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EDITORIAL

Safety considerations of biosimilars

Ross McKinnon
Associate Dean of research
School of Medicine
Flinders Centre for Innovation in Cancer
Flinders University

Michael Ward
Discipline leader of pharmacy education
School of Pharmacy and Medical Sciences
University of South Australia
Adelaide

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bioequivalence, biologic drug, biosimilar drug, generic drug, monoclonal antibody

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Over recent decades, some of the most important therapeutic advances have involved the use of biologic drugs. These are typically large complex molecules derived from a biological source, such as yeast or cell culture, rather than a chemical source. Examples of biologic drugs include monoclonal antibodies like infliximab and ipilimumab, and smaller proteins such as insulin and erythropoietin.

Patents on many originator biologic drugs are coming to an end allowing other companies to produce them. This is likely to cause significant price reductions in much the same way as generic manufacturers reduce the cost of small-molecule drugs. However, because of the complexity of biologic drugs, the traditional understanding of bioequivalence* with generic drugs cannot be directly applied.[1] For this reason, off-patent biologic drugs produced by alternative manufacturers are referred to as biosimilars or 'similar biological medicinal products' rather than generic medicines. They are subject to different regulatory considerations[2] compared to generic small-molecule drugs because their complexity and the way they are produced has the potential to result in variability in the final product between manufacturers and batches.

One of the most significant safety concerns with biosimilars is the potential risk of immune-based adverse reactions. Because of their molecular size, biologics can directly induce anti-drug antibodies which may have significant consequences for both safety and efficacy. This was highlighted by experience with erythropoietin over a decade ago when changes in manufacturing appeared to make the product more immunogenic. This significantly increased the risk of treatment-induced pure red cell aplasia and resulted in high fatality rates and rendered other patients dependent on blood transfusions.[3] More recently, Thailand experienced a significant number of cases of pure red cell aplasia following the introduction of 'bio-copy' erythropoietin products.[4] At the time in Thailand, these products were assessed using the same regulatory framework as for generic small-molecule drugs, which focuses on showing bioequivalence. This is drastically different from the current regulatory pathways for biosimilar drugs in Australia (and internationally) which demand clinical data showing that the biosimilar is equally as safe and efficacious as the originator biologic drug.

While the biosimilar regulatory framework attempts to address the concerns related to immunogenicity, potential uncertainty remains. In a recent clinical trial of a biosimilar etanercept, the incidence of patients with anti-drug antibodies was lower with the biosimilar (0.7%) than with the reference drug (13.1%).[5] The significance of this finding has been debated, particularly the transient nature and limited duration of anti-drug antibody positivity observed in these patients. This example highlights the complexities in this area including the technical challenges associated with detecting and quantifying anti-drug antibodies, the timing of patient assessments compared to the original studies of the reference product, and the assessment of the clinical impact of anti-drug antibodies.

In an attempt to balance the safety concerns of biosimilars against an overly onerous and costly clinical development pathway, clinical data are not required for approval of every potential indication.[2] Registration of the biosimilar for some indications might be based on clinical evidence of comparable clinical efficacy and safety in another indication. This potentially increases the uncertainty of the comparability of the biosimilar with the reference product.

It is possible that there are differences between conditions on the basis of the indication or the molecule. For example, the use of concurrent drugs such as an immunosuppressant often varies between indications, with the potential for differences in the risk of the formation of anti-drug antibodies. Likewise, the drug's mechanism of action may differ depending on the indication and it is possible that small differences in physicochemical characteristics could result in differences in clinical outcomes.

The extrapolation of indication has been recently illustrated with the approval of a biosimilar infliximab for inflammatory bowel disease following initial studies conducted in rheumatoid arthritis and ankylosing spondylitis. Although this creates a degree of uncertainty, surveys of gastroenterologists suggest that initial reservations subsided once they gained experience with the biosimilar.[6,7] Current data

* Bioequivalence is shown when, after administration, two products produce such similar plasma concentrations of the active ingredient that their clinical effects can be expected to be essentially the same.

suggest that the biosimilar infliximab is generally well tolerated and efficacious in inflammatory bowel disease in patients who have not previously received biological therapy.[8,9]

While clinical trials may show comparable safety and efficacy, the trial design may not look at switching between the reference product and the biosimilar. Open-label extension studies of phase III trials with the biosimilar infliximab, and the NOR-SWITCH study, a double-blind study assessing the safety and efficacy from originator to biosimilar infliximab, are providing reassuring data of the outcomes associated with switching therapy.[8,10,11] However, data relating to switching generally remain limited.

Administration of biologics is more complex than with small-molecule drugs. Switching or substituting a bioequivalent oral generic drug is often simple and may only require patient education about the difference in its appearance. However, because biologics are administered parentally, devices are required. Device design is proprietary so biosimilars will have a different device not only in appearance but also potentially in function. This could cause problems with safety. For instance with biosimilar insulin, many patients use pen devices but not all pens are compatible with the cartridges produced by the different biosimilar manufacturers. Although manageable through education, care needs to be taken to ensure that patients switching between products do not become confused.

Because of the uncertainties associated with the use of biosimilars, pharmacovigilance is important. Fundamental to this is accurate documentation and reporting of the specific products for each patient. At present naming conventions for biosimilars are still being established. Traceability may prove difficult in patients who undergo multiple switches or substitutions between the reference product and the biosimilar.[12]

In comparison with traditional small-molecule drugs, biosimilars have unique safety considerations. Owing to the diversity in their structural complexity and indications, safety will need to be considered on a drug-by-drug basis. Early experience indicates that once biosimilars become available, initial safety concerns will decrease. However, there remains a need for appropriate pharmacovigilance which considers the unique properties of these drugs. <

Ross McKinnon and Michael Ward have both provided educational presentations sponsored by AbbVie and Sanofi Aventis. Ross McKinnon has participated in Advisory Board activities for AbbVie.

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FURTHER READING

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LETTERS

Letters to the Editor

Treating osteoporosis

Aust Prescr 2016;39:190
http://dx.doi.org/10.18773/austprescr.2016.087

I read your summary of osteoporosis treatment[1] with a mixture of interest, and of dismay that I still have to treat 99 patients to prevent one serious fracture.

Without an accompanying analysis of serious adverse effects of the drugs, this does not inspire me to treat my patients at all. But there is another factor that has not been analysed – progress in the orthopaedic treatment and aftercare of fractures. Are there any data to suggest that the rationale for osteoporosis treatment – prevention of large bone fracture – is in fact less than it was in the past due to non-pharmacological advances in medicine?

At what point does the number needed to treat cross the line into ineffectiveness, or the line where the cure is worse than the disease?

Tim Metcalf
General practitioner
Bombala, NSW

REFERENCE

1. Gupta A, March L. Treating osteoporosis. Aust Prescr 2016;39:40-6. http://dx.doi.org/10.18773/austprescr.2016.028

Lyn March, one of the authors of the article, comments:

Thank you for your interest in our article. Serious adverse effects from osteoporosis medicines are very uncommon and hence the number needed to harm (approximately 1250 for atypical fractures after two years of treatment) is far greater than the number needed to treat.

The cost of osteoporotic fractures is high in terms of human suffering with pain, loss of mobility, loss of independence and increased risk of dying in the 3–5 years following the fracture, as well as costs to society through healthcare use, direct health costs and productivity loss.

The final decision needs to be made by weighing up potential harms and benefits for the individual patient, taking their preferences into account. The individual fracture risk calculators (e.g. Garvan, FRAX) can help with the decision making.

Unfortunately we do not have any advances in orthopaedic surgery that prevent or reduce the increased risk of subsequent fractures. Non-pharmacological interventions such as nutritional and exercise-based approaches are important components of the overall care. However in the setting of previous fractures, they need to be combined with drugs to reduce the risk of fracture.

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. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

Acute sinusitis

Aust Prescr 2016;39:191
http://dx.doi.org/10.18773/austprescr.2016.086

After reading Chris Del Mar's article on acute sinusitis and sore throat,[1] I would like to ask him if there is evidence for the commonest treatments that ear, nose and throat surgeons use for sinusitis. These include oral or topical steroids plus saline nasal rinses.

Bridget Clancy
Ear, nose, throat, head and neck surgeon
Warrnambool, Vic.

REFERENCE

1. Del Mar C. Acute sinusitis and sore throat in primary care. Aust Prescr 2016;39:116-8. http://dx.doi.org/10.18773/austprescr.2016.046

Chris Del Mar, the author of the article, comments:

A Cochrane review of four randomised trials and 1943 patients indicates that intranasal steroids at high doses do provide some relief of acute sinusitis, although only for mild disease, and with a number needed to treat of about 12.[1] Another Cochrane review of five randomised trials with a total of 1193 adults found no benefit for systemic steroids in acute sinusitis.[2]

A third Cochrane review of acute respiratory infections included 749 children and adults in five randomised controlled trials. Participants were randomised to saline nasal washouts or not. The trials had such mixed results (heterogeneity) that they could not be pooled, and were sufficiently vulnerable to bias that any benefits were deemed unreliable.[3] Combinations of these interventions have not been studied in Cochrane reviews.

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LETTERS

New drug for allergic rhinitis

Aust Prescr 2016;39:192
http://dx.doi.org/10.18773/austprescr.2016.088

I read the new drug comment on dust mite allergen extract for allergic rhinitis with interest.[1] I am not sure why this product is being marketed or even discussed if the only benefit is a small reduction in symptoms but insufficient effect to reduce the use of rescue medications. The effect on IgE concentrations is interesting, but obviously fails to translate into clinically (and financially) relevant benefits. There are also unwelcome and possibly distressing adverse effects.

It will not be going into my armamentarium just yet, unless there is something of major importance I am missing. I think not.

Jan Sheringham
Corlis fellow
Advocacy, continuing education and training
RACGP Victoria

REFERENCE

1. Dust mite allergen extract. Aust Prescr 2016;39:184-5. http://dx.doi.org/10.18773/austprescr.2016.077

The Editorial Executive Committee of Australian Prescriber comments:

Thank you for your letter. The purpose of the New Drugs section is to provide prescribers with independent information on new chemical entities marketed in Australia. These short summaries on how the drug works, the evidence for its approval and its adverse effects aim to help prescribers make their own decisions when deciding whether or not to prescribe a new drug.

As mentioned in the preamble for each drug comment, the information should be regarded as preliminary. In this instance, the comment was based on limited published data as is often the case. The Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value to prescribers.

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ARTICLE

Correcting iron deficiency

SUMMARY

Iron deficiency is the most common cause of anaemia. It has many different causes, so further investigations are required to establish an underlying aetiology.

An iron study is the first-line investigation and includes serum iron, ferritin, transferrin and transferrin saturation. Serum ferritin is normally a suitable indicator of iron stores but can be increased by inflammation to an extent that makes the ferritin unreliable for assessment of iron deficiency.

Oral iron replacement is the most appropriate first-line treatment in the majority of patients. Its efficacy can be limited by poor patient compliance due to the high rate of gastrointestinal adverse effects and the prolonged treatment course needed to replenish body iron stores.

Intravenous iron preparations are indicated when oral iron therapy has failed or rapid replenishment is required.

Ferric carboxymaltose can rapidly deliver a large dose of iron, making it the preparation of choice for outpatients.

Despite their excellent safety profiles, all intravenous iron preparations carry the risk of anaphylaxis. Patients require monitoring and access to resuscitation facilities.

