confirming that pregnancy is associated with a significantly raised incidence of deep vein thrombosis on long-haul flights.

This article omits a significant group of travellers and sends incomplete messages to readers.

Richard Porter
Specialist Obstetrician
Sydney

Associate Professor Frank Firkin and Associate Professor Harshal Nandurkar, authors of the article, comment:

Increased levels of oestrogen are associated with increased thromboembolic risk during long-haul flights, as discussed in our article, and it is natural to consider this to apply to pregnancy.

It is, however, fundamental that guidance on managing risk factors be based on published evidence or consensus that can reasonably be accessed. In the case of pregnancy there are major publications that do not support an unequivocal assertion of an association with pregnancy in general.

In an article describing life-threatening venous thromboembolism manifested by pulmonary embolism after long-haul flights, there were no cases in pregnant women in contrast to a number of cases in women taking oral oestrogens.[1] In addition, the most recent American College of Obstetricians and Gynecologists Committee Opinion states there is a lack of evidence of increased venous thromboembolism risk in pregnant women.[2]

References

1. Lapostolle F, Surget V, Borron SW, Desmaizieres M, Sordelet D, Lapandry C, et al. Severe pulmonary embolism associated with air travel. N Engl J Med 2001;345:779-83.
2. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 443: Air travel during pregnancy. Obstet Gynecol 2009;114:954-5.

Management of renal bone disease

***Darren M Roberts**, Advanced Trainee, and **Richard F Singer**, Staff Specialist, Department of Renal Medicine, The Canberra Hospital*

Summary

Renal bone disease occurs in patients with chronic kidney disease. There are changes in the concentrations of calcium, phosphate, vitamin D and parathyroid hormone. Systemic complications include renal osteodystrophy and soft tissue calcification, which contribute to morbidity and mortality. As the changes of renal bone disease are potentially modifiable, early referral to a nephrologist for monitoring and treatment is recommended. Early advice about diet and regular monitoring of calcium, phosphate and parathyroid hormone are necessary. Careful prescribing of drugs and dialysis to achieve specific biochemical targets can minimise the complications. Phosphate binders and vitamin D analogues are required by most patients with advanced renal failure.

Key words: kidney disease, parathyroid hormone, phosphate binders, vitamin D.

(Aust Prescr 2010;33:34–7)

Introduction

Renal bone disease is a general term for the spectrum of complex changes to mineral metabolism and bone strength seen in patients with chronic kidney disease.[1] It is characterised by altered calcium, phosphate and vitamin D homeostasis and an altered physiological response to parathyroid hormone. The consequences of these changes include diminished bone strength and mineralisation (renal osteodystrophy)[2–4] as well as soft tissue and vascular calcification which occasionally results in the clinical syndrome of calcific uraemic arteriolopathy.[5] These systemic complications are collectively referred to as chronic kidney disease mineral and bone disorder.[1] This disorder impacts on cardiovascular disease progression, morbidity and mortality.[6,7]

Renal osteodystrophy encompasses a number of histologically different conditions. These include both low (adynamic bone disease) and high (osteitis fibrosa) bone turnover states, as well as conditions of altered mineralisation. These conditions all decrease bone strength and predispose the patient to pathological fractures.[2,6]

Calcium and phosphate physiology

Plasma concentrations of calcium and phosphate are normally tightly regulated. Calcium absorption from the gut is stimulated by calcitriol whereas phosphate absorption largely varies with dietary intake and has less regulation by calcitriol. Most of the absorbed calcium and phosphate is stored in the bones with very small amounts present in the circulation. Both calcium and phosphate are filtered at the glomerulus. Calcium reabsorption is regulated by a calcium sensing receptor and increased by parathyroid hormone. Phosphate reabsorption is decreased by parathyroid hormone and fibroblast growth factor-23 and increased by calcitriol (see Fig. 1 online).

Calcitriol and vitamin D

Vitamin D (calciferol) is synthesised *in vivo* by photoactivation of steroid precursors in the skin. Calciferol is hydroxylated in the liver to calcidiol (25-hydroxycalciferol) which is subsequently bioactivated to calcitriol (1,25-dihydroxycalciferol) by 1-α-hydroxylase. Most circulating calcitriol is produced by 1-α-hydroxylation in the proximal tubule. It is now known that hydroxylation can also occur in many extra-renal tissues, where calcitriol is presumed to have a paracrine effect.[8] Calcitriol is the most potent vitamin D analogue, but calcidiol may have a significant role in immunomodulation, cancer reduction, insulin secretion and other effects.[9–11] Vitamin D analogues increase the body stores of calcium.

Parathyroid hormone

Parathyroid hormone maintains the concentration of ionised calcium. It is synthesised and released into the circulation in response to hypocalcaemia and hyperphosphataemia. Its synthesis is inhibited by vitamin D analogues and hypercalcaemia. Parathyroid hormone has multiple systemic effects including increased bone turnover by stimulation of both osteoblasts and osteoclasts. In the kidney it decreases excretion of calcium, increases excretion of phosphate and induces 1-α-hydroxylation of calcidiol. In normal physiology, an increase in parathyroid hormone has the net effect of increasing the concentration of calcium and decreasing the concentration of phosphate.

Pathophysiology and progression of renal bone disease

Early changes in chronic kidney disease are hyperphosphataemia, due to impaired excretion, and

hypocalcaemia, due to decreased calcitriol production. Calcitriol deficiency impairs mineralisation of bone (osteomalacia) and increases the risk of fracture. Hyperphosphataemia, hypocalcaemia and calcitriol deficiency induce parathyroid hormone release (Fig. 2). This is called secondary hyperparathyroidism and is treated by correction of the imbalance of calcium, phosphate and vitamin D.[12] However, prolonged stimulation of parathyroid hormone secretion leads to hyperplasia of the parathyroid glands and insensitivity to changes in calcium, phosphate and vitamin D. Consequently there is autonomous secretion of parathyroid hormone which, when it results in hypercalcaemia, is sometimes referred to as tertiary hyperparathyroidism.

In patients with severe chronic kidney disease the biological activity of parathyroid hormone appears to be reduced, probably due to the presence of unmeasured parathyroid hormone metabolites which have a counter-regulatory effect on bone. Pathologically elevated parathyroid hormone has multiple deleterious effects including osteitis fibrosa, cardiac fibrosis with ventricular failure, marrow fibrosis with erythropoietin resistance, and proximal myopathy.

Fibroblast growth factor-23 appears to be produced by osteocytes in response to hyperphosphataemia. It is phosphaturic and inhibits the formation of calcitriol which may exacerbate chronic kidney disease mineral and bone disorder.

Other effects of renal failure include metabolic acidosis. This increases the dissolution of calcium from bone and possibly alters deposition, exacerbating renal bone disease.

Symptoms

Many pathological changes due to renal bone disease are asymptomatic. With marked hyperparathyroidism there may be arthralgias, bone pains and deformity, neuropathy and marrow fibrosis with anaemia despite sufficient erythropoietin.[12] These patients have an increased risk of fracture. In advanced disease, calcification of cutaneous blood vessels may rarely progress to thrombosis (calcific uraemic arteriolopathy or calciphylaxis), resulting in painful ulcerating nodules that are associated with a high mortality.[12,13]

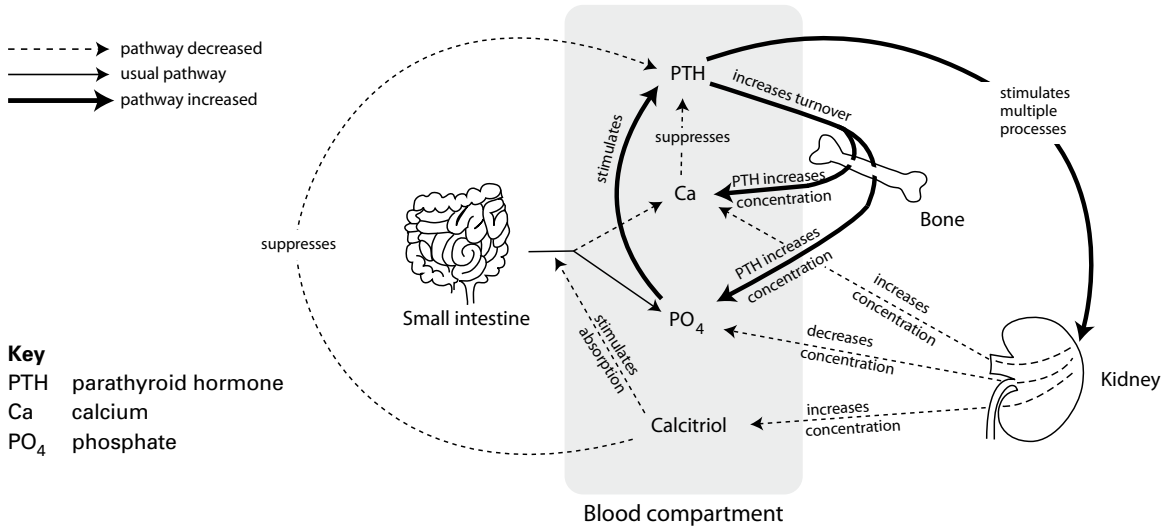
Diagnosis and monitoring

All patients with chronic kidney disease, particularly if the glomerular filtration rate (GFR) is under 60 mL/min, should be screened for renal bone disease regularly. The concentrations of calcium, phosphate and parathyroid hormone are closely monitored to guide therapy. Guidelines are available to assist with treatment decisions, although many are based on expert opinion from observational studies and there are small regional variations.[14,15] Treatment targets for patients with chronic kidney disease are based on the Caring for Australasians with Renal Impairment guidelines.[16,17] These targets are:

- phosphate – within the reference range
- albumin-corrected calcium – within the reference range if the GFR is 15–30 mL/min, but at the lower end of the range if the GFR is lower. Ionised calcium may be a more accurate measurement.[18]
- calcium-phosphate product – less than 4 $mmol^2/L^2$
- parathyroid hormone – when the GFR is less than 15 mL/min the target is 15–22 pmol/L, as undertreatment may

Fig. 2

Pathophysiology of renal bone disease



Impaired renal function leads to hyperphosphataemia, hypocalcaemia and hyperparathyroidism. This increases bone turnover which exacerbates hyperphosphataemia and hyperparathyroidism.

cause osteitis fibrosa (for example when parathyroid hormone exceeds 50 pmol/L) while over-suppression may cause adynamic bone disease (for example when parathyroid hormone is under 10 pmol/L). According to American guidelines, if the GFR is 15–29 mL/min the target is less than 12 pmol/L and if the GFR is 30–60 mL/min the target is the reference range (1.6–7.2 pmol/L).[19]

Calcidiol, calcitriol and alkaline phosphatase may also be monitored, but the extent to which this influences clinical decisions is less defined. For example, calcidiol less than 75 nmol/L is probably suboptimal, but the target concentration is uncertain. The role of fibroblast growth factor-23 and biomarkers of bone turnover used in osteoporosis have not been sufficiently evaluated in renal bone disease.

In stable disease, calcium and phosphate concentrations are checked every 1–3 months and parathyroid hormone is checked every 3–6 months. Calcidiol concentrations should usually be checked before starting treatment with calcitriol, but there is no recommendation regarding the frequency of ongoing testing.

Measuring bone mineral density to predict fracture risk in patients with chronic renal failure is controversial. The measurements do not differentiate between high, low and normal bone turnover states nor do they reliably detect abnormal mineralisation.[20–22] Consequently, they are unhelpful in guiding management.

Patient education to limit the progression of renal bone disease

The management of chronic renal failure is multidisciplinary. In particular, dietary education regarding a low phosphate diet may limit progression of chronic kidney disease mineral and bone disorder. Education regarding medication adherence, dialysis attendance and regular medical review is also important. Early referral to a specialist is recommended.

Treatment

Preventing renal bone disease is a priority because advanced disease responds poorly to treatment. Observational studies show that many patients do not achieve their desired treatment targets, although over the last decade some improvement has been observed.[7,14] There is an opportunity for both clinicians and patients to improve management to optimise clinical outcomes (see Fig. 3 online).

Phosphate reduction

Controlling phosphate concentrations helps to control the secretion of parathyroid hormone.

Dietary restriction

Dietary review and information regarding avoidance of foods high in phosphate, such as dairy products, cola soft drinks and nuts, may be needed in less severe renal disease. This is particularly important for patients with hyperphosphataemia and secondary hyperparathyroidism.[19] It is usually necessary once the patient reaches the end stage. The need for dietary restriction needs to be balanced against the risk of malnourishment.