Jonathan Baird-Gunning
Registrar
Acute and General Medicine[1]

Jonathan Bromley
Consultant physician
Gastroenterologist and General Medicine[1]
Clinical lecturer[2]

[1] Canberra Hospital
[2] Australian National University
Canberra

Keywords
anaemia, ferric carboxymaltose, ferritin, iron, iron deficiency, iron sucrose

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Introduction

In 2010, the global prevalence of anaemia was 32.9% and iron deficiency was the most common cause.[1] There are few population studies examining the prevalence of iron deficiency and epidemiological data can be methodologically flawed as anaemia is usually ascribed to iron deficiency.[2] Using anaemia as an indirect indicator, it can be estimated that most preschool children and women in non-industrialised countries and a significant proportion in industrialised countries are iron deficient.

In Australia the prevalence of iron deficiency varies depending on the study population. It affects approximately 10% of non-pregnant young women, and is estimated to be highly prevalent in indigenous communities.[3] Other at-risk groups for iron deficiency include the very young and the very old, and people with restrictive dietary patterns such as vegetarians and vegans.

Iron deficiency

Iron plays a key role in multiple metabolic pathways including respiration, energy production, DNA synthesis and cell proliferation. The clinical consequences of untreated iron deficiency are diverse. They include fatigue, exacerbations of certain diseases such as angina, neurobehavioural disorders such as restless leg syndrome,[4] and cognitive impairment in children.[5]

Iron deficiency can be due to multiple underlying causes (Table 1) and patients should be investigated according to guidelines to determine the underlying aetiology. The Gastroenterological Society of Australia has produced guidelines regarding appropriate investigation for patients with iron deficiency. Iron deficiency can be subdivided into:

- **absolute iron deficiency** due to insufficient iron stores
- **functional iron deficiency**, when demand from increased erythropoiesis temporarily outstrips supply
- **sequestration**, when existing iron stores are sufficient but become unavailable. Sequestration is usually a consequence of proinflammatory disease states such as chronic kidney disease, autoimmunity, infections and malignancy. Iron replacement is not required and is potentially harmful.

These mechanisms are not mutually exclusive.[6]

Assessing iron stores

An iron study is the investigation of choice in assessing iron stores. It measures serum iron, transferrin, transferrin saturation, total iron-binding capacity and ferritin. The Gastroenterological Society of Australia guidelines specify fasting iron studies, as dietary intake can affect serum iron concentrations. However as clinical decisions are rarely made on

Table 1 **Causes of iron deficiency**

Cause	Example
Physiological	
• increased demand	Infancy, rapid growth, pregnancy, menstrual blood loss
Environmental	Insufficient intake e.g. vegan diet
Pathological	
• decreased absorption	Gastrectomy, duodenal bypass, Crohn's disease
• chronic blood loss	Gastrointestinal tract – peptic ulcer disease, colorectal cancer, angiodysplasia Systemic bleeding – postoperative, recent trauma
Drug related	Non-steroidal anti-inflammatory drugs, proton pump inhibitors, glucocorticoids
Genetic	Iron-refractory iron deficiency anaemia

Table 2 **Interpreting iron profile results according to aetiology and severity**

	Anaemia of chronic disease	Iron deficiency without anaemia	Severe iron deficiency with anaemia
Serum iron	↓	↓	↓
Serum transferrin or serum total iron binding capacity	↓ or low normal	↑ or high normal	↑
Serum transferrin saturation (%)	↓	↓	↓
Serum ferritin	↑ or high normal	↓	↓
Blood film	Normal	Normal	Hypochromia and microcytosis

Box 1 **Dietary sources of iron**

Heme iron

Liver
Red meat
Seafood
Poultry

Non-heme iron

Beans
Dark green leafy vegetables
Dried fruit, raisins and apricots
Iron-fortified bread, cereal, pasta

this parameter alone, many people do not routinely follow these recommendations.[7] Among the iron studies, serum ferritin is the most sensitive and specific test for evaluating a patient's iron stores.[8] A serum ferritin of less than 30 microgram/L is diagnostic of iron deficiency and should prompt investigation for an underlying cause (see Fig.) and appropriate treatment.[9]

Transferrin is a protein that transports iron and reflects total iron-binding capacity. A transferrin saturation of less than 16% indicates an iron supply that is insufficient to support normal erythropoiesis.

Diagnosing iron deficiency can be challenging as ferritin is also an acute-phase protein, which can be elevated in the presence of infections, autoimmunity, chronic kidney disease and certain malignancies. In these scenarios ferritin can potentially overestimate the patient's iron stores. Serum ferritin up to 300 microgram/L can still be compatible with iron deficiency in the presence of inflammation and needs to be interpreted with other parameters measured in the iron profile and supportive red-cell indices such as mean corpuscular volume and a blood film (Table 2). Depending on the clinical urgency, it may be better to recheck the iron profile once the acute illness has settled before commencing replacement.

Assessing bone marrow iron stores with Prussian Blue staining is still considered the gold-standard investigation. However, this invasive investigation is rarely required for confirming iron deficiency.

Correcting iron deficiency

There are multiple strategies for correcting iron deficiency ranging from dietary advice to blood transfusion. The choice will be influenced by the severity of anaemia and the comorbidities of the patient.

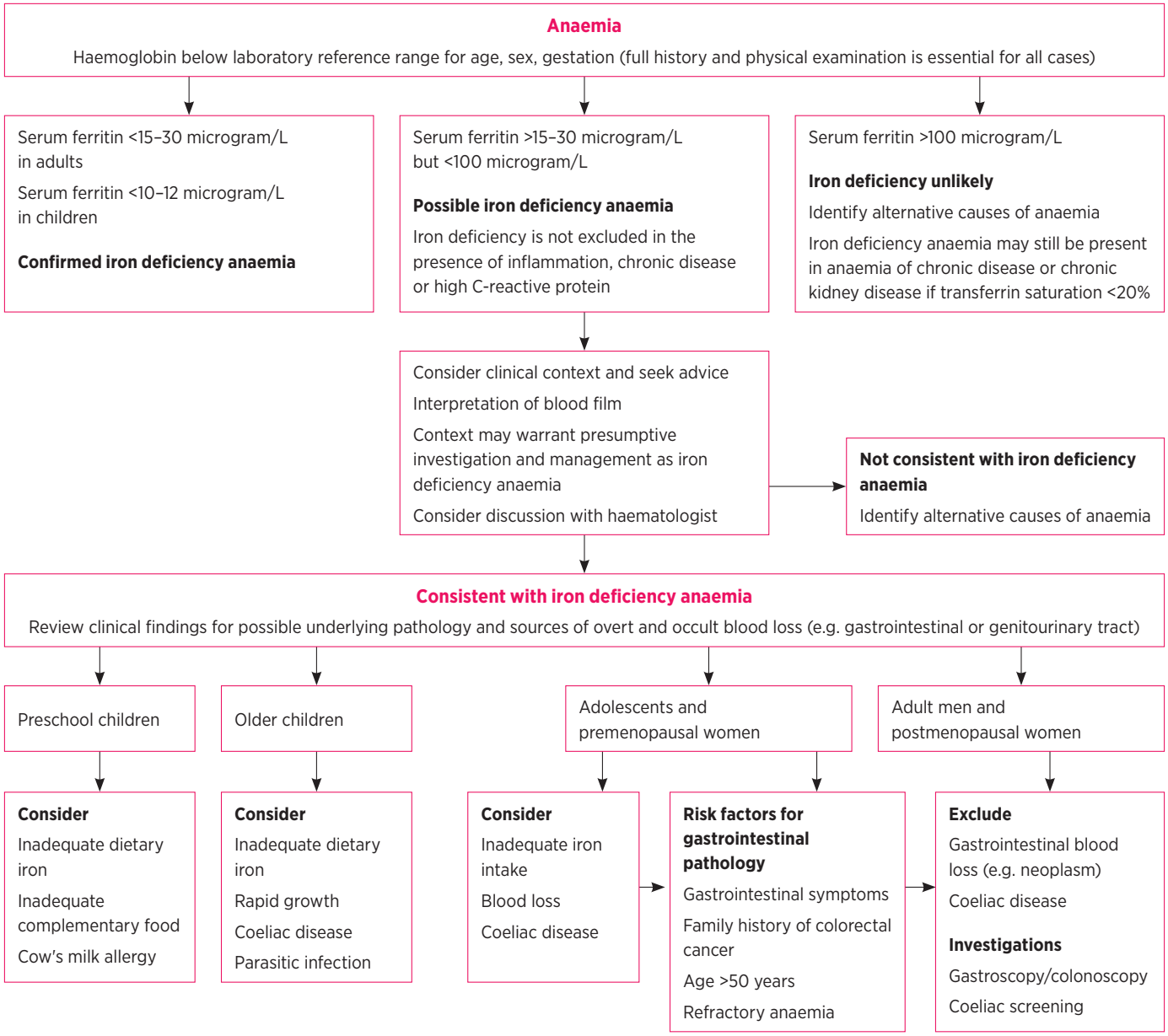
Diet

It is imperative to ensure that the patient has an adequate iron intake, particularly if they have a restrictive diet such as veganism. In general, plant iron is non-heme iron (Box 1) which is poorly absorbed, however co-ingestion of an antioxidant such as vitamin C (e.g. a glass of orange juice) may improve absorption.

Oral iron

Oral iron therapy should correct anaemia and replenish iron stores. Therapeutic Guidelines suggests ferrous sulfate at a dose of 325–650 mg daily (equivalent to 105–210 mg elemental iron), however other guidelines recommend higher doses.[10] There are no comparative trials evaluating effectiveness or tolerability. Ferrous fumarate and gluconate salts

Fig. **Investigation of iron deficiency**



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are equally effective in practice. Vitamin C enhances iron absorption[11] and is compounded with several iron preparations (Table 3).

Patients should be advised to take oral iron supplementation on an empty stomach as phosphates, phytates and tannates in food bind iron and impair absorption. Patients should also be advised to take iron either two hours before or four hours after the ingestion of antacids.

While there are obvious advantages to oral iron supplements such as cost, safety and ease of access, there are also several limitations. Adverse effects such as constipation, dysgeusia and nausea reduce adherence,[12] and hence effectiveness, particularly when the recommended duration of therapy is 3–6 months. Poor adherence is a common cause for failure to respond to oral iron therapy, however other causes should also be considered (Table 4).

Liquid iron replacement can be trialled in patients intolerant of iron tablets. It can be taken in divided daily doses reducing gastrointestinal adverse effects, however it can discolour teeth.

Table 3 **Oral iron preparations**

Brand name	Formulation	Elemental iron content
Ferro-gradumet	Ferrous sulfate 325 mg Controlled-release tablets	105 mg
Ferrograd C	Ferrous sulfate 325 mg Vitamin C 500 mg Controlled-release tablets	105 mg
FGF	Ferrous sulfate 250 mg Folic acid 300 microgram Controlled-release tablets	80 mg
Fefol	Ferrous sulfate 270 mg Folic acid 300 microgram Controlled-release capsules	87 mg
Ferro-F-tab	Ferrous fumarate 310 mg Folic acid 350 microgram Non-controlled-release tablets	100 mg
Ferro-tab	Ferrous fumarate 200 mg	65.7 mg
Ferro-liquid	Ferrous sulfate 30 mg/mL	6 mg/mL

Table 4 **Reasons for failure to respond to oral iron therapy**

Reason	Example
Inadequate iron intake	Non-adherence, insufficient iron content in supplement
Inadequate iron absorption	Concomitant consumption of inhibitors of iron absorption (e.g. tea, calcium) Coexisting inflammation with iron sequestration Intestinal mucosal disorders (e.g. coeliac disease) *Helicobacter pylori* infection Impaired gastric acid secretion (use of proton pump inhibitors)
Ongoing blood losses	Occult blood loss
Coexisting condition interfering with bone marrow response	Concomitant vitamin B_{12} or folate deficiency, primary bone marrow disease
Incorrect diagnosis	Haemoglobinopathy, anaemia of chronic disease or renal failure

Liposomal oral iron preparations are currently under evaluation.[3,13] These consist of iron encased in a phospholipid coat containing ascorbic acid, which prevents direct contact between iron and the intestinal mucosa thereby reducing gastrointestinal adverse effects.

Iron is toxic in overdose. It is therefore important to store oral iron products out of reach of children.

Parenteral iron

Parenteral iron is indicated when oral therapy has failed or when patients require rapid iron replacement. Intramuscular injections of formulations such as iron polymaltose are painful and can permanently stain the skin and should be avoided where possible. Intravenous infusion results in a rapid replenishment of iron stores with peak ferritin concentrations at 7–9 days after infusion.[14] In our experience the haemoglobin should rise within 2–3 weeks in the majority of patients. There are several intravenous iron preparations available in Australia (Table 5).

Ferric carboxymaltose

Ferric carboxymaltose is the preferred formulation in ambulatory settings, such as Hospital in the Home services and suitably equipped general practices, as it can deliver up to 1 g of iron in 15 minutes and has an excellent safety profile. It is superior to oral

iron in increasing serum ferritin and haemoglobin in the management of postpartum iron deficiency[15] and correcting preoperative anaemia.[16] Compared to placebo it alleviates the symptoms of heart failure,[17] and ferric carboxymaltose is non-inferior to ferrous sulfate in inflammatory bowel disease.[18]

The REPAIR-IDA trial was the largest randomised trial comparing ferric carboxymaltose to iron sucrose in patients with non-dialysis-dependent chronic kidney disease. The study demonstrated that ferric carboxymaltose was safe, effective and required fewer doses making it potentially more cost-effective than iron sucrose.[19] Other studies have also found favourable cost-effectiveness.[20]

One limitation is ferric carboxymaltose can only be infused in doses up to 1 g per week. It therefore cannot always provide the amount of iron required according to the Ganzoni formula (see Box 2). Two infusions at least one week apart may be needed.

Iron polymaltose

Iron polymaltose may be the preferred intravenous iron preparation for inpatients as a larger dose of iron can be infused in a single sitting. However, there are several logistical limitations such as preparation time (the case illustrating the Ganzoni formula would require 19 ampoules) and the lengthy duration of administration of up to five hours that requires frequent observations. This limits its use outside of hospital.

Iron sucrose

The use of iron sucrose is restricted by the Pharmaceutical Benefits Scheme to patients on chronic intermittent haemodialysis. It is more effective at improving haematocrit and ferritin than ferric chloride.[21]

Safety of intravenous iron

Hypersensitivity reactions, which can be fatal, can occur with all intravenous iron formulations[22] and the patient should be aware of this when giving consent. This risk is substantially lower with non-dextran formulations such as ferric carboxymaltose, iron polymaltose and iron sucrose. The estimated risk of serious anaphylactic reactions with ferric carboxymaltose is 0.1%. The European Medicines Agency recommended that all intravenous iron preparations should only be given in an environment where resuscitation facilities are available.[23]

Box 3 shows the common adverse effects associated with iron infusions. Infusion site reactions, such as pain, extravasation and injection site discolouration, occur at a rate of approximately 1.6% with ferric carboxymaltose. This is comparable to other intravenous iron formulations.

Table 5 **Intravenous iron preparations**

Compound	Maximum single dose	Duration of infusion
Ferric carboxymaltose (Ferinject)	1000 mg Repeat a week later	Up to 15 minutes depending on dose
Iron polymaltose (Ferrosig)	1000–2500 mg	Approximately 5 hours
Iron sucrose (Venofer)	100 mg during dialysis 3 times per week	15 minutes minimum

Box 2 **Ganzoni formula**

Total iron dose (mg iron) =
Body weight (kg) x (Target – Actual haemoglobin) (g/L)* x 0.24 + Iron for iron stores (mg iron)**

* Haemoglobin must be in g/L

** Iron stores

<35 kg body weight = 15 mg/kg body weight

>35 kg body weight = 500 mg

Example: 80 kg female with a haemoglobin of 80 g/L needs a dose of 80 x (150–80) x 0.24 + 500 = 1844 mg iron

Box 3 **Adverse effects of intravenous iron preparations**

Immediate adverse effects

Headache
Nausea
Vomiting
Dysgeusia
Arthralgia
Myalgia

Anaphylactoid

Wheezing
Flushing
Dyspnoea
Dizziness

Infusion site reactions

Localised pain
Discolouration of skin

Delayed adverse effects (1–2 days post infusion)

Mild fever
Headache
Arthralgia
Myalgia

REPAIR-IDA[19] reported a higher incidence of mild adverse events in patients treated with ferric carboxymaltose compared to iron sucrose. These included mild hypersensitivity reactions, nausea and flushing, however there was no statistically significant difference on the pre-specified safety end points. REPAIR-IDA did report an increase in the number of hypertensive episodes and hypophosphataemia with ferric carboxymaltose compared to iron sucrose.

This raised concerns regarding the safety of this formulation in patients with a high cardiovascular risk. However, subsequent meta-analysis has confirmed the safety of ferric carboxymaltose[24] and a recent prospective study has shown that ferric carboxymaltose reduces the risk of hospitalisations in patients with heart failure compared to placebo.[25] A recent meta-analysis has not reported an increased risk of serious infections with use of intravenous iron preparations.[24]

Conclusion

Iron deficiency anaemia is a common clinical problem that has a diverse range of causes and mandates further investigations to establish an aetiology. An iron study is a key investigation and serum ferritin is the most sensitive component. However, the ferritin concentration is affected by the presence of inflammation so a careful assessment of other results such as mean corpuscular volume and a blood film is required.

There are a number of oral iron preparations, however these are often poorly tolerated, limiting their effectiveness. Liquid iron replacement allows divided daily doses and reduces adverse effects. New liposomal preparations are under evaluation.

Intravenous iron should be considered as second-line therapy for patients who do not respond to oral iron or require rapid iron replacement. Ferric carboxymaltose is a non-dextran intravenous iron formulation that can deliver a large dose of iron in a short time. It has been evaluated in a number of patient populations and has been shown to be safe and effective. Ferric carboxymaltose is preferred to iron polymaltose for outpatients as it is easier to manage. ◀

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ARTICLE

Long-term prescribing of new oral anticoagulants

Paul KL Chin
Research fellow

Matthew P Doogue
Associate professor
Department of Medicine
University of Otago
Christchurch
New Zealand

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SUMMARY

Warfarin and the new oral anticoagulants are licensed for non-valvular atrial fibrillation and venous thromboembolism.

The choice of anticoagulant depends on the characteristics of the patient and the medicine. Key considerations include patient adherence, kidney and liver function, and potential interactions with concomitant drugs. Dosing should accommodate these factors.

Patients should be regularly monitored for bleeding, adherence to treatment, and changing comorbidities and concomitant drugs. Renal function should be checked at least annually.

Other than idarucizumab for dabigatran, there are no widely available antidotes for the new oral anticoagulants. In a patient with normal renal and hepatic function, drug concentrations and anticoagulant effect are expected to diminish by over 90% after stopping treatment for 48 hours.

Introduction

Three new oral anticoagulants (NOACs) – dabigatran, rivaroxaban and apixaban – were listed on the Pharmaceutical Benefits Scheme in 2012. These drugs are also known as non-vitamin K antagonists and are alternatives to warfarin for some long-term indications, including the prevention of thromboembolism in non-valvular atrial fibrillation and the treatment of venous thromboembolism (see Table).[1,2]

A key difference between NOACs and warfarin is in the use of coagulation testing. Warfarin dosing is guided by a coagulation test, the INR. With NOACs, coagulation monitoring was not used in the major randomised controlled trials that support their use.

Once the decision to anticoagulate has been made, the following questions need to be considered:

- Which anticoagulant drug should be prescribed?
- What dose should be used?
- What monitoring do patients need?
- How is bleeding managed if it occurs?

Choice of oral anticoagulant

All the major trials comparing NOACs to warfarin have been non-inferiority studies.[3] These trials were not designed to test superiority over warfarin in relation to thrombosis and bleeding, which is an important limitation of such claims based on the data. The trials found the newer drugs were non-inferior to warfarin for the primary outcomes (including thrombosis and bleeding) when used to treat atrial fibrillation and venous thromboembolism.

Matching the characteristics of the individual patient to the characteristics of each oral anticoagulant is important when choosing therapy.[4] The Table lists approved indications and key characteristics of oral anticoagulants. A major difference between NOACs is the contribution of the kidneys to drug clearance, which is greatest for dabigatran. Key decision points when choosing an oral anticoagulant are illustrated in the Figure.

Patient characteristics

Warfarin should be used for patients with mechanical heart valves as data for the NOACs are either lacking or show inferiority to warfarin. We recommend that patients established on warfarin with a high percentage of time in the therapeutic range (e.g. >70% of INR values at target)[5] should remain on warfarin.

The uncertainty around dosing of NOACs in severe liver impairment (e.g. Child Pugh C) or renal impairment (e.g. creatinine clearance <30 mL/min) means that warfarin is favoured in these patients. NOACs are not recommended during pregnancy or breastfeeding as there are alternatives associated with greater safety and efficacy data. Warfarin is teratogenic and thus contraindicated during pregnancy, but is compatible with breastfeeding as transfer into breastmilk is negligible.