Phosphate binders

Various compounds are available and all are taken with meals to adsorb dietary phosphate in the gut. Calcium salts are most commonly administered because they are cheap and help to maintain serum calcium. They tend to be unpalatable and constipating and may have the unwanted effect of causing hypercalcaemia.[23]

Sevelamer and lanthanum are newer drugs for patients intolerant of calcium salts. Sevelamer is a non-metal polymer-based binder that is not absorbed from the gut, while lanthanum is a rare earth metal which is minimally absorbed. These drugs are generally prescribed for hyperphosphataemia not controlled by calcium or when the calcium-phosphate product is greater than 4 $mmol^2/L^2$. Both drugs decrease phosphate absorption, but long-term data confirming health benefits are currently only available for sevelamer.[23,24]

Aluminium salts are effective phosphate binders, but are not recommended because aluminium accumulates in renal impairment. This can cause anaemia and neurological complications.

Renal replacement therapy

Dialysis removes phosphate and this is enhanced if the duration and frequency of dialysis are increased.

Vitamin D analogues

Multiple vitamin D analogues are available, but their relative advantages are debated.[25,26] Colecalciferol (vitamin D_3), and less commonly ergocalciferol (vitamin D_2) are oral formulations used in Australia by patients who do not require dialysis. In patients having dialysis, preliminary studies suggest colecalciferol partially corrects chronic kidney disease mineral and bone disorder.[27,28] However, routine supplementation is controversial and not currently recommended in every guideline. American guidelines recommend supplementation to a plasma concentration of calcidiol of more than 75 nmol/L.[19]

Calcitriol is listed on the Pharmaceutical Benefits Scheme for hypocalcaemia due to renal failure, but in clinical practice it is mainly prescribed to suppress elevated parathyroid hormone concentrations. Calcitriol is a potent vitamin D analogue so careful monitoring for hypercalcaemia is necessary.

Alfacalcidol (1-α-calciferol) and other dihydroxyvitamin D analogues such as paricalcitol (intravenous) and doxercalciferol are used less commonly in Australia.

All vitamin D analogues can cause hypercalcaemia and hyperphosphataemia. Appropriate monitoring and dose adjustment of phosphate binders is therefore required.

Other treatments

Cinacalcet

Cinacalcet is a calcium receptor sensitiser (calcimimetic) that inhibits parathyroid hormone release. It is usually used for patients receiving dialysis when parathyroid hormone exceeds 50 pmol/L, or is 15–50 pmol/L with hypercalcaemia, despite conventional treatment. Doses are titrated from 30 mg to 180 mg daily. Cinacalcet has the advantage of lowering parathyroid hormone, serum calcium and phosphate[29] (see Fig. 4 online).

Calcium salts

In addition to phosphate binding properties, calcium salts are often administered with vitamin D to suppress parathyroid hormone and to normalise body stores and ionised calcium for normal cell function. High doses should be avoided because they are associated with vascular calcification.[30]

Sodium bicarbonate

Correction of metabolic acidosis may be useful because studies of alkali therapy in patients who are not in renal failure suggest an improvement in bone parameters.[31–33] Sodium bicarbonate is poorly tolerated in higher doses due to flatulence, and imposes a sodium load which can exacerbate problems with fluid retention.

Bisphosphonates

Routine use of bisphosphonates is not currently recommended due to limited data on their efficacy and safety in patients having dialysis. Concerns include exacerbation of chronic kidney disease mineral and bone disorder (including adynamic bone disease and secondary hyperparathyroidism) and toxicity due to impaired clearance. However, they may reduce vascular calcification[34] and limit hypercalcaemia when there is high bone turnover.

Surgical parathyroidectomy

This is indicated for severe secondary or tertiary hyperparathyroidism that fails to respond to optimum medical treatment, particularly if the patient is symptomatic or if there is coexistent hyperphosphataemia, hypercalcaemia or evidence of high turnover bone disease. Surgical parathyroidectomy is potentially avoidable with careful treatment of the mineral and hormonal disturbances in chronic kidney disease.[7]

Conclusion

Renal bone disease is an important consequence of chronic kidney disease. Frequent monitoring of the plasma concentration of calcium, phosphate and parathyroid hormone is essential to minimise complications. Treatment includes dietary advice and titrated doses of oral phosphate binders such as calcium salts, vitamin D analogues, sodium bicarbonate and cinacalcet. Dialysis is beneficial for patients with end-stage renal failure. Early referral to a nephrologist to guide monitoring and treatment is recommended.

Note: Figures 1, 3 and 4 are available online at www.australianprescriber.com with this article in Vol 33 No 2.

References

The full list of references is available online at www.australianprescriber.com with this article in Vol 33 No 2.

1. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006;69:1945-53.
2. Jadoul M, Albert JM, Akiba T, Akizawa T, Arab L, Bragg-Gresham JL, et al. Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Kidney Int 2006;70:1358-66.
6. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004;15:2208-18.
7. Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney Int 2005;67:1179-87.
14. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2008;52:519-30.
16. Elder G, Faull R, Branley P, Hawley C. The CARI guidelines. Management of bone disease, calcium, phosphate and parathyroid hormone. Nephrology (Carlton) 2006; 11 Suppl 1:S230-61.
17. Hawley C, Elder G. The CARI guidelines. Biochemical targets. Nephrology (Carlton) 2006;11 Suppl 1:S198-216.
19. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42(4 Suppl 3):S1-201.

Conflict of interest: none declared

New oral anticoagulant drugs – mechanisms of action

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Summary

In 2008, two new oral anticoagulant drugs were registered in Australia for the prevention of venous thrombosis after elective knee or hip replacement. Rivaroxaban is a direct reversible competitive antagonist of activated factor X. Dabigatran etexilate is a direct reversible competitive antagonist of thrombin. Both drugs are effective anticoagulants which offer potential advantages over heparin and warfarin.

Key words: dabigatran etexilate, rivaroxaban.

(Aust Prescr 2010;33:38–41)

Introduction

Since the 1960s warfarin has been the only oral anticoagulant drug in regular use for treating patients with thromboembolic disease. In November 2008 the Therapeutic Goods Administration approved two new oral anticoagulant drugs – rivaroxaban and dabigatran etexilate – for the prevention of venous thrombosis in patients having elective knee or hip replacement.

Mechanisms of action

Rivaroxaban and dabigatran etexilate have low molecular weights. They have specific and restricted anticoagulant activities (Fig. 1). Although their mechanisms of action are different, the specificity of activity has no known clinical relevance and both drugs are effective anticoagulants.

Rivaroxaban is a competitive reversible antagonist of activated factor X (Xa). Factor Xa is the active component of the prothrombinase complex that catalyses conversion of prothrombin (factor II) to thrombin (factor IIa).

Dabigatran etexilate is a competitive reversible non-peptide antagonist of thrombin. Thrombin is a multifunctional enzyme which converts fibrinogen to fibrin, cross-linking fibrin monomers via activation of factor XIII and augmenting further thrombin production via the activation of factors V and VIII. It also activates platelets, generates anticoagulant activity via activation of protein C and initiates numerous cellular processes including wound healing. Most of the actions of thrombin are inhibited *in vitro* by dabigatran etexilate.

Pharmacokinetics

The essential properties of the new anticoagulants are compared to warfarin in Table 1. Their main advantages are a rapid onset of anticoagulant effect, more predictable pharmacokinetics, and a lower potential for clinically important interactions with food, lifestyle and other drugs. There is no requirement for routine monitoring and dose adjustment as required with warfarin.

Rivaroxaban

Rivaroxaban[1] 10 mg tablets are well absorbed (80% bioavailability) with no effect of food on absorption or pharmacokinetic parameters. Plasma concentrations peak at 2.5–4 hours. The plasma elimination half-life is 5–9 hours in young adults and 11–13 hours in older people due to the age-related decline in renal function. This permits once- or twice-daily dosing.

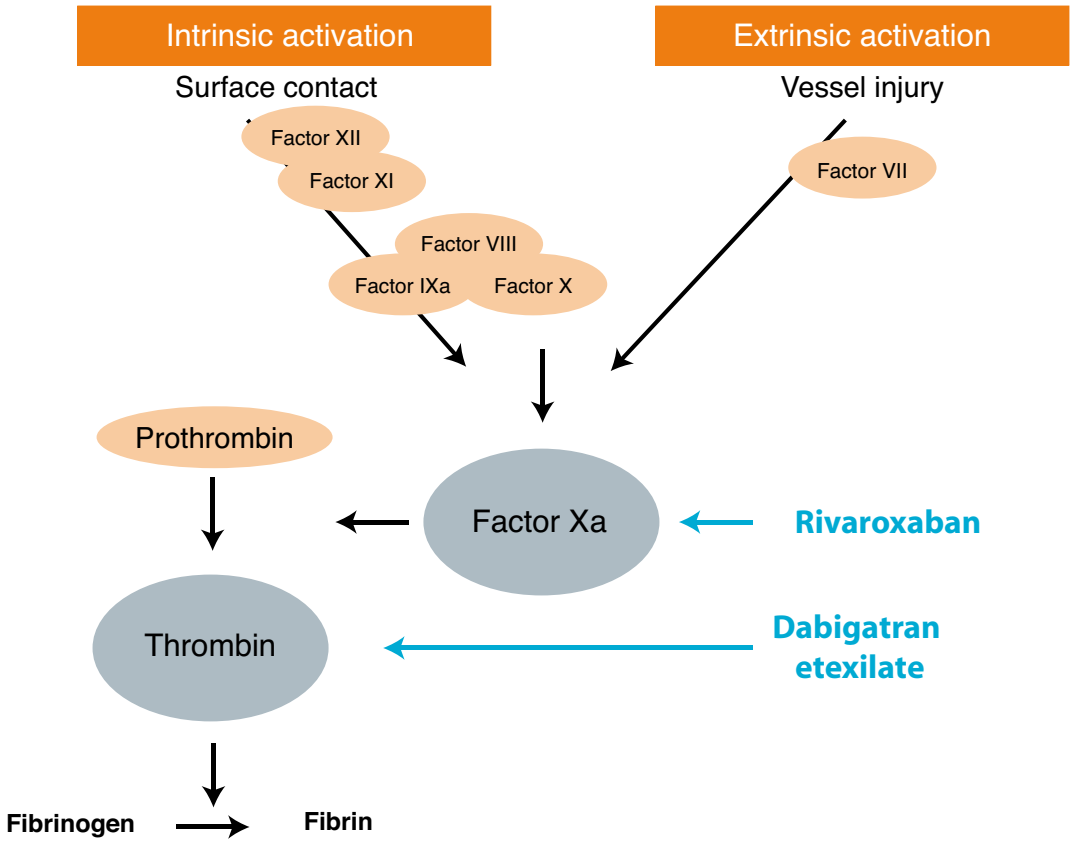
Rivaroxaban is metabolised by liver enzymes, principally cytochrome P450 3A4, and also by cytochrome-independent mechanisms. There are no known active metabolites. Rivaroxaban has a dual mechanism of excretion. Approximately 66% of the dose is excreted via the kidneys, in roughly equal proportions of rivaroxaban and inactive metabolites. The remainder is excreted by the faecal-biliary route. Intestinal excretion of rivaroxaban appears to be mediated, at least in part, by P-glycoprotein, a transport protein, because potent P-glycoprotein inhibitors will increase plasma concentrations of rivaroxaban.

Dabigatran

Dabigatran is a hydrophilic polarised membrane-impermeable molecule which is not absorbed after oral dosing. The oral formulation, dabigatran etexilate,[2] is a prodrug with low bioavailability (approximately 6.5%) and its absorption in the stomach and small intestine is dependent on an acid

Fig. 1

Site of action of new anticoagulant drugs



environment. To promote this microenvironment, dabigatran etexilate is formulated in tartaric acid-containing capsules. Esterases found in enterocytes, plasma and the liver rapidly convert dabigatran etexilate to dabigatran. The drug enters the portal vein as a combination of prodrug and active compound, but once in the liver bioconversion of the prodrug is completed. Plasma concentrations of dabigatran peak 0.5–2 hours after an oral dose.

The plasma elimination half-life is 7–9 hours, and 12–14 hours in older people. This permits once- or twice-daily dosing. About 20% of dabigatran is conjugated and excreted via the biliary system. The cytochrome P450 system plays no part in the metabolism of dabigatran and there are no active metabolites. The remaining 80% of circulating dabigatran is excreted unchanged via the kidneys. The medication is presented in two formulations, 75 mg and 110 mg capsules.

Interactions

Diseases and drug interactions may alter the anticoagulant effect of these drugs. This can reduce efficacy or increase the risk of bleeding.

Rivaroxaban

Disease- or drug-induced reductions in faecal and renal clearance can increase the anticoagulant effect of rivaroxaban. It is currently contraindicated in patients with severe liver disease because metabolic inactivation may be impaired, and in patients with severe renal impairment (creatinine clearance under 30 mL/min).

To date, clinical trials have found no significant pharmacokinetic interactions with aspirin, non-steroidal anti-inflammatory drugs, antacids, histamine H_2-receptor antagonists or digoxin. Caution is needed in patients receiving treatment with potent inhibitors of both CYP3A4 and P-glycoprotein, such as ketoconazole, macrolide antibiotics (for example clarithromycin) or protease inhibitors (for example ritonavir, atazanavir). These drugs increase the anticoagulant effect.

Dabigatran

Reduced renal clearance increases the total exposure (area under the concentration-time curve – AUC) and the elimination half-life of dabigatran. This can cause an exaggerated anticoagulant effect. In elderly patients with

Table 1

Comparison of oral anticoagulants

Property	Warfarin	Rivaroxaban	Dabigatran etexilate
Anticoagulant action	Reduced synthesis of functional clotting factors II, VII, IX and X	Direct competitive reversible inhibition of activated factor X	Direct competitive reversible inhibition of thrombin
Prodrug	No	No	Yes
Bioavailability	Almost 100%	80%	6.5%
Onset of anticoagulant action	36–72 hours	Within 30 minutes T_{max} 2.5–4 hours	Within 30 minutes T_{max} 0.5–2 hours
Duration of anticoagulant action	48–96 hours	24 hours	24–36 hours
Elimination half-life (anticoagulant activity)	20–60 hours	5–9 hours in young adults 11–13 hours in older adults	7–9 hours in young adults 12–14 hours in older adults
Predictable pharmacokinetics	No	Yes	Yes
Interactions with diet or alcohol	Yes, clinically significant	Low potential	Low potential
Drug interactions	Numerous clinically significant interactions	Potent cytochrome P450 3A4 and P-glycoprotein inhibitors augment anticoagulant effect (e.g. ketoconazole, clarithromycin, ritonavir)	Proton pump inhibitors reduce absorption Possible interactions with P-glycoprotein inhibitors and inducers
Dosing and dose adjustments	Dose individualised for each patient, requires frequent INR monitoring and adjustment	Fixed according to clinical indication	Fixed according to clinical indication
Monitoring	INR every 1–2 weeks	No routine monitoring required	No routine monitoring required
Use in liver failure	Contraindicated or caution advised	Contraindicated as hepatic metabolism	Possibly safe as no hepatic metabolism but caution advised
Use in severe renal impairment	No dose adjustment required	Increased drug exposure and elimination half-life in renal impairment Safety and dosing not yet established Contraindicated in severe renal impairment	Increased drug exposure and elimination half-life in renal impairment Safety and dosing not yet established Contraindicated in severe renal impairment
Use in pregnancy	Category D Teratogenic in first trimester	Contraindicated as safety not established (excluded from clinical trials)	Contraindicated as safety not established (excluded from clinical trials)
Reversibility after cessation	Several days, requires synthesis of clotting factors	24 hours, dependent on plasma concentration and elimination half-life	24–36 hours, dependent on plasma concentration and elimination half-life
Antidote	Immediate reversal with plasma or factor concentrate Reversal within hours with vitamin K	None available	None available

INR international normalised ratio

T_{max} time to maximum concentration

calculated moderate (creatinine clearance 30–50 mL/min) or severe (creatinine clearance 10–30 mL/min) renal insufficiency, the AUC was increased 2.7 and 6-fold respectively, while the plasma elimination half-life increased at least twofold. Dabigatran should not be used in patients with severe renal impairment (creatinine clearance under 30 mL/min). It does not undergo hepatic metabolism and no change in total dabigatran exposure was seen in 12 patients with moderate hepatic insufficiency (Child-Pugh B classification).

The absorption of dabigatran etexilate is reduced by 20–25% if patients are also given proton pump inhibitors.

Co-administration of dabigatran etexilate with food delays the peak plasma concentration by two hours and increases the AUC of dabigatran by 27%. In postoperative patients, the peak plasma concentrations are not achieved for 7–9 hours if dabigatran is given on the day of surgery. These two observations do not seem clinically important.

Clinical studies have not found pharmacokinetic interactions with atorvastatin or diclofenac, consistent with the observation that the cytochrome P450 system plays no role in the metabolism of dabigatran. Interactions have been found with P-glycoprotein inhibitors (quinidine, amiodarone) with increased total dabigatran exposure (AUC increased up to twofold). P-glycoprotein inducers may reduce systemic exposure of dabigatran. No changes in digoxin (a P-glycoprotein substrate) or dabigatran concentrations were noted when the drugs were co-administered.

Safety

Rivaroxaban and dabigatran etexilate have not been shown to be safe and effective in important groups of patients who may require anticoagulant therapy. These groups include patients with severe renal or hepatic impairment (dabigatran does not undergo hepatic metabolism and may be safe in patients with hepatic disease), children, and pregnant or lactating women.

The major adverse effect of all anticoagulant medications is bleeding. There is no published evidence yet that the new anticoagulant medications cause less bleeding than heparin or warfarin. Fatal and major bleeding will be further increased with concomitant anticoagulant and antiplatelet therapies. Antiplatelet medications should be avoided while on new anticoagulant medications, unless the benefits of combined therapy outweigh the risks. No antidotes to reverse rivaroxaban or dabigatran anticoagulant effects are available. The anticoagulant effect will not be reversed by administration of vitamin K or plasma infusion.

Compared to enoxaparin, there is no significant increase in abnormal liver function tests with either drug. The possibility of hepatotoxicity with rivaroxaban cannot be excluded until data are available from longer-term usage (up to 24 months) in venous thrombosis treatment, and stroke prevention studies.[3]

Conclusion

Rivaroxaban and dabigatran etexilate are two oral anticoagulant medications recently registered in Australia for prevention of venous thrombosis after lower limb arthroplasty. Both drugs have specific but different mechanisms of action, a rapid onset of anticoagulant activity, less variable pharmacokinetics than warfarin, and a low potential for interactions with diet and other drugs. They are given in fixed doses and do not require routine monitoring. The safety and efficacy of these drugs in the prevention of venous thrombosis in patients other than those having arthroplasty remains to be established in clinical trials.

References

1. Verma AK, Brighton TA. The direct factor Xa inhibitor rivaroxaban. Med J Aust 2009;190:379-83.
2. Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. Br J Clin Pharmacol 2007;64:292-303.
3. U.S. Food and Drug Administration. Minutes of Xarelto (rivaroxaban) cardiovascular and renal drugs Advisory Committee meeting. 2009 Mar 19. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM143660.pdf [cited 2010 Mar 12]

Dr Brighton has received an honorarium from Bayer for an advisory role on steering committees for the EINSTEIN phase II and III clinical studies (rivaroxaban). He has received honoraria from Boehringer Ingelheim for an Australian advisory committee role and lectures.

Self-test questions

The following statements are either true or false (answers on page 59)

1. The doses of rivaroxaban and dabigatran etexilate are adjusted according to the patient's INR.
2. The anticoagulant effects of rivaroxaban and dabigatran etexilate are reversed by vitamin K.

New oral anticoagulants – clinical applications

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Summary

Rivaroxaban and dabigatran etexilate are oral anticoagulants that promise to be as effective as warfarin, but easier to use. The new drugs have shown similar or greater efficacy than low molecular weight heparins and comparable safety in the prevention of venous thromboembolism after hip or knee arthroplasty. Unlike other anticoagulants, routine monitoring is not required during short-term use. The drugs are also being assessed for other indications that include treatment of venous thromboembolism and preventing stroke in atrial fibrillation. Only the results of ongoing studies will tell if they can match warfarin and the heparins across their full range of clinical indications.

Key words: arthroplasty, dabigatran etexilate, rivaroxaban, thromboembolism.

(Aust Prescr 2010;33:42–7)

Introduction

The two widely used classes of anticoagulant are the heparins, and the vitamin K antagonists such as warfarin. Heparins are best suited for short-term prevention and initial treatment of venous thromboembolism or arterial occlusion, but can be given long-term. Warfarin is the mainstay of long-term therapy and is also used for atrial fibrillation and patients with mechanical heart valves. These drugs are highly effective, but have well-known limitations in addition to the risk of bleeding. Heparins require injection or infusion. Warfarin has a narrow therapeutic window, variable dose response and multiple interactions with other drugs and concurrent illnesses, and there is a need for frequent laboratory monitoring of dose–effect.

Rivaroxaban and dabigatran etexilate are new oral anticoagulants which should be simpler to use than heparins or warfarin.[1,2] They have predictable oral bioavailability and pharmacokinetics, few drug interactions and are suitable for daily dosing.[3,4] One dose regimen should suit most patients regardless of body weight, age and gender without the need for laboratory monitoring.

Preventing venous thromboembolism after major joint surgery

As the Australian population ages there will be increasing demand for elective hip or knee replacement and surgery after hip fracture. As these procedures are often complicated by thromboembolism, clinical practice guidelines recommend effective anticoagulant prophylaxis for at least ten days after surgery.[5] Enoxaparin is the most widely used low molecular weight heparin. In Australia and Europe 40 mg is given daily, whereas in North America the dose is 30 mg 12-hourly. Despite prophylaxis, about 2.5% of patients develop symptomatic deep vein thrombosis or pulmonary embolism during the three months after major joint surgery. About two-thirds of cases occur after discharge from hospital.[6,7] In clinical trials subclinical deep vein thrombosis is found despite effective prophylaxis in up to 30% of patients when screening venography is done 7–10 days after surgery. The rate of clinical thromboembolism after hip replacement is reduced when prophylaxis is continued for 4–5 weeks after discharge. Selected patients who have an ongoing risk of

Box

Assessment of efficacy

- total venous thromboembolism – a composite of subclinical deep vein thrombosis detected at routine venography (the most frequent component) and confirmed clinical deep vein thrombosis, non-fatal pulmonary embolism, fatal pulmonary embolism or death from any cause (which are much less common)
- major venous thromboembolism – subclinical proximal deep vein thrombosis, symptomatic venous thromboembolism, and death related to venous thromboembolism or all-cause mortality
- clinical venous thromboembolism – non-fatal or fatal

Table 1

Comparative efficacy and safety of rivaroxaban after elective total hip or knee replacement

Study, surgery and patient numbers	Treatment dose and duration		Efficacy (rivaroxaban vs enoxaparin) (outcomes by the end of study treatments)			Safety (rivaroxaban vs enoxaparin)	
	Rivaroxaban	Enoxaparin	Total VTE	Major VTE	Clinical VTE	Major bleeding	Clinically relevant non-major or major bleeding
RECORD1 Total hip replacement n=4541 (3153 evaluable for 'total VTE')	10 mg/day for 30–42 days	40 mg/day for 30–42 days	1.1% vs 3.7% RRR 70% p < 0.001 NNT = 39	0.2% vs 2.0% RRR 88% p < 0.001 NNT = 58	0.3% vs 0.5%	0.3% vs 0.1%	3.2% vs 2.5%
RECORD2 Total hip replacement n=2509 (1733 evaluable for 'total VTE')	10 mg/day for 31– 39 days	40 mg/day for 10–14 days	2.0% vs 9.3% RRR 75% p < 0.0001 NNT = 14	0.6% vs 5.1% RRR 88% p < 0.0001 NNT = 22	0.2% vs 1.2% RRR 83% p = 0.004 NNT = 101	< 0.1% vs < 0.1%	3.3% vs 2.8%
RECORD3 Total knee replacement n=2531 (1702 evaluable for 'total VTE')	10 mg/day for 13–17 days	40 mg/day for 13–17 days	9.6% vs 18.9% RRR 49% p < 0.001 NNT = 11	1.0% vs 2.6% RRR 62% p = 0.02 NNT = 63	0.7% vs 2.0% RRR 65% p = 0.005 NNT = 77	0.6% vs 0.5%	3.3% vs 2.7%
RECORD4 Total knee replacement n=3148 (1924 evaluable for 'total VTE')	10 mg/day for 10–14 days	30 mg 12-hourly for 10–14 days	6.9% vs 10.1% RRR 31% p = 0.012 NNT = 32	1.2% vs 2.0% RRR 40% p = 0.124	0.7% vs 1.2% RRR 42% p = 0.187	0.7% vs 0.3%	3.0% vs 2.3%

VTE	venous thromboembolism
RRR	relative risk reduction by rivaroxaban
NNT	number of patients who need to be treated in order to prevent one thrombotic event during the relevant study period
Total VTE	(the primary measure of efficacy in these trials) subclinical deep vein thrombosis found by screening venography or non-fatal symptomatic venous thromboembolism or death from any cause
Major VTE	proximal deep vein thrombosis or non-fatal or fatal pulmonary embolism
Clinical VTE	symptomatic deep vein thrombosis or pulmonary embolism

Rates refer to events during or soon after study treatment

Rivaroxaban dose was 10 mg once daily, starting 6–8 hours after wound closure. In RECORD 1, 2 and 3, enoxaparin 40 mg was given 12 hours before surgery and then daily from 6–8 hours after wound closure. Enoxaparin dose in RECORD4 was 30 mg twice daily, starting 12–24 hours after surgery.

thromboembolism after knee replacement may also benefit from extended prophylaxis.[5]

Efficacy versus bleeding risk

Surgeons are wary of surgical bleeding after joint replacement, since wound haematoma delays recovery and may predispose to infections that can endanger the prosthesis. This adds importance to evidence regarding the balance of efficacy and risk of bleeding with the new anticoagulants.