Drug–drug interactions

Co-administration of medicines that are strong enzyme or transporter inducers (e.g. rifampicin) or inhibitors (e.g. erythromycin)[6] are expected to

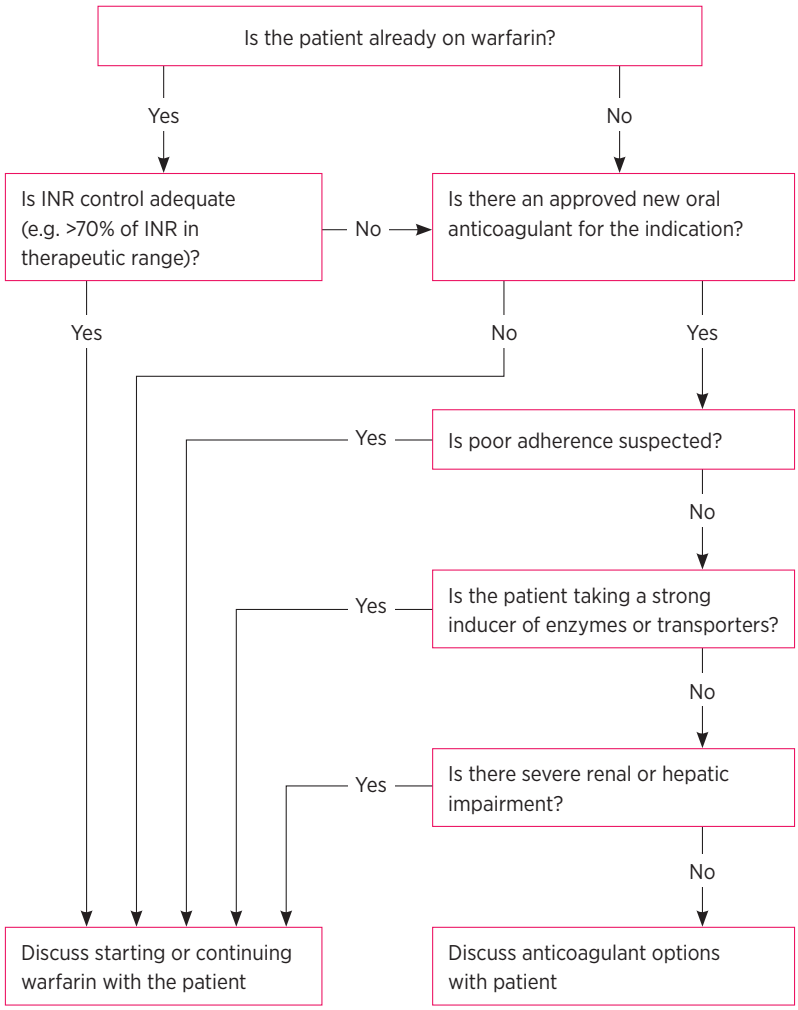
Table **Characteristics of oral anticoagulants**

	Warfarin	Apixaban	Dabigatran	Rivaroxaban
Brand	**Coumadin, Marevan**	**Eliquis**	**Pradaxa**	**Xarelto**
Licensed indications	AF, VTE, valvular heart disease	AF, VTE	AF	AF, VTE
Dosing frequency	daily	twice daily	twice daily	daily †
Oral bioavailability ‡	100%	50%	7%	>80% §
Excretion unchanged in urine ‡	0%	34%	80%	36%
Major metabolic/transport pathways	CYP2C9	CYP3A4, P-glycoprotein	P-glycoprotein #	CYP3A4, P-glycoprotein
Drug half-life ¶				
healthy young individuals	40 hours	10 hours	14 hours	7 hours
chronic kidney disease				
moderate	not reported	not reported	19 hours	9 hours
severe	–	–	28 hours	10 hours
chronic liver disease				
moderate	not reported	not reported	12 hours	10 hours
severe	–	–	not reported	not reported
Effect of chronic disease on anticoagulant concentrations **				
chronic kidney disease				
moderate	not reported	30% increase	210% increase	50% increase
severe	–	40% increase	530% increase	60% increase
chronic liver disease				
moderate	not reported	9% increase	6% decrease	120% increase
severe	–	not reported	not reported	not reported
Effect of concomitant drugs on anticoagulant concentrations ††	Amiodarone increases anticoagulant	Erythromycin increases anticoagulant	Verapamil increases anticoagulant	Erythromycin increases anticoagulant
	Rifampicin decreases anticoagulant	Rifampicin decreases anticoagulant	Rifampicin decreases anticoagulant	Rifampicin decreases anticoagulant

AF atrial fibrillation VTE venous thromboembolism CYP cytochrome P450
All values are means.
† Initial dosing in normal renal function is twice daily, maintenance dose is once daily.
‡ Values in healthy young individuals.
§ When administered with food (when fasting, the oral bioavailability of rivaroxaban 20 mg is 66%).
# Dabigatran etexilate, the prodrug of dabigatran, but not dabigatran itself, is a P-glycoprotein substrate.
¶ Kidney and liver disease usually reduce drug clearance and thus increase drug half-lives.
** For example, 100% increase indicates that concentrations were double that of the reference healthy group.
†† See Australian Medicines Handbook interaction tables for more examples of drugs that inhibit or induce metabolic or transport pathways (https://amhonline.amh.net.au/interactions).
Source: References 1, 2

cause significant changes in oral anticoagulant drug concentrations, with corresponding changes in anticoagulation effect (Table).[1] While drug interactions with warfarin can be managed by dose adjustment and INR monitoring, it is less clear how to proceed with dabigatran, rivaroxaban and apixaban. We recommend avoiding concomitant strong inhibitors and inducers of cytochrome P450 (CYP) 3A4 and P-glycoprotein with NOACs. The Table lists some examples of interacting drugs, with more comprehensive lists available in the Australian Medicines Handbook.

Fig. **Choosing an oral anticoagulant for long-term use**



Patient preference

After drug and patient characteristics have been considered, patient preferences and the prescriber's experience with different anticoagulants should be considered. For example, some patients prefer to avoid frequent blood tests. Conversely other patients taking warfarin view INR monitoring as a benefit rather than a barrier to therapy, and gain reassurance from these tests.[7] There should still be regular blood tests for renal function, given that all NOACs are subject to some degree of renal elimination. Finally, as NOACs have shorter half-lives than warfarin (Table), warfarin may be preferred if daily adherence is a problem. Patients will have a lower clinical risk of thrombosis if they forget to take warfarin than if they forget to take one of the NOACs. Apixaban and rivaroxaban may be kept in dosette boxes. In contrast, dabigatran should be kept in its foil blister pack or bottle to minimise the risk of degradation.

Dose

Pharmacokinetic and pharmacodynamic factors should be considered when selecting doses of the NOACs. Pharmacokinetic factors affecting drug concentrations are outlined in the Table, and include renal and hepatic impairment and concomitant interacting medicines that affect drug metabolism (e.g. CYP3A4) or P-glycoprotein. Pharmacodynamic factors affect the risk of thromboembolism or bleeding independently of any effect on drug concentrations. There is overlap between factors that raise thromboembolic risk (age over 65 years, hypertension, known vascular disease such as previous stroke or myocardial infarction, heart failure, diabetes, female gender) and bleeding risk (age over 65 years, uncontrolled hypertension, previous stroke, abnormal renal and liver function, bleeding history, excess alcohol and concomitant medicines such as antiplatelet drugs, non-steroidal anti-inflammatory drugs and selective serotonin reuptake inhibitors).[8,9]

Dosing guidance in the product information is a good starting point to select the dose. However, some of the information is inconsistent or unclear, especially for pharmacokinetic drug interactions.

When considering the risk of bleeding, for patients with one pharmacokinetic factor such as moderate renal impairment, doses can be adjusted in proportion to the predicted changes in anticoagulant concentrations outlined in the Table. This was not done in the trials of apixaban, dabigatran and rivaroxaban, but the principles of dose-individualisation are well established across many drugs. There is evidence that dose adjustment of dabigatran beyond what was described in the trial protocol for atrial fibrillation is associated with improved clinical outcomes.[10] Dosing patients with several coexisting factors is difficult without a reliable method of monitoring the drug's anticoagulant effect.

Clinical and laboratory monitoring

Clinical monitoring begins with monitoring patient events and educating the patient to report bleeding. Poor adherence is the most common cause of treatment failure so adherence should be encouraged and monitored.[11,12] Patient characteristics such as comorbidities and concomitant medications can change. This may alter the risks of thrombosis and bleeding so dose adjustment or a change in treatment may need to be considered. As a minimum, these components of clinical monitoring should occur with every prescription of an oral anticoagulant (see Box).

Renal function

Renal function should be monitored regularly because renal impairment increases the risk of bleeding with all of the NOACs.[12,13] We suggest 6–12 monthly monitoring, and additional testing with changing clinical circumstances, such as a change in diuretics in patients with heart failure. It is important to note that all of the oral anticoagulant trials used the Cockcroft-Gault estimation of creatinine clearance to gauge renal function (in mL/min). If the laboratory estimate of glomerular filtration rate (eGFR) is used, the values (in mL/min per 1.73m^2) should be adjusted for the patient's body surface area, especially at the extremes of size.[14]

Coagulation tests

There is increasing recognition that coagulation tests are valuable for informing the management of an acute thrombotic or bleeding event in patients taking NOACs.[15] In contrast, the role of the tests in guiding dosing in the ambulatory setting remains controversial, partly because of questions about the choice of test and target range.[1] Routine screening coagulation tests – including the INR, activated partial thromboplastin time (aPTT) and thrombin time (TT) – all correlate to varying degrees with plasma concentrations of the NOACs.[15] However, as the relationships between each of these tests and anticoagulant concentrations varies by drug and by laboratory, interpretation should be performed in consultation with local specialists. Specific advice about interpretation of coagulation tests is available from the Australasian Society of Thrombosis and Haemostasis.[13]

Management of bleeding

In addition to gauging the severity of bleeding, the patient's recent intake of oral anticoagulants should be evaluated. For example, a clear history of an overdose preceding the bleeding event may inform subsequent decisions for long-term anticoagulation. Laboratory tests may also be needed. Other more definitive tests to identify the bleeding site, such as gastrointestinal endoscopy, are performed as required.

Box **Patient monitoring with new oral anticoagulants**

Clinical

Adherence to therapy

Symptoms and signs of bleeding

Changing comorbidities such as new heart failure

Concomitant medicines

Laboratory

Renal function

Other tests as clinically indicated e.g. blood counts, liver function tests

For minor bleeding, such as mild epistaxis, local measures may be adequate. For more serious bleeding, such as an intracranial haemorrhage, discontinue the anticoagulant at least until the bleeding has been stabilised and the clinical status of the patient (including ongoing bleeding risk) has been sufficiently evaluated. When bleeding is severe, the patient should be referred to hospital.

While 'antidotes' to apixaban, dabigatran and rivaroxaban exist,[16] they are parenterally delivered recombinant proteins that are not readily available outside of drug development trials. The exception is idarucizumab, which was recently approved.[17] Otherwise, the main antidote is time. Drug concentrations and anticoagulant effect are expected to diminish by more than 90% after treatment has been stopped for four half-lives. The Table lists average half-lives according to anticoagulant and renal and hepatic function. These data may be used to inform the timing of when the anticoagulant should be interrupted before a procedure with a low risk of bleeding. Stopping 2–3 drug half-lives before such procedures has been suggested.[13]

Are NOACs better than warfarin?

The purported benefits of the newer oral anticoagulants over warfarin include predictable pharmacokinetics, fewer interactions with foods and other drugs, a lack of a need for routine laboratory coagulation monitoring, and quicker onset and 'offset' of action.

The claim that NOACs have predictable pharmacokinetics is misleading. For example, for a given dosage of dabigatran, the 10th to 90th centiles of observed steady-state concentrations encompassed a five-fold range of values.[18] This degree of variability is typical for most drugs.[19] Hence, it is remarkable that clinical outcomes from fixed-dose NOACs have been found to be non-inferior to INR-targeted warfarin. These non-inferiority trial findings are supported by observational studies of real-world use, especially for dabigatran,[20,21] albeit not entirely.[22]

The lack of an established need for routine coagulation monitoring with NOACs may be convenient for patients who do not have ready access to INR testing for warfarin therapy. However, it makes monitoring adherence and managing thrombotic events more difficult.[13] Also, although NOACs have fewer food and drug interactions than warfarin,[2] the relative lack of familiarity with interactions and routine monitoring means that prescribers may miss important interactions.

The quicker onset and 'offset' of action with NOACs is both a positive and a negative. On the one hand, the need for bridging with parenteral anticoagulants may be obviated with NOACs. Conversely, missing even a single dose could result in a period of minimal anticoagulation[12] (see the Table for half-lives).

A limitation of both the interventional and observational data so far is the relative lack of longitudinal information. The best available evidence is for dabigatran in atrial fibrillation, where the rates of major thrombotic and bleeding events were comparable to warfarin over five years.[23] Similar data for the other oral anticoagulants, and with 'indefinite' use for venous thromboembolism, are expected.