In clinical trials the efficacy of the new drugs was assessed by the incidence of total, major and clinical venous thromboembolism (see box). The primary measure of efficacy was the incidence of 'total venous thromboembolism'. A reduction in this composite end point has been accepted by government regulators and most guideline development groups as indicating efficacy. However, others argue that a composite of proximal vein thrombosis with clinical thromboembolism or even symptomatic pulmonary embolism alone should be the main measure. This debate is unfinished.[8]

Bleeding was reported as 'major' or 'clinically relevant but non-major'. The studies also reported bleeding from the wound, but this was not always considered as major bleeding if re-operation was not needed.

Rivaroxaban

This orally active factor Xa inhibitor was compared with enoxaparin in four double-blind randomised trials for the prevention of venous thromboembolism. These were RECORD1 and RECORD2 for total hip replacement,[9,10] and RECORD3 and RECORD4 for total knee replacement[11,12] (Table 1). The rivaroxaban dose was 10 mg once daily starting 6–8 hours after wound closure. The enoxaparin dose was 40 mg once daily in RECORD 1, 2 and 3 (the studies most relevant to Australian practice) and 30 mg 12-hourly in RECORD4. Study drugs were given for about five weeks after hip replacement in RECORD1 and for about two weeks after knee replacement in RECORD3 and RECORD4. RECORD2 compared five weeks of rivaroxaban with 10–14 days of enoxaparin after hip replacement.

Efficacy (Table 1)

Rivaroxaban was more effective than enoxaparin in RECORD 1, 3 and 4, when used for a similar duration. For total thromboembolism there was a statistically significant relative risk reduction of 30–70%. For major thromboembolism the risk reduction was 40–90% which was statistically significant in RECORD1 and RECORD3. Clinical venous thromboembolism during two weeks after knee replacement was reduced in RECORD3 from 2.0 to 0.7% (relative risk reduction 65%, p = 0.005).

RECORD2, where rivaroxaban was continued for three weeks longer than enoxaparin, was primarily a comparison of treatment durations rather than an equal comparison of competing anticoagulants. It confirmed the value of post-discharge prophylaxis after hip replacement. Continuing rivaroxaban prophylaxis reduced cases of clinical venous thromboembolism within six weeks of surgery from 1.2% to 0.2% (p = 0.004) when compared with 10–14 days of enoxaparin.[10]

Pooled analysis of the results of the comparisons with 40 mg once-daily enoxaparin (RECORD 1, 2 and 3) found that after two weeks symptomatic venous thromboembolism and all-cause mortality was reduced from 0.8% to 0.4% by rivaroxaban (p = 0.005).[13]

Bleeding (Table 1)

The rates of major or clinically relevant non-major bleeding were similar with rivaroxaban and enoxaparin 40 mg once daily. The apparent increases in bleeding were small and statistically insignificant. An overview found that rates of wound infection and re-operation due to bleeding were low and comparable.[13] The near absence of 'major' bleeding is explained in part by a study definition which excluded wound-related bleeding unless it was fatal or led to re-operation.

Dabigatran etexilate

This orally active thrombin inhibitor has been compared with enoxaparin in three double-blind randomised trials (Table 2). One trial was in hip replacement (RE-NOVATE)[14] and two were in knee replacement (RE-MODEL and RE-MOBILIZE).[15,16] All compared two doses of dabigatran (220 mg once daily and 150 mg once daily) with enoxaparin. Treatment continued for 28–35 days in RE-NOVATE, 6–10 days in RE-MODEL, and 12–15 days in RE-MOBILIZE.

The studies most relevant to Australia are RE-NOVATE and RE-MODEL as dabigatran was given as a half-dose 1–4 hours after surgery, and 40 mg once-daily enoxaparin was started on the evening before surgery. In RE-MOBILIZE the initial half-dose of dabigatran was given 6–12 hours after surgery and 30 mg enoxaparin 12-hourly was started 12–24 hours after surgery.

Efficacy (Table 2)

Both doses of dabigatran were statistically 'non-inferior' to enoxaparin in RE-NOVATE and RE-MODEL. In RE-MOBILIZE the total rates of venous thromboembolism with the two dabigatran regimens were significantly higher than with twice-daily enoxaparin.

Bleeding (Table 2)

The rates of major or clinically relevant non-major bleeding were similar with the two dabigatran regimens and with enoxaparin. An overview showed a slight excess of bleeding with dabigatran 220 mg once daily, compared with enoxaparin 40 mg once daily, but this was not statistically significant.[17]

Response to bleeding

Rivaroxaban and dabigatran etexilate have no antidote. Circulating half-lives of 9–13 hours (rivaroxaban) and 12–14 hours (dabigatran) mean the first response to bleeding should be local and supportive since the drugs will wash out quickly once treatment is withdrawn. Routine tests of coagulation are unhelpful. Recombinant factor VIIa to bypass factor Xa or thrombin inhibition may help to control massive bleeding, although clinical experience is lacking.

Other adverse effects

Ximelagatran, the first orally active thrombin inhibitor, caused severe liver toxicity so all new oral anticoagulants are being closely watched for this and other unexpected organ effects. So far, an excess of liver effects has not been reported with rivaroxaban or dabigatran etexilate. There has not been an excess of myocardial infarction after surgery, which was another concern with ximelagatran. Other

Table 2

Comparative efficacy and safety of dabigatran etexilate after elective total hip or knee replacement

Study, surgery, patient numbers and treatment duration	Treatment		Efficacy (dabigatran vs enoxaparin)			Safety (dabigatran vs enoxaparin)	
	Dabigatran	Enoxaparin	Total VTE	Major VTE	Clinical VTE	Major bleeding	Clinically relevant non-major or major bleeding
RE-NOVATE Total hip replacement n = 3494 (2651 evaluable for efficacy) 28–35 days	220 mg once daily	40 mg once daily	6.0% vs 6.7% RRR 10.5% 'non-inferior'	3.1% vs 3.9%	1.0% vs 0.4%	2.0% vs 1.6%	6.2% vs 5.0%
	150 mg once daily		8.6% vs 6.7% RRR –28% 'non-inferior'	4.3% vs 3.9%	0.9% vs 0.4%	1.3% vs 1.6%	6.0% vs 5.0%
RE-MODEL Total knee replacement n = 2076 (1541 evaluable for efficacy) 6–10 days	220 mg once daily	40 mg once daily	36.4% vs 37.7% RRR 3.5% 'non-inferior'	2.6% vs 3.5%	0.15% vs 1.3%	1.5% vs 1.3%	7.4% vs 6.6%
	150 mg once daily		40.5% vs 37.7% RRR –7.4% 'non-inferior'	3.8% vs 3.5%	0.6% vs 1.3%	1.3% vs 1.3%	8.1% vs 6.6%
RE-MOBILIZE Total knee replacement n = 3016 (1896 evaluable for efficacy) 12–15 days	220 mg once daily	30 mg 12-hourly	31.1% vs 25.3% RRR –29% 'inferior' (p = 0.023)	3.4% vs 2.2%	0.6% vs 0.7%	0.6% vs 1.4%	3.3% vs 3.8%
	150 mg once daily		33.7% vs 25.3% RRR –33% 'inferior' (p < 0.001)	3.0% vs 2.2%	0.7% vs 0.7%	0.6% vs 1.4%	3.1% vs 3.8%

VTE	venous thromboembolism
RRR	relative risk reduction by dabigatran
Total VTE	(the primary measure of efficacy in these trials) subclinical deep vein thrombosis found by screening venography or non-fatal symptomatic VTE or death from any cause
Major VTE	proximal deep vein thrombosis or non-fatal or fatal pulmonary embolism
Clinical VTE	derived from symptomatic deep vein thrombosis or pulmonary embolism or venous thromboembolism-related death reported separately in the dabigatran studies

Dabigatran doses were 220 mg once daily and 150 mg once daily, beginning after surgery with a half-dose. In RE-NOVATE and RE-MODEL, the half-dose was given 1–4 hours after surgery and the enoxaparin dose was 40 mg once daily starting on the evening before surgery. In RE-MOBILIZE, the half-dose was given 6–12 hours after surgery and 12-hourly enoxaparin 30 mg was started 12–24 hours after surgery. A new drug is considered 'non-inferior' (no less effective) than standard therapy if study outcomes meet predefined statistical targets, as in RE-NOVATE and RE-MODEL.

adverse events were equally distributed between treatment groups.

Spinal or epidural anaesthesia

Over two-thirds of patients in these studies had surgery under regional (spinal or epidural) anaesthesia with or without a general anaesthetic, but study protocols required epidural anaesthesia to cease before the first (postoperative) dose of oral anticoagulant.

How do the new drugs compare with each other?

There are well-known limitations to any use of results from separate clinical trial programs to estimate relative efficacy of different drugs. Nevertheless, for rivaroxaban and dabigatran, in these large studies the demographics of study populations appear similar, as were study inclusion and exclusion criteria, so results should be broadly comparable – provided comparisons are of relative and not absolute outcome rates.

With that proviso, the results with rivaroxaban appear more impressive, since 10 mg once daily started 6–8 hours after surgery was superior to enoxaparin 40 mg once daily for several outcomes with a similar risk of bleeding. The efficacy and bleeding risk of dabigatran etexilate 220 mg once daily was similar to enoxaparin 40 mg once daily. While dabigatran etexilate 150 mg once daily was formally 'non-inferior' to enoxaparin, the total rates of venous thromboembolism were consistently higher than with 220 mg once daily or with enoxaparin 40 mg once daily and bleeding rates were not reduced. However, the definitions used for 'major bleeding' differed and reported bleeding rates with enoxaparin were consistently higher in the dabigatran trials, as were the total rates of venous thromboembolism. Comparisons with enoxaparin 30 mg 12-hourly (a higher total daily dose) are less relevant to Australian clinical practice.

Future developments

Ongoing or recently published studies include evaluating the new oral anticoagulants for acute and longer-term treatment of venous thrombosis and pulmonary embolism, and in acute coronary syndromes. Prevention of systemic embolism in atrial fibrillation is also being studied.[18]

Conclusion

Both drugs are acceptable alternatives to enoxaparin 40 mg once daily for the prevention of venous thromboembolism after elective hip or knee replacement. While rivaroxaban is more effective than enoxaparin, dabigatran etexilate is no less effective. Bleeding risks are small and appear to be similar to those with enoxaparin. Attempts to draw fine distinctions about the relative safety of the two drugs are prevented by systematic differences between the two sets of study results. An advantage of the new drugs is the lack of the need for routine monitoring. Oral daily dosing will appeal especially to patients who need 3–4 weeks of continued prophylaxis after discharge from hospital.

References

1. Lohrmann J, Becker RC. New anticoagulants – the path from discovery to clinical practice. N Engl J Med 2008;358:2827-9.
2. Eikelboom JE, Weitz JI. Dabigatran etexilate for the prevention of venous thromboembolism. Thromb Haemost 2009;101:2-4.
3. Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939 – an oral, direct Factor Xa inhibitor – after multiple dosing in healthy male subjects. Eur J Clin Pharmacol 2005;61:873-80.
4. Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. Br J Clin Pharmacol 2007;64:292-303.
5. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism. American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133:381S-453S.
6. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thromb Haemost 2003;90:446-55.
7. Bjornara BT, Gudmundsen TE, Dahl OE. Frequency and timing of clinical venous thromboembolism after major joint surgery. J Bone Joint Surg Br 2006;88:386-91.
8. Norrie J. Trials of venous thromboembolism prevention. Lancet 2007;370:915-7.
9. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008;358:2765-75.
10. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008;372:31-9.
11. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008;358:2776-86.
12. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009;373:1673-80.
13. Eriksson BI, Kakkar AK, Turpie AG, Gent M, Bandel TJ, Homering M, et al. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. J Bone Joint Surg Br 2009;91:636-44.
14. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al; RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007;370:949-56.
15. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al; RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost 2007;5:2178-85.
16. RE-MOBILIZE Writing Committee, Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty 2009;24:1-9.
17. Wolowacz SE, Roskell NS, Plumb JM, Caprini JA, Eriksson BI. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. Thromb Haemost 2009; 101:77-85.

18. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parek A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.

Professor Gallus has received honoraria from Astellas, Bayer, Bristol-Myers Squibb, Pfizer and Sanofi-Aventis for an advisory role on phase II and phase III clinical studies (rivaroxaban, apixaban, idrabiotaparinux and YM150), and Boehringer Ingelheim for an Australian advisory committee role.

Self-test questions

The following statements are either true or false (answers on page 59)

3. When used in the prevention of venous thromboembolism, dabigatran etexilate and rivaroxaban cause fewer bleeding complications than enoxaparin.
4. Patients given dabigatran etexilate or rivaroxaban to prevent venous thromboembolism should have their platelet count checked after one week of therapy.

Book review

Therapeutic Guidelines: Respiratory. Version 4.