Conclusion

Instead of considering whether NOACs are 'superior' to warfarin, it is more constructive to see them as useful arrows in the prescriber's quiver of oral anticoagulants. A patient with adequate renal and hepatic function, not taking other drugs that may interact, and who wishes to minimise blood tests, is a good candidate for apixaban, dabigatran or rivaroxaban. However, if adherence is a potential problem, it may be safer to recommend warfarin. While it is plausible that dose adjustment guided by routine laboratory coagulation monitoring will improve outcomes, the extent of the clinical benefit remains to be seen.[1] Until then, prescribers should be vigilant in monitoring adherence and renal function to optimise the benefits of NOACs. ◀

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Dental note

Treating patients on new anticoagulant drugs

Christopher Daly
Chair
Dental Therapeutics Committee
Australian Dental Association
Sydney

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Introduction

Patients on anticoagulant drugs are at risk of postoperative bleeding after invasive dental treatments, especially extractions and oral surgery. A new class of oral anticoagulants has recently been introduced for the treatment and prevention of thromboembolism. Currently dabigatran (Pradaxa), apixaban (Eliquis) and rivaroxaban (Xarelto) are available.

Warfarin has evidence-based safety parameters and dental treatment protocols.[1] It can be monitored with the INR and its effect can be quickly reversed. As the drug has been used widely for over 50 years, dental and medical practitioners have had long experience in managing dental patients taking warfarin. In contrast, there are no specific evidence-based guidelines for the dental management of patients taking the new oral anticoagulants.

Guidelines

Recent reviews[2-4] have not identified any randomised controlled trials, case-control studies or systematic reviews of the new drugs in patients having dental procedures. There is no firm clinical evidence on which to base a decision to either continue or discontinue the drugs before invasive dental treatment. To date, all published guidelines have been based purely on expert opinion and the consensus of multidisciplinary writing groups[4-7] or on clinical experience.[8]

All guidelines recommend that dentists should take a cautious approach when performing invasive dental treatments for patients taking the new anticoagulants. Unlike warfarin, where the dose can be adjusted according to the INR, the new drugs are prescribed at fixed doses. Depending on the pharmacokinetics of the drug, patients with liver disease or impaired renal function may have a higher risk of bleeding following invasive dental treatments as they may have an increased plasma concentration of the drug. Referral to an oral and maxillofacial surgeon should be strongly considered for patients requiring extractions who have liver disease or impaired renal function, or complex medical histories, or who are also taking antiplatelet drugs.[8] A referral should also be considered when the required extractions are complex, extensive or have a high risk of postoperative bleeding.

The need for referral to an oral and maxillofacial surgeon is highlighted by a case[8] in which an 84-year-old man taking dabigatran for atrial fibrillation developed significant postoperative bleeding, following drainage of an abscess and extraction of 18 teeth under general anaesthesia, despite tight suturing of the extraction sockets. The patient had to be returned to theatre for further suturing and haemorrhage control. However, the bleeding only stopped 24 hours after cessation of the dabigatran.

Currently, the most detailed guidelines for the dental management of patients taking the new anticoagulants are those from the Scottish Dental Clinical Effectiveness Programme.[6] These list specific dental procedures which are associated with postoperative bleeding and classify them as having a low risk or higher risk of bleeding complications (Box). For low-risk procedures, interruption of anticoagulation is not recommended. For high-risk procedures, the Scottish guidelines[6] provide a detailed schedule for the timing of cessation and resumption for each specific drug.

Box Risk of bleeding with specific dental procedures

Low risk of postoperative bleeding complications

Simple extractions (1–3 teeth, with restricted wound size)

Incision and drainage of intra-oral swellings

Detailed six-point full periodontal examination

Root surface instrumentation and subgingival scaling

Direct or indirect restorations with subgingival margins

Higher risk of postoperative bleeding complications

Complex extractions, adjacent extractions that will cause a large wound or >3 extractions at once

Flap-raising procedures:

- elective surgical extractions
- periodontal surgery
- preprosthetic surgery
- periradicular surgery
- crown lengthening
- dental implant surgery

Gingival recontouring

Biopsies

Source: Reference 6

Managing risk

Before undertaking any treatment, dentists must obtain a thorough medical history from the patient. This includes the name, dose and prescriber of all drugs. Ideally, patients on anticoagulants should have been informed by their prescribing doctor about the potential risks of bleeding complications with dental procedures, and the need to inform their dentist about their treatment. A medical history should also identify other drugs that can result in postoperative bleeding problems, especially antiplatelet drugs such as clopidogrel, prasugrel, ticagrelor, aspirin, non-steroidal anti-inflammatory drugs and some complementary medicines.

Anticoagulation must only be interrupted by the patient's prescribing doctor. The timing of cessation and resumption will be influenced by the patient's renal function, the bleeding risk of the procedure and the drug's half-life.[7] Trough concentrations occur 12 hours after the last intake for dabigatran and apixaban (taken twice daily) and 24 hours after the last intake of rivaroxaban (taken once daily).[5] Any decision to interrupt anticoagulant therapy must only be taken after careful consideration of the risk of a thromboembolic event, such as stroke, if the drug is stopped versus the risk of postoperative bleeding. Such decisions need to be made on a case-by-case basis and involve communication between the medical and dental practitioners. Patients also need to be told of the potential risks involved with interrupting or not interrupting their anticoagulation so that they can make an informed decision.

Procedures

Less invasive options should be used when clinically feasible to avoid dental procedures with a high risk of bleeding if anticoagulation is not interrupted. For example, perform root canal therapy instead of extraction.[2] Similarly, it would be preferable to delay invasive dental treatment if possible for a patient who is only being anticoagulated for a short time, for example following joint replacement surgery.

Extraction of 1–3 teeth without interrupting anticoagulation is recommended by most guidelines.[5-7] This is in keeping with recommendations[1] for extractions in patients on warfarin when the INR is under 4. The same holds true for subgingival scaling and root planing. However, each patient must be assessed individually and, if there is marked gingival inflammation present, the risk of bleeding complications may be higher. In such situations only treat a small area and ensure haemostasis before proceeding to another area. When treatment interruption is not advised, the Scottish guidelines[6] recommend treatment early in the day. Although this timing is more likely to coincide with peak drug concentration if the anticoagulant is taken in the morning, the risk is judged to be outweighed by allowing monitoring and management of postoperative bleeding during normal surgery hours.

Following dental extraction in an anticoagulated patient, the socket should be packed with haemostatic material and should also be sutured. Apart from providing compression, suturing assists in retaining the haemostatic packing material and the clot. Pressure and compression should then be applied to the socket until bleeding stops. Printed postoperative instructions should be given to all patients. These should include a contact number for the treating clinician as well as clear instructions to attend a hospital emergency department or ring 000 if there is uncontrollable bleeding and the practitioner cannot be contacted.

Many patients are elderly and a carer or other responsible adult should accompany them to their appointment and stay with them for at least 24 hours after dental extraction or other oral surgery. This is most important if they live alone. These precautions are necessary due to the potential serious outcomes with uncontrollable bleeding.

Antidote

To date, one major disadvantage of the new drugs compared to warfarin has been the lack of a reversal agent to help deal with uncontrollable bleeding. This has recently changed with the approval of idarucizumab,[9] a humanised monoclonal antibody against dabigatran. Parenteral idarucizumab can be given when rapid reversal of dabigatran is required for emergency surgery or urgent procedures, or for life-threatening or uncontrolled bleeding. Antidotes for the other new drugs are not yet available.

Conclusion

If a patient taking a new anticoagulant drug requires a dental procedure with a high risk of postoperative bleeding, a decision must be made whether or not to stop the drug. This decision requires discussion with the patient's medical practitioner. For many procedures with a low risk of postoperative bleeding, anticoagulation can be continued.

Conflict of interest: none declared

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ARTICLE

Paediatric pharmacokinetics and drug doses

Kate O'Hara
Pharmacist
PhD candidate
Discipline of Clinical Pharmacology and Toxicology
School of Medicine and Public Health
University of Newcastle
New South Wales

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SUMMARY

The pharmacokinetics of many drugs are different in children compared to adults. The pharmacokinetic processes of absorption, distribution, metabolism and excretion undergo changes due to growth and development.

Finding the correct doses for children is complicated by a lack of pharmacokinetic studies. Children's doses cannot always be extrapolated directly from adult studies.

Many paediatric doses are based on the child's age or weight. These may need adjustment depending on the child and the clinical response.

It is important to check dose calculations. The calculated childhood dose should not usually exceed the adult dose.

Introduction

While the adage that children are not small adults has existed for some time, most paediatric doses are still extrapolated from adult studies. Children experience large amounts of growth and development during early childhood which can dramatically affect the pharmacokinetics of different drugs. The lack of paediatric clinical trials and dosing information has been highlighted by the US Food and Drug Administration (FDA) and the European Medicines Agency as areas of clinical need, and there is now a requirement for more paediatric data in the evaluation of new drugs.[1]

In the absence of data, the use of many drugs in children, especially neonates, is often off label. The off-label use of drugs is associated with an increased risk of adverse effects, particularly in patients under the age of two years.[2] It is particularly difficult to predict pharmacological effects in neonates as development occurs quickly, resulting in rapid changes in drug metabolism over short periods of time which create difficulty in predicting doses.[3,4]

Understanding the differences in physiology at different stages of development (Table 1), compared to adults, assists with designing dose regimens. The different drug effects seen in children can be toxic, as seen with valproate hepatotoxicity and tetracycline-stained tooth enamel, or enhanced, as seen with some treatments for leukaemia.[5] Drugs with a wide safety margin are good options for treating children as pharmacokinetic changes are unlikely to result in toxicity or ineffectiveness. For drugs with narrow safety margins, such as gentamicin or phenytoin, even small changes can cause serious toxicity. Table 2 shows examples of the differences between dosing children and adults.

Absorption

The composition of intestinal fluids and the permeability of the gut vary during childhood. Absorption of orally administered drugs is affected by changes in gastric pH which decreases during infancy to reach adult values by two years of age.[6] Infants are at higher risk of toxicity via skin absorption due to a larger surface area to volume ratio and they also absorb more of a drug across skin due to their thinner stratum corneum.[7] This explains why infants have an increased risk of methaemoglobinaemia with topical anaesthetics.[8]

Distribution

The volume of distribution changes throughout childhood as stores of fat and water change. Infants have a higher percentage of extracellular water, and stores of body fat increase throughout childhood. Changes in volume of distribution can alter the drug's half-life, requiring adjustment of the dosing interval, as seen with digoxin.

Table 1 **Childhood age classes**

Class	Age
Neonate	0–28 days
Infant	>28 days – 12 months
Toddler	>12–23 months
Preschool child	2–5 years
School age child	6–11 years
Adolescent	12–18 years

Table 2 **The effect of paediatric physiology on pharmacokinetics of common drugs**

Drug	Pharmacokinetic differences	Effect
Gentamicin	Volume of distribution decreases throughout childhood along with percentage of total body water	Higher mg/kg doses used in younger children to ensure therapeutic peaks
Codeine	Conversion to morphine difficult to predict along with reduced clearance	Accumulation more likely. Not recommended for children due to safety concerns
Theophylline	Increased clearance	Higher mg/kg doses required in infants and children
Phenytoin	Decreased oral absorption due to high stomach pH and decreased protein binding in infants	Decreased bioavailability, however lower serum concentrations required due to lower protein binding
Benzyl alcohol (common excipient)	Decreased clearance	Accumulation in infants leading to fatal 'gasping syndrome'
Levetiracetam	Increased clearance	Higher mg/kg dose required in patients up to 12 years of age
Methylphenidate	Decreased clearance	Lower dose required in children (6–12 years) compared to adolescents

Dosing information for obese children is limited and has been identified as an area for research. Obese children can be dosed using ideal body weight and the dose adjusted based on clinical effect. They are at higher risk of toxicity from drugs such as paracetamol that do not distribute into fat, if actual weight is used to calculate the dose.