Melbourne: Therapeutic Guidelines Limited; 2006. 295 pages. Price $39, students $30, plus postage

***Scott Twaddell**, Advanced Trainee in Respiratory and Sleep Medicine, Conjoint Fellow, University of Newcastle, John Hunter Hospital, Newcastle, NSW*

Version 4 of Therapeutic Guidelines: Respiratory continues the tradition of easy to access content and eminent readability that has become the hallmark of this series. The Respiratory Expert Group has again condensed a large volume of information into a pocket-sized quick reference manual.

Chapter 1 uses the familiar 'Getting to know your drugs' format and outlines the pharmacology, indications and importantly many of the adverse effects of common respiratory drugs. The broad content of the rest of the book covers all areas of respiratory practice from obstructive lung diseases through interstitial and pleural diseases to oxygen therapy. It also includes state-based information on access requirements to services such as domiciliary oxygen. There are clear, brief explanations of some difficult management areas, such as sleep disorders and in particular non-invasive ventilation, especially in the acute setting.

Perhaps the next version could include an expanded discussion on pulmonary artery hypertension (formerly called idiopathic pulmonary hypertension). With the advent of various treatments for pulmonary artery hypertension, these patients are increasingly managed by respiratory physicians as part of multidisciplinary teams. The brief mention of cor pulmonale secondary to chronic obstructive pulmonary disease and the use of diuretics also oversimplifies an often difficult management problem. These criticisms are slightly unfair as this is clearly not intended to be an exhaustive text and information on specialised management of these conditions is available elsewhere.

This book will find application with students, junior doctors and their more senior colleagues. I believe it has managed to find a balance between presenting enough detail to inform decision-making while maintaining the formula of best practice standards and brevity.

Editor's note: Information about pulmonary hypertension can be found in Therapeutic Guidelines: Cardiovascular. Version 5 (published in June 2008).

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Medicines Safety Update No. 2; 2010

ACSOM membership announced

On 2 February 2010 Mark Butler, the Parliamentary Secretary for Health, announced the membership of the new Advisory Committee on the Safety of Medicines (ACSOM) for 2010–13. ACSOM replaces the Adverse Drug Reactions Advisory Committee (ADRAC) as the key advisory committee to the Therapeutic Goods Administration (TGA) on medicines safety.

The Committee will be chaired by Professor Emily Banks, a pharmacoepidemiologist and senior research fellow at the National Centre for Epidemiology and Population Health. Professor Banks has extensive experience in quantitative evaluation of the benefits and risks of medicines.

The Committee comprises medical experts, a pharmacist and a health consumer expert. The members are: Associate Professor Christopher Beer, Professor Nick Buckley, Associate Professor Danny Liew, Dr Kristine Macartney, Ms Alison Marcus, Dr Jane Robertson, Associate Professor Simone Strasser and Professor Duncan Topliss.

Once again the TGA thanks the past and outgoing ADRAC members for their contribution to the monitoring of medicines safety in Australia and looks forward to working with the members of ACSOM.

ACSOM recommendations will be published on the TGA website.

Safety of fish oil and omega-3 fatty acids

Dr Mary Boyd Turner, Office of Medicines Safety Monitoring

Introduction

The anticoagulant properties of fish oil products and the consequent risk of bleeding tendency have led to safety concerns, in particular concerning the risk of postoperative bleeding. Anecdotally, it is understood that some surgeons and anaesthetists may delay procedures if their patients are taking fish oil and, while there is no specific clinical guideline to support this, there is some support in the medical literature. Thomas *et al* (2008) has reported epistaxis and easy bruising with the use of fish oils and suggested that these may potentiate the action of warfarin and present a risk to haemophiliacs.[1]

Fish oil contains the omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). There is good evidence indicating that DHA and EPA in the form of fish oil supplements have beneficial cardiovascular effects. This is presented in a comprehensive review undertaken by Colquhoun *et al* for the Australian National Heart Foundation (NHF), published in 2008.[2]

The most commonly proposed mechanism for the anticoagulant activity of fish oils relates to changes in the ratio of phospholipids in platelet membranes. *In vitro*, fish oils competitively inhibit cyclo-oxygenase which decreases synthesis of thromboxane A_2 from arachidonic acid (ARA) in platelets. The cyclo-oxygenase mediated generation of thromboxane A_2 from ARA in platelets plays an important role in blood coagulation. Consumption of fish-rich diets or fish oil supplements may reduce platelet aggregation through reduction of platelet ARA concentration and cyclo-oxygenase mediated generation of thromboxane A_2 from EPA.

DHA has the potential to influence platelet aggregation by competing with ARA for membrane incorporation in platelets and thereby reducing available ARA for thromboxane A_2 generation. Other mechanisms such as decreasing platelet growth and clotting factors are also postulated to play a role.[3,4]

There is some evidence for other benefits of fish oil. These include use for infant eye/brain development, inflammation, nutrition (in gastrointestinal disorders), mental health disorders, Alzheimer's disease and rheumatoid arthritis. While fish oil products are widely used, this suggests the potential for more extensive applications.[5]

Summary of the literature

A literature search identified only three case reports presenting bleeding events or changes in laboratory results in patients taking fish oil and anticoagulant medication.[6–8] Evidence from several randomised placebo-controlled trials and reviews is presented below.

Leaf *et al* (1994) undertook a randomised controlled trial in 551 candidates for percutaneous intraluminal coronary angioplasty to investigate whether omega-3 fatty acids prevented restenosis. Subjects were randomised to receive high doses of EPA and DHA or placebo for 14 days before, and six months after, angioplasty. All patients also received 325 mg of aspirin for six months post angioplasty. While the intervention did not prevent restenosis, there was no statistically significant difference in bleeding time between groups.[9]

The safety of postoperative fish oil was evaluated by Heller *et al* (2002) in a randomised, double-blind, placebo-controlled trial of 44 patients administered high doses of omega-3 fatty acids in parenteral nutrition after major abdominal surgery. No significant between-group difference was seen in bleeding events.[10]

Commentary by Lichtenstein (2005) on clinical data concerning dietary supplements affecting antithrombotic therapy included the conclusion on safety from an evidence-based review on the effects of omega-3 fatty acids on cardiovascular disease, prepared for the US Agency for Healthcare Research and Quality in 2004. It was noted that while clinical bleeding was a theoretical concern, in the studies reviewed there was no difference in the overall number of bleeding events between supplement and control groups. It was concluded that adverse events related to consumption of fish oil appeared to be minor.[11]

Harris (2007) reviewed 19 clinical trials of candidates for vascular surgery or femoral artery puncture who were administered omega-3 fatty acids in addition to anticoagulant medications. In 14 of these trials, the fatty acids were administered one and 42 days prior to surgery, and in 5 studies, postoperatively, at doses varying from 1.4 to 21 g/day. It was concluded that clinically significant bleeding events were 'virtually non-existent'.[12]

The effects of prescription omega-3 acids (POM) and aspirin, alone and in combination, on platelet function in 10 healthy subjects were investigated by Larson *et al* (2008). This was an open-label four-week sequential therapy trial with each subject their own control. It was found that while platelet aggregation was not affected by POM alone, it was affected by aspirin and by aspirin with POM.[13]

Tavazzi *et al* (2008) published the results of a randomised, double-blind, placebo-controlled trial looking at the effect of n-3 polyunsaturated fatty acids (PUFA) in patients with chronic heart failure (New York Heart Association class II–IV). Participants were assigned to n-3 PUFA 1 g/day (n=3494) or placebo (n=3481). Analysis of those discontinuing the study due to adverse events was undertaken, and showed no significant difference between the treatment and placebo groups.[14]

Watson *et al* (2009) undertook a retrospective record review of 182 subjects treated with high-dose fish oil, aspirin and clopidogrel and 182 controls on aspirin and clopidogrel alone, with a mean follow-up period of 33 months. One major bleed was seen in the treatment group (a patient with rectal cancer requiring transfusion) and none in the control group (p=1.0). There were more minor bleeds in the control group compared to the treatment group but the difference was not statistically significant. It was concluded that high-dose fish oil is safe in combination with aspirin and clopidogrel, and does not increase the risk of bleeding compared with that seen with aspirin and clopidogrel alone.[15]

Consumer use of fish oil and omega-3 fatty acids

Research shows that the popularity of complementary medicine (CM) use, and particularly fish oil, is worldwide and likely increasing.

The results from a Canadian National Population Health Survey undertaken in 2000–01 including 11,424 adults were published by Singh *et al*. These showed the prevalence of use of natural health products within the two days preceding was 9.3%, with fish oils the fourth most common product.[16]

An analysis of data by Elmer *et al*, collected as part of the Cardiovascular Health Study cohort study of risk factors for coronary heart disease (CHD) and stroke in adults 65 years and older, aimed to determine the prevalence of CM use concurrent with prescription and over-the-counter (OTC) medications and assess the risk for adverse interactions.[17] Fish or cod liver oil was the fourth most common CM, with 2.28% of study participants using it over the four periods. Its use was categorised as a possible or theoretical risk for bleeding adverse events, rather than a significant risk.

Ramsay *et al* published the results of a retrospective analysis of pharmaceutical care plans for patients starting warfarin, who attended an anticoagulation clinic in 2003, to ascertain their CM use.[18] Of the 631 plans analysed it was found that 170 (26.9%) patients were taking some form of CM. Approximately 60% of these were taking a CM that could interact with warfarin. Overall, more than 10% of the patients were taking fish or cod liver oil.

Regulation

Currently in Australia, fish oil ingredients derived from whole body and liver of fish are permitted for use in complementary and some OTC (listed) medicines. There is also a recognised component name, 'omega-3 marine triglycerides'. There are no quantity restrictions for any of the ingredients or the components in the ingredients, and the use of these substances does not attract any advisory statements for labelling purposes.

Information from adverse event reports with omega-3 fatty acids and fish oil in the TGA adverse drug reaction database showed that to February 2010, there had been a total of 92 reports, dating back to 1987, with 11 of these describing

bleeding. These products were the sole suspect medication in only three (3.2%) cases. This finding is consistent with reports in international databases.

Notwithstanding the limitations of spontaneous adverse event reporting, these data suggest that there are relatively few reported bleeding-related adverse events with fish oil preparations, and that only a small proportion may be solely attributed to these products.

Health Canada permits a number of health claims for fish oil including the maintenance of good health, cardioprotection, assistance in reduction of serum triglycerides, and promotion of healthy mood balance. A June 2009 fish oil monograph indicates that no statements are required in relation to cautions, warnings, contraindications, and known adverse reactions.[19]

In 2004, the US Food and Drug Administration endorsed a qualified health claim indicating that, 'Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease'. It states that, 'Dietary supplements should not recommend or suggest in their labelling a daily intake exceeding 2 grams of EPA and DHA'.[20]

Included in the Australian NHF 2008 review were recommendations for consumption of combined DHA and EPA through use of omega-3 fatty acids or fish oil, or fish intake. These were for:

- all adult Australians to lower their risk of CHD
- women who are planning pregnancy, pregnant or breastfeeding
- children
- adult Australians with documented CHD
- Australians with lipid abnormalities.[2]

The NHF review did not consider fish oils to have a significant effect on haemostasis and did not include a cautionary statement.[2]

Similar recommendations have been made by the American Heart Association. These are qualified with statements to indicate that patients taking high dose omega-3 fatty acids should be under the care of a physician, and that high intake could cause bleeding in some people.[21]

In its information sheet on fats and oils, the British Heart Foundation supports intake of omega-3 fatty acids for cardioprotection. This indicates that patients taking warfarin and fish oil supplements concomitantly should consult with their medical practitioner because of the possibility of bleeding risk.[22]

Summary

- Current evidence and recommendations for usage support fish oil for cardioprotection in patients with or without diagnosed CHD, decreasing triglycerides, and in women who are planning pregnancy, pregnant or breastfeeding, and children.
- There are multiple proposed additional uses for fish oil.
- It is likely that the use of fish oil will significantly increase.
- Regulatory agencies consider that fish oil and omega-3 fatty acid containing products are safe with some requiring warnings about the theoretical possibility of bleeding events and drug interactions in their product information.
- Evidence in relation to the safety concern about possible bleeding indicates that the theoretical possibility of increased bleeding tendency is not reflected functionally in results of human studies.

Conclusion

Healthcare practitioners should ensure they are aware of all medications – including prescription, over-the-counter and complementary products – being taken by their patients. Despite the lack of evidence of a systematic safety concern, it would appear reasonable to be mindful of the theoretical risk of bleeding with fish oil when monitoring patients treated with fish oils and anticoagulants.

Bays (2007), in an article entitled 'Safety considerations with omega-3 fatty acid therapy', suggests:

- discontinuing high-dose fish oil consumption or supplementation during an acute bleeding illness, such as during and immediately after a haemorrhagic stroke, or in patients with or at high risk for haemorrhagic stroke
- discontinuing fish oil therapy 4–7 days before elective procedures with a high risk for bleeding complications, as often occurs with aspirin, warfarin, and clopidogrel, even though infusion of fish oils after major abdominal surgery through parenteral nutrition does not appear to result in clinically significant bleeding and has been suggested to be safe with specific regard to coagulation and platelet function
- considering the potential antithrombotic and cardiovascular benefits of restarting fish oil therapies postoperatively, given that thrombotic and cardiovascular events may occur following major surgery.[3]

The author would like to thank colleagues from the TGA's Office of Complementary Medicines for their contribution.

References

1. Thomas AM, Gambert SR. Hazards from the health food store – Part II. Clin Geriatr 2008;16:34-40.
2. Heart Foundation. Position statement: Fish, fish oils, n-3 polyunsaturated fatty acids and cardiovascular health. Melbourne: NHF; 2008.
3. Bays HE. Safety considerations with omega-3 fatty acid therapy. Am J Cardiol 2007;99:35C-43C.
4. Lien EL. Toxicology and safety of DHA. Prostaglandins, leukotrienes, and essential fatty acids. Prostaglandins Leukot Essent Fatty Acids 2009;81:125-32.
5. Medline Plus. Drugs, supplements, and herbal information. www.nlm.nih.gov/medlineplus/druginformation.html [cited 2010 Mar 12]
6. Buckley MS, Goff AD, Knapp WE. Fish oil interaction with warfarin. Ann Pharmacother 2004;38:50-2.

7. McClasky EM, Landrum Michalets E. Subdural hematoma after a fall in an elderly patient taking high-dose omega-3 fatty acids with warfarin and aspirin: case report and review of the literature. Pharmacotherapy 2007;27:152-60.
8. Jalili M, Dehpour AR. Extremely prolonged INR associated with warfarin in combination with both trazodone and omega-3 fatty acids. Arch Med Res 2007;38:901-4.
9. Leaf A, Jorgensen MB, Jacobs AK, Cote G, Schoenfeld DA, Scheer J, et al. Do fish oils prevent restenosis after coronary angioplasty? Circulation 1994;90:2248-57.
10. Heller AR, Fischer S, Rossel T, Geiger S, Siegert G, Ragaller M, et al. Impact of n-3 fatty acid supplemented parenteral nutrition on haemostasis patterns after major abdominal surgery. Br J Nutr 2002;87(Suppl 1):S95-S101.
11. Lichtenstein AH. Remarks on clinical data concerning dietary supplements that affect antithrombotic activity. Thromb Res 2005;117:71-3.
12. Harris WS. Expert opinion: omega-3 fatty acids and bleeding – cause for concern? Am J Cardiol 2007;99:44C-46C.
13. Larson MK, Ashmore JH, Harris KA, Vogelaar JL, Pottala JV, Sprehe M, et al. Effects of omega-3 acid ethyl esters and aspirin, alone and in combination, on platelet function in healthy subjects. Thromb Haemost 2008;100:634-41.
14. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al; Gissi-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223-30.
15. Watson P, Joy P, Nkonde C, Hessen S, Karalis D. Comparison of bleeding complications with omega-3 fatty acids and aspirin and clopidogrel versus aspirin and clopidogrel in patients with cardiovascular disease. Am J Cardiol 2009;104:1052-4.
16. Singh SR, Levine M. Potential interactions between pharmaceuticals and natural health products in Canada. J Clin Pharmacol 2007;47:249-58.
17. Elmer GW, Lafferty WE, Tyree PT, Lind BK. Potential interactions between complementary/alternative products and conventional medicines in a Medicare population. Ann Pharmacother 2007;41:1617-24.
18. Ramsay NA, Kenny MW, Davies G, Patel JP. Complementary and alternative medicine use among patients starting warfarin. Br J Haematol 2005;130:777-80.
19. Health Canada. Natural health product monograph: Fish oil. 2009 Jun 22. www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_fish_oil_huile_poisson-eng.php [cited 2010 Mar 12]
20. US Food and Drug Administration. Letter responding to health claim petition dated June 23, 2003 (Wellness petition): omega-3 fatty acids and reduced risk of coronary heart disease (Docket No. 2003Q-0401). 2004 Sep 8. www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm072936.htm [cited 2010 Mar 12]
21. American Heart Association. Fish and omega-3 fatty acids. www.americanheart.org/presenter.jhtml?identifier=4632 [cited 2010 Mar 12]
22. British Heart Foundation. Information sheet: Fats and oils. 2008. www.bhf.org.uk [cited 2010 Mar 12]

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.

Alfuzosin

Xatral SR (Sanofi-Aventis)

10 mg prolonged-release tablets

Approved indication: benign prostatic hyperplasia

Australian Medicines Handbook section 13.2.1

Alpha$_1$ adrenergic blocking drugs such as prazosin can be used in the treatment of benign prostatic hyperplasia. They work by relaxing the smooth muscle of the bladder and prostate. Prescribers can now consider using alfuzosin as an alternative to prazosin, tamsulosin and terazosin in patients who have symptoms of benign prostatic hyperplasia.

Early studies used 2.5 mg and 5 mg tablets, but the manufacturer is now marketing a 10 mg prolonged-release formulation. The tablet is taken daily after a meal as bioavailability is reduced if it is taken on an empty stomach. The half-life is about nine hours and only slightly increases with age. Most of a dose is metabolised, then excreted in the faeces. As this metabolism involves cytochrome P450 3A4, alfuzosin may interact with inhibitors of this enzyme such as the imidazole antifungals. Hepatic insufficiency is a contraindication.

In the early 1990s, 5 mg sustained-release tablets were studied for three months in 390 men with symptomatic benign prostatic hyperplasia. A twice-daily dose significantly reduced symptom scores and the urine flow rate improved significantly more with alfuzosin than with placebo. The amount of residual urine was also significantly reduced.[1]

A pooled analysis of three subsequent studies of a 10 mg sustained-release formulation reported results after 12 weeks of treatment. Compared with 482 men given placebo, the 473 who were randomised to receive alfuzosin had a significant improvement in lower urinary tract symptoms. The absolute decrease in the 35-point international prostate symptom score (IPSS) was 4.2 points with placebo and 6 points with alfuzosin. There was also a significant improvement in the urinary peak flow rate.[2]

In an open-label extension of one of these studies, 310 men took alfuzosin 10 mg for nine months. The improvements in the IPSS and urine flow were maintained.[3]

Another one of the trials included 158 patients taking 0.4 mg tamsulosin, which is also an alpha$_1$ adrenergic blocker. After 12 weeks their IPSS had reduced by 6.5 points which was identical to the reduction seen in the 154 patients who were randomised to take alfuzosin 10 mg. These changes were significantly greater than the 4.6 point reduction seen in the 153 patients who took placebo.[4]

When alfuzosin was compared with doxazosin in 210 men, both drugs significantly improved urinary flow rates over 14 weeks. The reduction in the IPSS was significantly greater with doxazosin (9.2 points) than with alfuzosin (7.5 points). The residual volume of urine was also significantly less with doxazosin. However, this trial used the 2.5 mg and 5 mg formulations of alfuzosin and the mean dose was less than 10 mg, which is now the recommended dose.[5]

Alfuzosin has also been studied as an adjunctive treatment in the management of acute urinary retention. Following catheterisation, 238 men were given daily alfuzosin and 122 were given a placebo. The catheters were removed after two doses and treatment continued for the day after removal. A return to satisfactory micturition was achieved by 61.9% of the alfuzosin group and 47.9% of the placebo group. A group of 165 responders was then randomised to take alfuzosin or a placebo for six months. During this period surgery for prostatic hyperplasia was needed by 17.1% of the alfuzosin group and 24.1% of the placebo group. Approximately 14 men would need to be treated for six months for one to avoid surgery.[6]

As alpha$_1$ adrenergic blocking drugs cause vasodilation, adverse effects such as postural hypotension may be expected. Patients may complain of dizziness or faintness. Particular caution is required if alfuzosin is prescribed for patients who are taking antihypertensive drugs.

In the pooled analysis 9.5% of patients taking alfuzosin stopped treatment compared with 8.7% of the placebo group. Symptoms associated with vasodilation occurred in 6.6% of elderly patients and 8.3% of those with hypertension.[2] In a meta-analysis alfuzosin caused significantly more dizziness, hypotension or syncope than placebo.[7]

Alfuzosin has been available overseas for many years. No specific safety problems have emerged, but there could be a risk of the 'floppy iris syndrome', a complication in cataract surgery, which has been reported with similar drugs such as tamsulosin.

Although alfuzosin has some statistically significant effects, their clinical relevance is less clear. As the IPSS has to change by at least three points to be noticed, the benefit of alfuzosin over placebo is modest. In the pooled analysis, placebo increased the maximum urinary flow by 12.5%, while alfuzosin increased it by

26.1%. However, the absolute increases were 1.1 mL/second and 2.3 mL/second. The difference, of 1.2 mL/second, may not be clinically important.[2]

A meta-analysis has evaluated the efficacy of all the alpha$_1$ adrenergic blocking drugs used to treat the symptoms of benign prostatic hyperplasia. It found no difference between the drugs. They all improve symptom scores and peak urinary flow.[7]

T T manufacturer provided additional useful information

References *

1. Buzelin JM, Roth S, Geffriaud-Ricouard C, Delauche-Cavallier MC; ALGEBI Study Group. Efficacy and safety of sustained-release alfuzosin 5 mg in patients with benign prostatic hyperplasia. Eur Urol 1997;31:190-8.
2. Roehrborn CG, van Kerrebroeck P, Nordling J. Safety and efficacy of alfuzosin 10 mg once-daily in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. BJU Int 2003;92:257-61.
3. van Kerrebroeck P, Jardin A, van Cangh P, Laval KU; ALFORTI Study Group. Long-term safety and efficacy of a once-daily formulation of alfuzosin 10 mg in patients with symptomatic benign prostatic hyperplasia: open-label extension study. Eur Urol 2002;41:54-61.
4. Nordling J. Efficacy and safety of two doses (10 and 15 mg) of alfuzosin or tamsulosin (0.4 mg) once daily for treating symptomatic benign prostatic hyperplasia. BJU Int 2005;95:1006-12.
5. De Reijke TM, Klarskov P. Comparative efficacy of two α_1-adrenoreceptor antagonists, doxazosin and alfuzosin, in patients with lower urinary tract symptoms from benign prostatic enlargement. BJU Int 2004;93:757-62.
6. McNeill SA, Hargreave TB, Roehrborn CG; ALFAUR Study Group. Alfuzosin 10 mg once daily in the management of acute urinary retention: results of a double-blind placebo-controlled study. Urology 2005;65:83-90.
7. Nickel JC, Sander S, Moon TD. A meta-analysis of the vascular-related safety profile and efficacy of α-adrenergic blockers for symptoms related to benign prostatic hyperplasia. Int J Clin Pract 2008;62:1547-59.

Clofarabine

Evoltra (Hospira)

vials containing 20 mg/20 mL

Approved indication: paediatric acute lymphocytic leukaemia

Australian Medicines Handbook section 14.1.3

Acute lymphocytic leukaemia is the most common childhood malignancy. Although chemotherapy has improved survival, many children have a high risk of relapse. As chemotherapy can be ineffective in relapsed disease there is a need for new therapies.

Clofarabine is a purine nucleoside analogue. It has structural similarities to the purine antagonists cladribine and fludarabine. After dilution and slow intravenous infusion, clofarabine is converted intracellularly to a metabolite which inhibits DNA synthesis and induces apoptosis. There is little hepatic metabolism with 50–60% of the dose being excreted unchanged in the urine. The terminal half-life is approximately five hours.

The approval of clofarabine is based on a phase II study of 61 people whose acute lymphocytic leukaemia was refractory or had relapsed at least twice. Their ages ranged from 1 to 20 years with a median of 12 years. Clofarabine was infused for five consecutive days every 2–6 weeks for up to 12 cycles depending on the toxicity of the treatment. As judged by blood counts and bone marrow aspirates, 20% of patients had a complete remission and 10% had a partial remission. Some of these remissions were in patients whose leukaemia had been refractory to previous treatment.[1]

Clofarabine is an antimetabolite so it frequently causes serious adverse effects. In the first two treatment cycles 72% of the patients had severe febrile neutropenia.[1] Multi-organ failure, haematemesis, hypotension, jaundice and septic shock occur commonly. A rapid reduction in leukaemia cells can cause cytokine release and tumour lysis syndrome, so intravenous fluids are recommended for the five days of each treatment cycle. Most patients experience nausea, vomiting and diarrhoea so antiemetic drugs should be considered. Skin reactions, such as palmar-plantar erythrodysaesthesia syndrome, are very common. During the phase II trial, 25% of the patients died within 30 days of treatment or as a result of a drug-related adverse effect.[1]

The median survival time for the patients in the trial was 13 weeks.[1] Survival improves in patients who respond, but this outcome may be confounded because these patients may subsequently have bone marrow transplantation. Median overall survival is 63 weeks in patients who respond and may be longer in those who have a transplant. Most of the responses to clofarabine occur in the first two treatment cycles. Patients were only able to complete a median of two cycles in the trial, so it may not be worthwhile persisting with treatment in those who do not respond by then. In view of the limited information about clofarabine, its use has been restricted to children with relapsed or refractory disease who have already received two previous treatment regimens.