Infants have lower concentrations of circulating plasma proteins reducing protein binding.[7] This results in higher distribution and lower peak concentrations of protein-bound drugs such as cefazolin.[8]

Metabolism

The metabolism of drugs is the most complex difference between adults and children. Cytochrome P450 (CYP) enzymes are active in the fetus. Enzyme activity begins to increase during the later stages of pregnancy with different rates of individual enzyme development seen in infants who are born preterm.[9] The pattern of active enzymes changes over the first few months of life to reach or exceed adult levels at around two years of age.[7] While most enzymes increase in activity over the first few months of life, some such as CYP3A7 are replaced by other enzymes, in this case CYP3A4. The development of metabolic processes, such as glucuronidation, is less clear, but is thought to take at least three years to achieve full activity.[9]

Liver blood flow may be relatively high in infants. This could affect first-pass metabolism particularly for drugs with a high extraction ratio, like propranolol.

Elimination

Excretion is an important step in the final removal of the drug and any metabolites from the body. It relies on effective renal and hepatic function that develop over time. Preterm neonates develop renal excretion pathways more slowly than term neonates.[10] Glomerular filtration rates reach adult levels by about two years of age.[11]

Dosing and development

The change from treating children and neonates as little adults has occurred gradually. Previously size and gestational age were viewed as the main determinants of drug clearance, but this has been replaced with the view that the capacity and functions of individual organs and the development of biochemical pathways are of greater importance.[9] The development of drug metabolism and clearance pathways begins in the fetus and continues throughout childhood.[12] A study by the FDA examined different methods of predicting paediatric clearance of drugs based on adult values, and concluded that no single method of prediction is suitable for all drugs or age groups.[4]

Dosage regimens based entirely on age are often inaccurate and may lead to adverse effects, toxicity or lack of clinical effect. There is a lack of pharmacokinetic studies in children of different ages.

Dosing information is difficult to determine in children as traditional pharmacokinetic studies are hard to conduct in children and are subject to a greater range of ethical considerations. These studies require large amounts of blood to be taken over periods of time and this is not considered ethical in children. The development of population pharmacokinetic modelling has allowed paediatric-specific dosing information to be developed.[13] These new techniques will assist in developing safer dosing information for children over time by reducing the burden of pharmacokinetic studies. Although improving, no mathematical method of dose estimation can replace clinical studies using actual outcomes, surrogate measures or therapeutic drug monitoring.[14]

Weight-based and surface-area-based dosing regimens are simple and are used in most clinical situations. However, with the lack of specific paediatric data, these dosing equations are often based on adult data and then scaled based on size and age as an approximation for drug activity in children. Paediatric growth and development is not a linear process. Scaling from adult doses based on weight alone is not adequate for determining doses across the range of developmental processes that occur throughout childhood.[7] While this method may have some value in older children and adolescents, who have similar values to adults for body composition and organ function, it lacks utility in toddlers and neonates.

Therapeutic drug monitoring in conjunction with clinical review can be used to assess effectiveness and safety, but only when information about the safe and effective concentrations in children is available. Even for vancomycin, for which therapeutic drug monitoring is commonly performed, this information is not available.[15] More information is available regarding the safe and effective concentrations of antiepileptic drugs in children, although therapeutic drug monitoring cannot predict all adverse effects, such as hepatotoxicity with sodium valproate.

Practical advice

When prescribing for children it is appropriate to use a paediatric reference source. Use a reputable dosing reference, such as the AMH Children's Dose Companion.[16] As many doses are given in mg/kg, knowing the child's weight is important. In some cases the dose may have to be based on the ideal weight. Children on long-term treatment will need dose adjustments as they grow.

An incorrect dose, particularly in infants, could have catastrophic adverse effects. It is good practice for two people to double check dose calculations, such as the prescriber and dispensing pharmacist. Usually the calculated dose should not exceed the adult dose.

The recommended dose may not be the optimum dose for some children. It may then be necessary to adjust the dose according to the clinical response.

Ensure the calculated dose is able to be administered safely to the child. Doses can be rounded to ensure they are able to be measured by parents and carers accurately.

Conclusion

There is often a lack of pharmacokinetic studies in children of different ages. This can make it difficult to know what the optimum dose is for a child. Many doses are based on the child's age or weight. This does not always allow for the different rates of childhood development. It may be necessary to adjust doses according to the clinical response. ◁

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ARTICLE

The practice pharmacist: a natural fit in the general practice team

SUMMARY

There is evidence that pharmacist integration into the general practice team may improve clinical and non-clinical outcomes.

The roles of the practice pharmacist can be considered under three categories – patient-directed roles, clinician-directed roles and system- or practice-directed roles.

The integration of pharmacists into the general practice team would reduce fragmentation of patient care and medication misadventure.

If practice pharmacist services are to be flexible to suit the heterogeneity of general practices, a flexible funding model is needed.

Christopher Freeman
Clinical lecturer[1]
Consultant practice pharmacist[2]

Deborah Rigby
Adjunct senior lecturer[1]
Advanced practice pharmacist[3]

John Aloizos AM
General practitioner[3]
Senior clinical reference lead[4]

Ian Williams
General practitioner[2]
Chair[5]

[1] School of Pharmacy University of Queensland
[2] Camp Hill Healthcare
[3] Garden City Medical Centre
[4] Australian Digital Health Agency
[5] Brisbane South PHN
Brisbane

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Introduction

The healthcare needs of the community are becoming more complex. An increasing number of patients have multiple morbidities and require complex and intensive medical care.[1] Complicated medicine regimens are being managed by multiple prescribers.[2] Despite focused interventions designed to curb harms associated with medicine use, hospital admissions related to medicines were estimated to cost $1.2 billion in 2011–12.[3] An Australian report found that up to 12% of people attending general practice had experienced an adverse drug event in the previous six months.[3]

In Australian primary care, there has been a shift in philosophy and practice from siloed, fragmented care towards patient-centred, coordinated, multidisciplinary care. Use of the practice's clinical information system for care planning and care coordination (including medication management) is increasing. It is now common to see nurses and allied health professionals integrated into the general practice team with models such as the patient-centred medical home described as a future best practice.[4] However, most community pharmacists practise independently of general practice teams.

Australia has followed the international lead in exploring the role of the practice pharmacist.[5] This is defined as 'a pharmacist who delivers professional services from or within a general practice medical centre with a coordinated, collaborative and integrated approach with an overall goal to improve the quality use of medicines of the practice population'.[6]

The concept of the practice pharmacist has been supported by the Pharmaceutical Society of Australia, the Consumers Health Forum of Australia and United General Practice Australia.[7-9]

The evidence

The majority of the current evidence examining an integrated model of pharmacist and GP care is positive. A recent systematic review and meta-analysis of pharmacist-delivered services in general practice included 38 studies. Of these, 25 reported positive effects on at least one primary outcome measure and 13 demonstrated no effect.[10] Interventions usually involved medication review, with or without other activities delivered with the GP such as education, medication monitoring and adjusting therapy. Four clinical markers were used to assess the effect of interventions – blood pressure, glycosylated haemoglobin, cholesterol, and the Framingham Risk Score. Results of the meta-analysis favoured the pharmacist intervention with significant improvements observed in all clinical markers compared to the control groups. Positive effects were more likely to be seen with pharmacist-delivered multifaceted interventions in conjunction with follow-up of patients compared to interventions that delivered a service in isolation. There was limited or no effect on outcomes related to quality of life, patient satisfaction, symptoms, and use of health service.

Individual studies have shown improvements in other outcomes including:

- identification and reduction of medicine-related problems
- patient adherence to medicines
- process measures such as timeliness
- appropriateness of prescribing
- reduction in total number of medications.[11-16]

The transition of patients with chronic and complex diseases from hospital to the community is a critical time with an increased risk of medication misadventure and re-hospitalisation.[17] A UK study found that sending discharge letters to practice pharmacists as well as GPs improved the coordination of care and implementation of consultant recommendations for treatment.[18]

The large-scale PINCER trial found that a practice pharmacist-led intervention to reduce clinically important medicine-related problems was cost-effective.[19] Australian studies have also reported cost savings ranging from $44–$100 per patient.[20,21] A 2015 report commissioned by the Australian Medical Association and published by Deloitte Access Economics indicated that for every $1 invested, $1.56 in benefits could be generated. This equates to $544.87 million in savings over four years.[22]

One of the key elements described in the literature is that, in addition to becoming integrated into the general practice team, the pharmacist's access extended to the patient's electronic health record.[11-16,18-21] This allows the practice pharmacist to view the patient's past medical history, pathology, specialist correspondence and previous medicines, which are all crucial when providing pharmaceutical care. It also facilitates better care coordination and collaboration between the practice pharmacist, GP and other members of the integrated team.

The role of the practice pharmacist

Local studies have determined the views of pharmacists, GPs and consumers on potential roles for a practice pharmacist. Studies which detail the role of the practice pharmacist in the intervention can also be considered.[10,11,14,19,23,24]

These roles can be considered under three broad categories – patient-directed roles, clinician-directed roles, and system- or practice-directed roles (Box).

A recent survey of Australian pharmacists[6] found that 26 were working in or from a general practice medical centre. The most common services they undertook included comprehensive medication review, responding to clinical enquiries from GPs and responding to enquiries from other health professionals.

Challenges to describing the role of the practice pharmacist also exist. Perceptions of the pharmacist as solely being a dispenser of medicines or a retailer creates uncertainty around their utility within an integrated medical team in the minds of the medical profession, patients and funders. Some of the roles listed in the Box are currently conducted, in varying degrees, by other members of the general practice team. Adoption of these by a practice pharmacist could be viewed by some as a threat. Allowing the pharmacist to assume the lead in these roles would enable established team members to focus on their core roles while making best use of the pharmacist's unique skill set.

No two general practices are alike. The role of the pharmacist should therefore be flexible to meet the needs of the community based on the individual skills or interests of GPs and pharmacists. For example, uncontrolled asthma may be particularly common in the local population and thus the role of the pharmacist should be targeted toward this. There must also be core services provided by the pharmacist which allow a degree of consistency and enable large-scale and longitudinal review of the model and its benefits.

Box Roles that may be conducted by a practice pharmacist

Patient-level activities

Comprehensive medication review
Focused medication review #
Medication reconciliation
Transition care
Adverse drug reaction review
Therapeutic drug monitoring
Drug information
Dose adjustments/prescribing *
Medication cost

Clinician-level activities

Drug information
Education
Student/registrar training

Practice/system-level activities

Clinical prescribing review and feedback
Drug sample management
Medication recall/shortage management
Public health initiatives
Pharmacovigilance

\# a focused review on particular disease or medicine, for example a review of antihypertensive therapy
* models of pharmacist integration in the UK, Canada, New Zealand and the USA incorporate models of pharmacist prescribing in collaboration with the patient's GP

Funding practice pharmacists

A number of potential barriers to integrating pharmacists into general practice have been highlighted – namely a lack of remuneration and 'turf wars'.[23,24] The latter appears to be a perceived and not a realised barrier given the support for this

model by both medical and pharmacy organisations. The absence of dedicated and sustainable funding to facilitate pharmacist integration continues to be the biggest barrier to implementation.