T manufacturer provided only the product information

Reference *†

1. Jeha S, Gaynon PS, Razzouk BI, Franklin J, Kadota R, Shen V, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol 2006;24:1917-23.

Melatonin

Circadin (Sigma)

2 mg prolonged-release tablets

Approved indication: primary insomnia

Australian Medicines Handbook section 18.4

Melatonin is a hormone which is secreted by the pineal gland at night-time. Its secretion is part of the normal circadian rhythm and promotes sleep. This resulted in a theory that low concentrations of melatonin may be associated with difficulty sleeping.

A study of 59 volunteers and 517 patients with insomnia found that the patients had lower urinary concentrations of a melatonin metabolite. When 396 of the patients were given an evening dose of melatonin, those with lower concentrations of the metabolite had a greater clinical response than those with higher concentrations. They had a better quality of sleep and they found it easier to get to sleep. The following morning they were more alert than the patients with higher urinary concentrations.[1]

Several randomised controlled trials then looked at using melatonin to treat primary sleep disorders. A meta-analysis of 16 of these studies found that melatonin was as well tolerated as placebo, but was not very efficacious. Patients given melatonin fell asleep 12 minutes earlier than those given a placebo. The effect was greater (39 minutes) in the small sub-group with delayed sleep phase syndrome. Melatonin did not increase sleep efficiency (the proportion of time in bed spent asleep) significantly more than placebo.[2]

Another meta-analysis looked at sleep disorders secondary to other conditions or sleep restriction, for example jet lag. It found no evidence that melatonin was of any benefit.[3]

The meta-analysis of primary insomnia concluded that larger controlled trials were needed.[2] One subsequent trial in general practice randomised 170 patients, over the age of 55 years, with primary insomnia to take 2 mg modified-release melatonin or placebo. After three weeks there was no significant difference in getting to sleep, but sleep quality and alertness the next day were significantly improved with melatonin.[4]

A similar trial in general practice randomised 177 patients to take 2 mg modified-release melatonin and 177 to take a placebo. After three weeks, patients given melatonin fell asleep approximately nine minutes faster than the placebo group. They also had greater improvements in their quality of sleep and morning alertness, however total sleep time was not significantly improved.[5]

Adverse events occurred in 37% of the patients given melatonin and 32% of the patients given placebo. The most frequently reported symptoms were headache, back pain, asthenia and pharyngitis.

Melatonin undergoes significant first pass metabolism and most of the dose is excreted in the urine as metabolites. This metabolism involves cytochrome P450 1A1, 1A2 and possibly 2C19. It may be inhibited by drugs such as cimetidine, fluvoxamine, oestrogen and the quinolones, and induced by smoking and drugs such as carbamazepine and rifampicin. Melatonin is not recommended for patients with liver impairment and the effect of renal impairment is unknown. As the half-life of melatonin is less than an hour a modified-release formulation is needed. After a meal it takes three hours to reach the maximum plasma concentration, so it is recommended that the modified-release tablet is taken one or two hours before bedtime and after food. Patients should not drink alcohol with melatonin, as alcohol may cause the immediate release of the drug from the modified-release formulation.

There appear to have been no direct comparisons with benzodiazepines, but the results of a separate placebo-controlled trial with zolpidem have been used to assess the relative efficacy of melatonin. Overall patients given zolpidem fall asleep sooner than those given melatonin, but both drugs improve sleep quality. Melatonin should not be used in combination with other hypnotics. Stopping melatonin does not appear to cause more withdrawal symptoms than placebo,[4] but its use is restricted to a maximum of three weeks. It can only be prescribed to patients with primary insomnia over the age of 55 years. Many of these patients will be disappointed with the effect, as only about 30% respond to treatment. When the placebo effect is discounted, nine people would need to be treated for three weeks for one person to have improved sleep quality and to function better the next morning.[5]

T T manufacturer provided additional useful information

References †A

1. Leger D, Laudon M, Zisapel N. Nocturnal 6-sulfatoxymelatonin excretion in insomnia and its relation to the response to melatonin replacement therapy. Am J Med 2004;116:91-5.
2. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders: a meta-analysis. J Gen Intern Med 2005;20:1151-8.
3. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ doi:10.1136/bmj.38731.532766.F6 (published 2006 Feb 10)
4. Lemoine P, Nir T, Laudon M, Zisapel N. Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. J Sleep Res 2007;16:372-80.
5. Wade AG, Ford I, Crawford G, McMahon AD, Nir T, Laudon M, et al. Efficacy of prolonged release melatonin in insomnia patients aged 55-80 years: quality of sleep and next-day alertness outcomes. Curr Med Res Opin 2007;23:2597-605.

Nebivolol

Nebilet (CSL)

1.25 mg, 5 mg and 10 mg tablets

Approved indication: hypertension, chronic heart failure

Australian Medicines Handbook section 6.4.3

Nebivolol is indicated for the treatment of essential hypertension (no age limit), and for stable chronic heart failure in combination with conventional therapies for patients aged 70 or older. It works by blocking the $beta_1$ adrenergic receptor, and has mild vasodilatory properties mediated through nitric oxide release. At doses up to 10 mg, it is selective for the $beta_1$ adrenergic receptor, but at higher doses (and in poor metabolisers) it inhibits both $beta_1$ and $beta_2$ adrenergic receptors.

Peak plasma concentrations of this drug are reached 1.5–4 hours after oral administration. It is metabolised by cytochrome P450 2D6 and its elimination half-life is around 10 hours in most people (fast metabolisers), but 3–5 times longer in people who are slow metabolisers. Metabolites are excreted in urine and faeces in varying proportions depending on the individual's metabolism. As there are variations in the metabolism of nebivolol, the dose should be adjusted according to individual needs. Poor metabolisers may require a lower dose.

Once-daily nebivolol (1.25–40 mg) has been shown to reduce blood pressure in patients with mild–moderate hypertension in a number of placebo-controlled trials.[1,2] A nine-month extension of these trials compared nebivolol monotherapy to nebivolol given with other antihypertensive treatments in 845 people. (Of these patients, 81 had previously received placebo and 764 had received nebivolol.) Patients were given nebivolol monotherapy (5–20 mg). If they did not have an adequate response to this, a diuretic, calcium channel blocker (amlodipine) or another antihypertensive drug was added to their treatment. By the end of the study, mean diastolic and systolic blood pressures had decreased by 15 mmHg and 14.8 mmHg in the nebivolol group (606 patients) and by 12 mmHg and 16.2 mmHg in the nebivolol plus diuretic group (206 patients) from baseline of the original studies. There were too few patients in the other groups to conclude whether treatment had worked.[3]

In a meta-analysis of hypertension drugs, response rates to nebivolol (5 mg daily) were similar to other beta blockers, calcium channel antagonists and the angiotensin receptor antagonist losartan. Response rates to nebivolol were higher than for angiotensin converting enzyme inhibitors.[4]

In one of the original hypertension trials that tested nebivolol (1.25–40 mg) for 12 weeks, headache (6–9%), fatigue (1.2–4.8%) and dizziness (1–9%) were commonly reported adverse events. Patients treated with the higher doses of nebivolol (20 mg and 40 mg) had significantly more adverse events, possibly because nebivolol becomes less selective at higher doses. There were two serious adverse events that were thought to be possibly related to nebivolol (20 mg and 40 mg dose). Both were abnormal ECG readings which resolved spontaneously without treatment being interrupted. High-density lipoprotein cholesterol decreased significantly with increasing nebivolol dose, and increases in serum uric acid and phosphorus were observed at doses of 5 mg and above.[1] In the extension study, there were three patients with serious adverse events that were thought to be related to the study drug. These included right upper quadrant pain, bradycardia and peripheral oedema, and sexual dysfunction. Obese patients (≥ 30 kg/m^2) tended to have more adverse events than patients who were not obese.[3] In the meta-analysis, adverse event rates for nebivolol were lower than for other beta blockers, calcium channel antagonists and losartan. The tolerability of nebivolol and ACE inhibitors was similar.[4]

In Australia, nebivolol has also been approved as an add-on treatment for heart failure in older patients. This is based on the SENIORS trial in 2128 patients aged 70 years and over with heart failure. This was a *post hoc* analysis and patients were not randomised to receive different doses of nebivolol. They were started on placebo, or a low dose of nebivolol which was gradually increased to 10 mg, if tolerated, over a maximum of 16 weeks. The target dose was reached by two-thirds of the patients in the nebivolol group and was associated with a significant reduction (relative risk reduction of 4.2%) in the composite end point of all-cause mortality or hospitalisation (due to a cardiovascular event), compared to placebo. However, nebivolol did not significantly reduce all-cause mortality alone. There was no significant benefit with low-dose nebivolol and patients who could not tolerate it had a higher risk of death or hospitalisation than those on placebo. It is not clear how nebivolol compares to other beta blockers in this population.[5]

In the heart failure trial, around 20% of patients had aggravated cardiac failure regardless of whether they were taking placebo or nebivolol. However, bradycardia was considerably more common with nebivolol than with placebo (11% vs 2.5% of patients). Dizziness was reported by 14% of patients in the nebivolol group and 13% in the placebo group.[5]

Spontaneous adverse events reported overseas with this drug have included abnormal liver function, acute pulmonary oedema, acute renal failure, myocardial infarction, Raynaud's phenomenon, thrombocytopenia and skin disorders including rashes. However, their frequency and causal relationship with nebivolol is not known.

Nebivolol has the potential to interact with many drugs, therefore it is important to read the product information before prescribing it. Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, quinidine, thioridazine and cimetidine, are likely to increase nebivolol concentrations so patients' blood pressure should be monitored closely in case dose adjustment is required. Nebivolol is not recommended with the calcium channel

antagonists verapamil and diltiazem, class I antiarrhythmic drugs (flecainide, disopyramide, lignocaine, mexiletine) and with centrally-acting antihypertensives (clonidine, moxonidine, methyldopa). Nebivolol should not be used with other beta blockers, including eye drops.

As beta blockade can depress myocardial contractility, it can worsen heart failure so nebivolol should not be given to patients with acute heart failure or untreated congestive heart failure. Other contraindications include sick sinus syndrome (without pacemaker), severe bradycardia, heartblock (more than first degree), hypotension, severe circulatory disturbances, metabolic acidosis and history of bronchospasm.

As with other beta blockers, patients should be warned against stopping nebivolol abruptly as this can exacerbate angina and precipitate myocardial infarction and ventricular arrhythmias.

When used for hypertension, dose adjustment is required in patients with renal impairment. There are no data on the use of nebivolol in patients receiving dialysis. For chronic heart failure, dose adjustment is not needed in mild to moderate renal insufficiency. Nebivolol is not recommended for patients with severe renal impairment. This drug is contraindicated in patients with hepatic impairment.

Nebivolol seems to be as effective as other antihypertensive drugs at lowering blood pressure and it benefits some patients with heart failure. However, until long-term data on its clinical use are available, it is probably better to continue to use the more established beta blockers.

T manufacturer provided only the product information

References *

1. Weiss RJ, Weber MA, Carr AA, Sullivan WA. A randomized, double-blind, placebo-controlled parallel-group study to assess the efficacy and safety of nebivolol, a novel β-blocker, in patients with mild to moderate hypertension. J Clin Hypertens 2007;9:667-76.
2. Saunders E, Smith WB, DeSalvo KB, Sullivan WA. The efficacy and tolerability of nebivolol in hypertensive African American patients. J Clin Hypertens 2007;9:866-75.
3. Papademetriou V. Comparison of nebivolol monotherapy versus nebivolol in combination with other antihypertensive therapies for the treatment of hypertension. Am J Cardiol 2009;103:273-8.
4. Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: a meta-analysis. Am J Cardiovasc Drugs 2008;8:35-44.
5. Dobre D, van Veldhuisen DJ, Mordenti G, Vintila M, Haaijer-Ruskamp FM, Coats AJS, et al. Tolerability and dose-related effects of nebivolol in elderly patients with heart failure: data from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS) trial. Am Heart J 2007;154:109-15.

Pneumococcal polysaccharide conjugate vaccine

Synflorix (GlaxoSmithKline)

0.5 mL suspension in pre-filled syringes

Approved indication: prevention of *Streptococcus pneumoniae* infections

Australian Medicines Handbook section 20.1

This vaccine is indicated for the prevention of invasive pneumococcal disease (including pneumonia and acute otitis media) in children aged 6 weeks to 2 years. The current conjugate vaccine for this age group contains polysaccharides from seven *S. pneumoniae* serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), whereas this new vaccine contains an additional three serotypes (1, 5 and 7F). Most of the polysaccharides in the new vaccine are conjugated to protein D (a conserved *Haemophilus influenzae* surface protein) rather than diphtheria toxoid which is used in the current vaccine.

The World Health Organization (WHO) has recommended that approval of pneumococcal vaccines for invasive disease can be based on immunogenicity data alone rather than efficacy trials. New vaccines should be non-inferior to the current seven-valent pneumococcal vaccine. Based on efficacy studies, the WHO has defined an antibody threshold which correlates to protection. This antibody must also be able to opsonise *S. pneumoniae* and promote phagocytosis by immune cells.

The new vaccine was found to be non-inferior to the seven-valent vaccine in an immunogenicity trial of 1650 babies. They were given three intramuscular doses before the age of six months and antibody titres in sera were measured a month after the last injection. An increase in titres was seen after a booster at 12 months indicating that babies had developed immune memory to the polysaccharides.[1] (Antibody data for serotypes 1, 5 and 7F could not be compared to the seven-valent vaccine.)

Protection against acute otitis media is more difficult to achieve than protection against invasive infections. In a trial of 4968 babies, an eleven-valent experimental vaccine containing the ten serotypes of this new vaccine conjugated to protein D was compared to a control vaccine for hepatitis A. After vaccination (at 3, 4, 5 and 12–15 months), efficacy against acute otitis media during the follow-up period was 58% for vaccine serotypes, and efficacy against ear infections caused by non-typeable *H. influenzae* was 35%.[2] Although not significant, the incidence of recurrent ear infections and the number of children needing grommets were less in the pneumococcal vaccine group.

When given at the same time, the pneumococcal vaccine did not affect the immunogenicity of a combined vaccine against hepatitis B, diphtheria, tetanus and acellular pertussis, *H. influenzae* type b and poliomyelitis.[2] About 40% of infants had injection-site reactions after the vaccination. Irritability and mild fever were also common and can be treated with an antipyretic drug.[3]

The vaccine should be given by intramuscular injection, so caution is urged in children with thrombocytopenia or coagulation disorders because of the risk of bleeding. The safety and efficacy of this vaccine has not been established in children who have an increased risk of pneumococcal infections such as those with sickle cell disease, splenic dysfunction, HIV, malignancy or nephrotic syndrome.

The vaccine should not be withheld or delayed in premature babies, but their respiration should be monitored for 2–3 days after the first vaccination. Antibody responses in immunocompromised children may be reduced.

This vaccine should be given to infants at 2, 4 and 6 months (in the thigh), with a booster at 12 months (in the upper arm). As with the current pneumococcal vaccine, it can be co-administered with other vaccines recommended in the Australian immunisation schedule.

Based on immunological data, this vaccine should protect most babies from invasive pneumococcal disease such as pneumonia, bacteraemia and meningitis caused by the vaccine serotypes. The vaccine was efficacious against acute otitis media, but it is not known if it will be any better than the current vaccine, or how it will perform in communities where uncommon serotypes have become more prevalent.[4] Because this vaccine contains protein D from *H. influenzae*, it should offer some protection against ear infections caused by non-typeable *H. influenzae*.

T T manufacturer provided additional useful information

References

1. Vesikari T, Wysocki J, Chevallier B, Karvonen A, Czajka H, Arsène JP, et al. Immunogenicity of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) compared to the licensed 7vCRM vaccine. Paediatr Infect Dis J 2009;28:S66-S76.
2. Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, Kaliskova E, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomised double-blind efficacy study. Lancet 2006;367:740-8.
3. Prymula R, Chlibek R, Splino M, Kaliskova E, Kohl I, Lommel P, et al. Safety of an 11-valent pneumococcal vaccine conjugated to non-typeable *Haemophilus influenzae*-derived protein D in the first 2 years of life and immunogenicity of the co-administered hexavalent diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio virus, *Haemophilus influenzae* type b and control hepatitis A vaccines. Vaccine 2008;26:4563-70.
4. Marsh RL, Smith-Vaughan H, Beissbarth J, Hare K, Kennedy M, Wigger C, et al. Molecular characterisation of pneumococcal serotype 16F: established predominant carriage and otitis media serotype in the 7vPCV era. Vaccine 2007;25:2434-6.

Rizatriptan benzoate

Maxalt (MSD)

10 mg wafers

Approved indication: migraine

Australian Medicines Handbook section 16.3.2

It is almost twenty years since the launch of sumatriptan, the first serotonin ($5HT_1$) receptor agonist. While sumatriptan benefited many patients with migraine, it was not ideal because of its low oral bioavailability and short half-life. This led to the development of other 'triptans'.

Rizatriptan is a serotonergic agonist which mainly acts on $5HT_{1B}$ and $5HT_{1D}$ receptors. This constricts the extracerebral and intracranial arteries which become dilated during an attack of migraine.

The wafers have a bioavailability of 45%. Food may affect absorption, but appears to have no effect on efficacy. Rizatriptan is metabolised by monoamine oxidase so it should not be prescribed for patients who have taken monoamine oxidase inhibitors in the previous two weeks. Plasma concentrations are also increased by propranolol, so a lower dose of rizatriptan is recommended in patients taking this beta blocker. Most of the metabolites of rizatriptan are excreted in the urine. The half-life is similar to that of sumatriptan (2–3 hours).

An early dose-ranging study compared rizatriptan with sumatriptan and placebo. The study assessed 449 patients and found that headache was reduced within two hours in 18% of the placebo group, 46% of the sumatriptan group and 52% of the patients who took 10 mg rizatriptan. This dose relieved pain completely in 26% of patients compared with 22% of the sumatriptan group and 3% of the placebo group. The headache returned in 41% of the patients taking rizatriptan 10 mg and 41% of the sumatriptan group.[1] If the headache returns, patients can take another dose of rizatriptan, but doses must be at least two hours apart and not exceed 30 mg in 24 hours.

As rizatriptan has been marketed overseas for several years, there are many studies of its use in migraine, however only some of these studied the wafer formulation. Two hours after a dose, 66% of patients with moderate to severe headache will respond to a wafer and 47% will respond to a placebo.

A meta-analysis found more patients responded to a 10 mg dose of rizatriptan than to a 100 mg dose of sumatriptan. Significantly more were pain free after two hours, but the headache was more likely to return within 24 hours in patients taking rizatriptan.[2]

The meta-analysis was used to calculate the number of patients who need to be treated for 100 to have sustained relief for 24 hours. These figures were 490 for sumatriptan 100 mg, and 458 for rizatriptan 10 mg. To treat 100 patients successfully required a total of 534 doses of sumatriptan 100 mg, or 516 doses of rizatriptan 10 mg.[3]

Rizatriptan has also been compared with other analgesics for migraine. In one placebo-controlled study 200 patients were randomised to take rizatriptan tablets, paracetamol, or both. After two hours 90% of the patients taking both drugs had responded compared with 77% of the rizatriptan group, 70% of the paracetamol group and 46% of the placebo group. Over 24 hours 62% of the patients taking both drugs had sustained relief, but this was not statistically superior to the 53% of the rizatriptan group and the 42% of the paracetamol group.[4]

Adverse events occur at a similar frequency to reactions to sumatriptan 100 mg.[2] Common adverse effects of rizatriptan include tiredness and dizziness. Like other drugs in the class, rizatriptan can cause pain in the chest and neck. It is contraindicated in ischaemic heart disease or uncontrolled hypertension. There is a risk of serotonin syndrome, particularly in patients taking serotonin reuptake inhibitors. Ergot alkaloids should not be used within six hours of rizatriptan.

T T manufacturer provided additional useful information

References *

1. Visser WH, Terwindt GM, Reines SA, Jiang K, Lines CR, Ferrari MD; Dutch/US Rizatriptan Study Group. Rizatriptan vs sumatriptan in the acute treatment of migraine. A placebo-controlled, dose-ranging study. Arch Neurol 1996;53:1132-7.
2. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-$HT_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 2001;358:1668-75.
3. Mullins CD, Weis KA, Perfetto EM, Subedi PR, Healey PJ. Triptans for migraine therapy: a comparison based on number needed to treat and doses needed to treat. J Manag Care Pharm 2005;11:394-402.
4. Freitag F, Diamond M, Diamond S, Janssen I, Rodgers A, Skobieranda F. Efficacy and tolerability of coadministration of rizatriptan and acetaminophen vs rizatriptan or acetaminophen alone for acute migraine treatment. Headache 2008;48:921-30.

Ustekinumab

Stelara (Janssen-Cilag)

45 mg/0.5 mL solution for injection

Approved indication: psoriasis

Australian Medicines Handbook section 8.2.1

Ustekinumab, a humanised monoclonal antibody, is a new treatment for moderate to severe psoriasis (see 'Treatments for psoriasis', Aust Prescr 2009;32:14-8). It suppresses the immune system by blocking the inflammatory actions of interleukin (IL)-12 and IL-23, which contribute to the symptoms of psoriasis.

In a placebo-controlled study of 320 patients, ustekinumab improved symptoms of moderate to severe psoriasis in a dose-dependent manner.[1] Ustekinumab was then investigated in two crossover trials involving 1996 patients (PHOENIX 1 and PHOENIX 2). In both trials, patients were randomised (1:1:1) to receive ustekinumab 45 mg or 90 mg subcutaneously (at 0, 4 and then every 12 weeks), or placebo (at 0 and 4 weeks). After 4 weeks the patients in the placebo group crossed over to receive ustekinumab 45 mg or 90 mg (at 12 and 16 weeks and then every 12 weeks after that). The primary end point of the trials was the proportion of patients whose symptoms had improved by 75% after 12 weeks of treatment. Overall, significantly more patients in the ustekinumab groups reached this end point than in the placebo groups (67% with 45 mg and 71% (66–76%) with 90 mg vs 3% for placebo). These responses were maintained for up to a year in patients who continued treatment. After patients taking placebo crossed over to receive ustekinumab, a similar pattern of improvement was seen.[2,3] A subgroup analysis of the trials indicated that the efficacy of ustekinumab was slightly lower in obese patients and those aged 65 years or over.

In the PHOENIX 2 trial, patients who had partially responded after seven months of treatment (50–75% improvement in symptoms) were re-randomised to receive ustekinumab every eight weeks or to continue with the 12-week schedule. After a year, more patients receiving the 90 mg intensified dose responded to treatment than those receiving the original 12-week dosing (69% vs 33%). In contrast, patients did not respond to intensification of the 45 mg dose.[3]

Ustekinumab has been compared to etanercept, another psoriasis drug, in a trial of 855 patients. After 12 weeks of treatment, both doses of ustekinumab – 45 mg or 90 mg – seemed to be more effective than etanercept 50 mg given twice weekly. Of the patients, 72% and 65% receiving ustekinumab had improved symptoms compared to only 57% with etanercept. Adding etanercept to ustekinumab treatment did not improve response rates further. The trial is ongoing and will assess the effect of interrupting and restarting therapy on patients' symptoms.

In the PHOENIX trials, adverse events were similar between treatment and placebo groups with the most common complaints being upper respiratory tract infections, headache and arthralgia. Serious adverse effects with ustekinumab 45 mg included angina, stroke, hypertension, intervertebral disc protrusion, dactylitis, clavicular fracture, sciatica and nephrolithiasis. With the 90 mg dose, there was one sudden cardiac death in a 33-year-old patient. This was thought to be related to dilated cardiomyopathy. Other events included cellulitis, benign meningioma, transient palpitations and ventricular extrasystoles, and coronary artery disease requiring surgery. There were two serious infections with ustekinumab 90 mg (cellulitis and herpes zoster) and one basal cell carcinoma.[2,3] Depression was a common adverse event.

After a year of treatment, some patients had developed antibodies to ustekinumab. This was more common in patients who had only partially responded to treatment compared to those who had had a better response (12% vs 2%).[3]

Because of its immunosuppressant effects, ustekinumab is contraindicated in patients with clinically important active infections, chronic infections or a history of recurrent infections. There is a risk that latent infections may reactivate so patients should be assessed for tuberculosis and given appropriate treatment if necessary before starting ustekinumab. Live vaccines such as BCG (Bacillus Calmette-Guérin) should not be given. As with other immunosuppressants, ustekinumab may increase the risk of malignancy. It should not be given with other systemic treatments for psoriasis, or with phototherapy.

When ustekinumab is given at 0 and 4 weeks and then every 12 weeks, steady-state serum concentrations are achieved by week 28. If a patient has not responded by this time, treatment should be stopped. Ustekinumab has a long half-life (approximately three weeks) and due to the mechanism of action, its effects may last for several months.

Ustekinumab appears to be effective for psoriasis, and will probably prove popular with patients since injections are only needed every 12 weeks. However, because of the increased risk of serious adverse effects, ustekinumab is only indicated for patients who have not responded to other systemic treatments or cannot tolerate them.

[X] manufacturer did not respond to request for data

References

1. Krueger GG, Langley RG, Leonardi C, Yeilding N, Guzzo C, Wang Y, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007;356:580-92.
2. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371:1665-74.
3. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675-84.

The T-score ([T]) is explained in 'New drugs: transparency', Aust Prescr 2009;32:80–1.

* 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.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/pmeds/auspar.htm)

Answers to self-test questions

1. False
2. False
3. False
4. False

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