At a time of healthcare funding review and reform, careful consideration is required by funding bodies, policy makers and the pharmacy profession when examining models of remuneration. Various funding models have been suggested[7,25,26] which need to be pragmatically considered in tandem with current health policy reforms. If the services by practice pharmacists are to be flexible, a flexible funding model is needed. A rigid model, such as fee-for-service may not allow services to be customised to the specific needs of the medical centre and the community. A blended funding model, in which payment for services undertaken by the practice pharmacist is calculated and remunerated in a variety of ways from government and private payers, could be explored.[27] These hybrid models are used to address shortcomings associated with single-based funding models.[28] Many other allied health professional services delivered through general practice are funded via private sources such as private health insurers and patient contributions. Importantly, whichever funding model is implemented, appropriate governance and methods of reviewing the use of funds should be established and enforced.

What does this mean for community pharmacists?

A practice pharmacist has the potential to reduce fragmentation of care, improve medication management and improve communication between GPs and pharmacists working within community pharmacies. Medication reconciliation is a critical process to reduce medication errors on transfer of patients from hospital back to the home or residential aged care. Creating an accurate medication list for the patient is beneficial to the patient's usual GP as well as community pharmacists, especially when packing dose administration aids.[26] A practice pharmacist can also be a link to existing community pharmacy services. Patients will benefit from improved liaison between community pharmacists and GPs.

What needs to be done beyond remuneration?

General practice-based pharmacists may need to apply different skills compared to many pharmacists working in other settings. The Advanced Pharmacy Practice Framework for Australia supports the recognition of pharmacists with skills and experience for the practice pharmacist role.[29]

A role description needs to be developed to help medical centres and fund-payers understand the diverse range of activities of a practice pharmacist. Greater awareness of the clinical governance role and practice improvement initiatives is required.

The introduction of the practice pharmacist within a complex and challenging health system may have some associated risks, whether these are fiscal, clinical, or otherwise. Evaluation and clinical governance of services to patients and the practice as a whole should be established from the outset and considered from a variety of perspectives.

Conclusion

The primary purpose of a practice pharmacist would be to support GPs to minimise the risks associated with medicines and optimise patient outcomes through the quality use of medicines. Integrating pharmacists into general practice would reduce fragmentation of care and medication misadventure using the distinctive knowledge and skills of pharmacists. Collaborative medication management between the GP and the pharmacist could reduce costs to the health system from adverse drug events and sub-optimal adherence to medication regimens. Funding models need to be further investigated to ensure cost-effectiveness of flexible models of care. <

Christopher Freeman is a Director at the Pharmaceutical Society of Australia and the Australian Association of Consultant Pharmacy.

Deborah Rigby is a member of the Board of Directors of NPS MedicineWise.

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ARTICLE

Midwifery prescribing in Australia

SUMMARY

Suitably qualified Australian midwives may prescribe drugs. By June 2016, 250 midwives were endorsed to prescribe.

The range of drugs that midwives may prescribe is determined by state and territory legislation. There are therefore significant variations across the country in what can be prescribed.

Midwives must undertake additional training to become competent to prescribe. Clear guidelines for consultation and referral also underpin safe prescribing.

Kirsten Small
Lecturer[1]

Mary Sidebotham
Associate professor of Midwifery[1]

Jennifer Fenwick
Professor of Midwifery and Clinical chair[2]

Jennifer Gamble
Professor of Midwifery[1]

[1] School of Nursing and Midwifery
Griffith University
Brisbane

[2] Gold Coast University Hospital
Southport
Queensland

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Introduction

Prescribing rights are being granted to a range of non-medical health professionals. Some midwives can now prescribe as a result of an expansion in their role.[1]

As part of the Australian Government's maternity service reform agenda,[2] national legislation was amended in 2010 to enable midwives to become 'Medicare eligible'.[3] Women who consult midwives with this notation on their registration can access Medicare rebates for midwifery services. These midwives can also request Medicare-funded pathology and radiology services.

After completing a program of education approved by the Nursing and Midwifery Board of Australia, eligible midwives can also prescribe drugs within their scope of midwifery practice. The aim of this part of the national maternity reform agenda was to enhance women's choice and increase access to timely and appropriate health care.

Who can become a midwifery prescriber?

Only midwives who are Medicare eligible are able to become prescribers. The Box lists the prerequisites for Medicare eligibility. The Australian Health Practitioners Regulatory Agency is responsible for processing applications for Medicare eligibility. Midwives granted this notation on their registration may obtain a Medicare provider number and provide Medicare rebatable maternity services. They must be working in private practice, have professional indemnity insurance and have collaborative arrangements in place with a specified medical practitioner or healthcare service.[4]

Education

Entry to practice education for midwives can be delivered at undergraduate level, or registered nurses can complete a postgraduate entry to practice program. All entry to practice programs include physiology, pharmacology and communication so that on graduation midwives are able to appropriately advise women on the correct use of medicines, and to safely administer drugs that have been prescribed by a doctor. National competency standards state that midwives have 'the ability to initiate, supply and administer relevant pharmacological substances in a safe and effective manner within relevant state or territory legislation'.[5] Unlike some other professions such as medical practitioners and dentists, midwives do not gain authority to prescribe on graduation from an entry to practice program.

To obtain the authority to prescribe, midwives must successfully complete an additional accredited program of education.[6] These programs are postgraduate courses of at least one semester's duration and meet the standards and criteria for accreditation approved by the Nursing and Midwifery Board of Australia.

Box Prerequisites for Medicare eligibility

Midwives must meet the following criteria:

1. Current general registration as a midwife in Australia with no restrictions on practice
2. Midwifery experience that constitutes the equivalent of three years full-time post initial registration as a midwife
3. Current competence to provide pregnancy, labour, birth and postnatal care to women and their infants
4. Successful completion of an approved professional practice review program for midwives working across the continuum of midwifery care
5. 20 additional hours per year of continuing professional development relating to the continuum of midwifery care
6. Successful completion of:
   a) an accredited and approved program of study determined by the Nursing and Midwifery Board of Australia to develop midwives' knowledge and skills in prescribing, or
   b) a program that is substantially equivalent to such an approved program of study, as determined by the Board.

Source: Reference 4

The curriculum requirements include the diagnostic process, pharmacology, legal and regulatory frameworks, and how to generate inpatient and outpatient prescriptions. The courses address the importance of working collaboratively with other healthcare providers involved in the care of the woman and baby. A variety of assessment methods are used to ensure that midwives demonstrate mastery of the knowledge and skills required for safe prescribing.[6]

Successful completion of an accredited course enables the midwife to apply to the Australian Health Practitioner Regulatory Agency for endorsement of their registration to include the authority to prescribe. Once endorsed, the midwife may apply to the Pharmaceutical Benefits Scheme (PBS) for a prescriber number and to obtain PBS stationery for prescriptions.

There was a significant delay between the introduction of legislative changes and the availability of an accredited educational course.[7] One university commenced enrolling students in the first accredited course in July 2012. Four universities now offer accredited courses and it is anticipated that other education providers will offer courses in response to an increasing demand.

Competency and responsibility

NPS MedicineWise outlines the responsibilities of all Australian prescribers to select drugs that are clinically effective, safe, cost-effective and are acceptable to the patients.[8] The Australian College of Midwives' National Midwifery Guidelines for Consultation and Referral[9] outline the conditions for which consultation with, or referral to, a medical practitioner is recommended. These frameworks serve to create a safe environment for midwifery prescribing.

Protocols to guide midwifery prescribing in Australia have not been developed, however prescribing occurs within a defined scope of practice and with clear guidelines for professional accountability and responsibility.[5] This scope of practice includes prescribing for the woman and her infant, up to the end of the sixth postnatal week. No formal process is in place for supervision or monitoring of midwifery prescribing. While there is no regulatory requirement for midwives to notify the woman's medical practitioner that a prescription has been generated, good communication with members of the woman's care team is included in the guidelines for professional practice, so this would be expected to occur.

Midwifery prescribing is well established in New Zealand and the United Kingdom within a similar professional framework. Research undertaken to date has found no evidence to suggest poor outcomes arising from the introduction of non-medical prescribing in those countries.[10]

What can midwives prescribe?

The Nursing and Midwifery Board of Australia has developed a formulary to help midwives select appropriate drugs.[11] This lists drugs, the indication for their use and the duration of their use. It includes drugs such as antibiotics, opioids and uterotonics.

The formulary arose from a collaborative process involving midwives and obstetricians. It offers no rationale for the choice to include or exclude certain drugs from the list and it gives no evidence to support the indications. The formulary has not been reviewed since its inception, and there appears to be no program for review.

Each Australian state and territory has its own drug regulations, and the governance of midwifery prescribing varies from one jurisdiction to another. Western Australian legislation requires midwives to only prescribe drugs according to the formulary.[12] Victoria and Tasmania have generated a list of approved drugs, and place no restrictions on the indications for prescribing each drug or the duration of treatment.[13,14] Queensland does not permit the prescribing of Schedule 8 drugs, but Schedule 4 drugs that are used in midwifery may legally be prescribed.[15] New South Wales, South Australia and the Northern Territory have placed no limitations on midwifery prescribing, and provide full access to all the drugs used within the scope of midwifery care.

Some of the drugs available through the PBS, such as antibiotics, attract subsidies when prescribed by midwives. Midwives in the Australian Capital Territory are restricted to only prescribe the drugs on the PBS list for midwives.[16] The absence of a PBS listing does not prevent midwives in all other states from being able to legally prescribe these drugs as a private prescription.

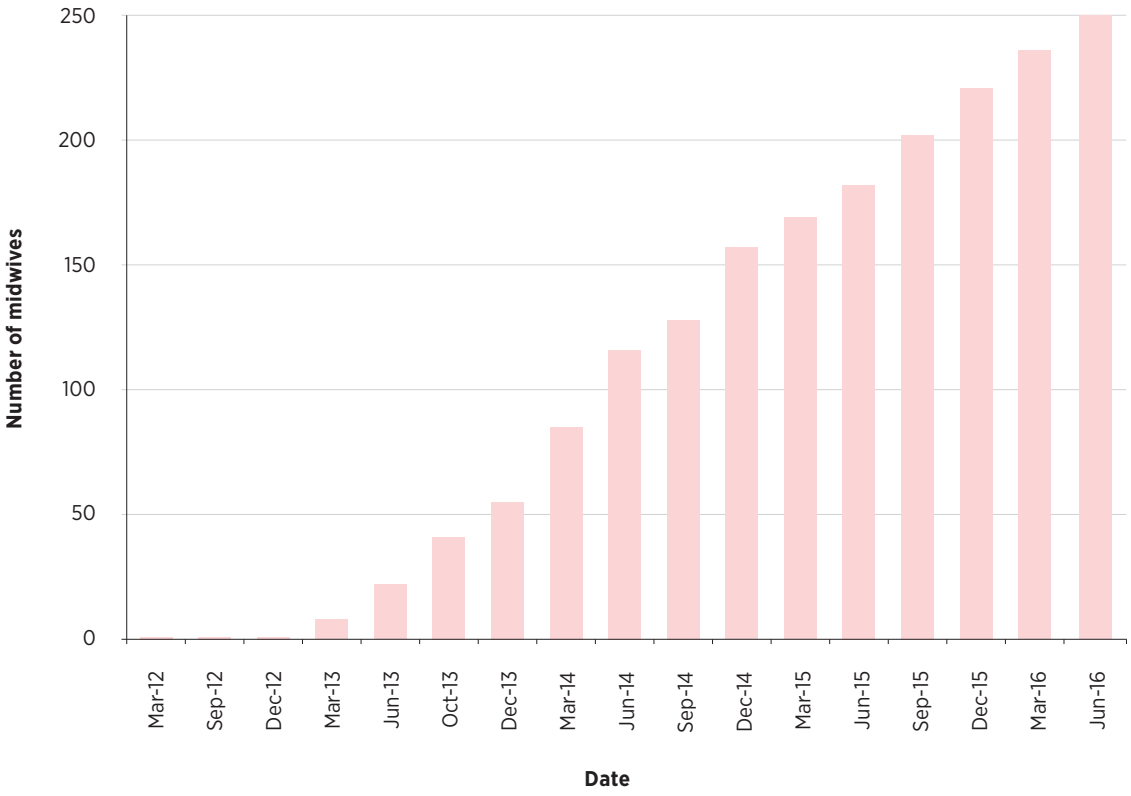
How many midwives are prescribing?

The first midwife obtained the authority to prescribe in Australia in June 2012,[17] by receiving retrospective recognition of a non-accredited course. It was not until completion of the first accredited course late in 2012 that additional midwives were endorsed. The numbers of prescribers have increased significantly since that time with 250 midwives having been endorsed by June 2016 (see Fig.).

The future of midwifery prescribing

As increasing numbers of midwives complete accredited programs of education and commence prescribing, it is important to confirm that their prescribing is safe, appropriate and addresses the needs of women and their babies. No published research has yet addressed midwifery

Fig. **Number of midwives with endorsement to prescribe**



Source: Reference 17

prescribing, as distinct from other forms of non-medical prescribing. We do not currently know what proportion of endorsed midwives actually prescribe, which drugs are used and the reasons they are prescribed.

It is important that a body of research evidence is developed concerning midwifery prescribing and its outcomes, in order to inform the ongoing development of midwifery education. Non-medical prescribers require ongoing support from doctors, pharmacists and other non-medical prescribers in order to integrate prescribing into their practices.[18] Widespread acceptance of midwifery prescribing in Australia will enable midwives to access the support they need to become effective prescribers. As momentum grows there will be a need to identify ongoing professional development requirements and to establish a framework that ensures such education is available and accessible.

It is likely that Australia will see an expansion of midwifery and non-medical prescribing in line with international experience.[19] There is a growing call to move from a postgraduate prescribing qualification to include prescribing in the undergraduate curriculum. Good evidence will be required to justify such a transition.

Conclusion

Midwifery prescribing in Australia continues to grow but there is significant variation in the range of drugs that can be prescribed. Further research is required to ensure that midwifery prescribing is achieving the aims of the maternity reform process in offering enhanced access to appropriate health care, with more choice of care provider. ≺

Conflict of interest: none declared

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FEATURE

Medicines Australia Code of Conduct: breaches

The Medicines Australia Code of Conduct guides the promotion of prescription products by pharmaceutical companies.[1] Each year Medicines Australia publishes a report, from its Code of Conduct Committee, which details all the complaints that have been received about advertising and other promotional activities. The Table shows the complaints where at least one breach was identified, and more details can be found in the full report.[2] The complaints were dealt with under the current (18th) edition of the Code of Conduct.[1]

The number of companies found to have breached the Code of Conduct is small compared to all the promotional activity undertaken by the pharmaceutical industry. Most of the complaints came from competitors or Medicines Australia's own Monitoring Committee. Only the complaint about the advertising of agomelatine came from a health professional. This case hinged on the references used to support the claims in the advertisement.

There was an appeal against the Code of Conduct Committee's decision in the abiraterone case. This included discussion of the definition of 'energy' in three different dictionaries.

The Monitoring Committee considered that a two-course lunch for two specialists was inappropriate. The price of the meal was $153.86, but it cost the company $10,000 in fines.

Key words
Medicines Australia, codes of conduct

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Table **Breaches of the Code of Conduct July 2015 – June 2016**

Company	Brand (generic) name	Material or activity	Sanction
Bristol-Myers Squibb	Sprycel (dasatinib)	Misleading promotional material	$50 000 fine, material withdrawn
Bristol-Myers Squibb	Opdivo (nivolumab)	Unregistered product, company commissioned article	$10 000 fine
Janssen-Cilag	Zytiga (abiraterone)	Misleading promotional claims	$100 000 fine, material withdrawn, corrective letter to specialists
Merck Serono	Not applicable	Excessive hospitality	$10 000 fine
Roche Products	Gazyva (obinutuzumab)	Inappropriate interaction with consumer media	$100 000 fine
Servier Laboratories	Valdoxan (agomelatine)	Misleading advertising	$100 000 fine, material withdrawn

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FEATURE

Top 10 drugs

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Tables 1–3 show the top 10 subsidised drugs for the year July 2015 – June 2016. The figures are based on PBS and RPBS prescriptions from the date of supply, and do not include private prescriptions or prescriptions under the co-payment.

This year's tables are notable for the arrival of the drugs which aim to eradicate hepatitis C. Table 3 shows that since the drugs were subsidised in March 2016 the expenditure on sofosbuvir alone, or in combination with ledipasvir, is approaching $1 billion.

Table 1 **Top 10 drugs by DDD/1000 pop/day**

	Drug	DDD/1000 pop/day *
1.	atorvastatin	52.81
2.	perindopril	33.82
3.	rosuvastatin	33.56
4.	amlodipine	30.66
5.	paracetamol	26.85
6.	irbesartan	25.60
7.	esomeprazole	23.18
8.	candesartan	22.71
9.	ramipril	20.40
10.	telmisartan	18.87

Table 2 **Top 10 drugs by prescription counts**

	Drug	Prescriptions
1.	atorvastatin	7 630 309
2.	esomeprazole	6 889 031
3.	rosuvastatin	6 540 962
4.	paracetamol	5 056 087
5.	pantoprazole	4 747 823
6.	perindopril	4 049 113
7.	metformin	3 578 536
8.	pregabalin	3 237 101
9.	fluticasone and salmeterol	3 003 985
10.	salbutamol	2 975 537

Table 3 **Top 10 drugs by cost to government**

	Drug	Cost to government (A$)	DDD/1000 pop/day *	Prescriptions
1.	ledipasvir and sofosbuvir	570 730 056	†	25 205
2.	sofosbuvir	372 094 623	0.14	18 738
3.	adalimumab	335 857 859	0.62	194 405
4.	ranibizumab	241 256 012	†	163 595
5.	aflibercept	231 194 036	†	155 404
6.	esomeprazole	170 554 177	23.18	6 889 031
7.	etanercept	166 538 773	0.32	97 291
8.	trastuzumab	157 134 211	†	50 217
9.	fluticasone and salmeterol	148 878 399	†	3 003 985
10.	insulin glargine	146 202 125	7.71	367 253

* DDD/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people in every thousand Australians are taking the standard dose of a drug every day. DDD includes use in combination products. The calculation is based on ABS 3101.0 – Australian Demographic Statistics for December 2015 (as at March 2016).

† The World Health Organization has not allocated a DDD for this drug.

DDD defined daily dose

PBS Pharmaceutical Benefits Scheme

RPBS Repatriation Pharmaceutical Benefits Scheme

Source: Department of Health, October 2016. © Commonwealth of Australia

New drugs

Armodafinil

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First published 19 September 2016

Approved indication: sleep disorders

Nuvigil (Teva Pharmaceuticals)
50 mg, 150 mg and 250 mg tablets
Australian Medicines Handbook Appendix A

Armodafinil is a psychostimulant that aims to improve wakefulness. It is indicated for narcolepsy, obstructive sleep apnoea or hypopnea syndrome (added to continuous positive airways pressure) and for chronic shift work sleep disorder when non-drug approaches have not worked.

Armodafinil is related to modafinil, which is already registered in Australia for the same indications.[1] Modafinil is a 1:1 mixture of R and S isomers whereas armodafinil consists only of the R isomer. Like modafinil, armodafinil's exact mechanism of action is unknown.

The absorption, metabolism and elimination of armodafinil are very similar to modafinil. However, after oral administration peak serum concentrations and exposure (area under the curve) are higher for armodafinil than for modafinil at the same dose. Armodafinil is not therefore bioequivalent to modafinil and cannot be directly substituted.

Armodafinil should be taken once a day in the morning for narcolepsy and obstructive sleep apnoea, and one hour before starting work for those with shift work sleep disorder. As with modafinil, the armodafinil dose should be reduced in people with severe hepatic impairment. Lower doses should also be considered in older people due to reduced clearance of the drug.

Armodafinil (150 mg or 250 mg) has been assessed in several 12-week placebo-controlled trials (see Table).[2-5] In daytime maintenance of wakefulness tests, patients with narcolepsy or obstructive sleep apnoea stayed awake up to 4.5 minutes longer with armodafinil than with placebo.[2-4] In night-time multiple sleep latency tests, patients with excessive sleepiness due to shift work disorder stayed awake on average 2.7 minutes longer with armodafinil than with placebo.[5]

The most common adverse events with armodafinil were headache, nausea, dizziness and insomnia. In the trials, 7% of people discontinued the drug because of an adverse event. Headache was the most common reason, but others included psychiatric symptoms such as anxiety, agitation, irritability and depression. There have been cases of suicide in patients taking armodafinil.

In a 12-month open-label trial in 328 patients with narcolepsy, obstructive sleep apnoea or shift work disorder, rare but serious adverse events that were possibly related to armodafinil included chest pain, pulmonary embolism, myocardial infarction and exacerbation of depression.[6]

Rashes have been reported with armodafinil, including a fatal case of Stevens-Johnson syndrome. The drug should be stopped immediately if a rash develops.

The potential drug interactions with armodafinil are expected to be similar to modafinil. Armodafinil weakly induces cytochrome P450 (CYP) 3A4 so may

Table **Efficacy of armodafinil in sleep disorders**

Disorder	Trial (patients treated)	Mean change in minutes of wakefulness from baseline*		
		Armodafinil 150 mg	Armodafinil 250 mg	Placebo
Narcolepsy	Harsh et al. (196 patients)[2]	+1.3 (baseline=12.1)	+2.6 (baseline=9.5)	-1.9 (baseline=12.5)
Obstructive sleep apnoea or hypopnea syndrome	Hirschkowitz et al. (259 patients)[3]	+2.3 (baseline=23.7)	–	-1.3 (baseline=23.3)
	Roth et al. (392 patients)[4]	+1.7 (baseline=21.5)	+2.2 (baseline=23.3)	-1.7 (baseline=23.2)

* The ability to stay awake during the day was measured in maintenance of wakefulness tests using polysomnography at baseline and after 12 weeks of treatment. Results are a mean of four tests conducted at 2-hour intervals.

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, 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. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

reduce concentrations of drugs that are metabolised by this enzyme such as hormonal contraceptives, cyclosporin, carbamazepine and midazolam. Armodafinil also inhibits CYP2C19 and may increase concentrations of CYP2C19 substrates such as omeprazole, phenytoin, diazepam, propranolol and clomipramine. More frequent monitoring of INR may be required with co-administered warfarin.

Because of its interaction with hormone contraceptives, women taking armodafinil should use alternative contraception. Armodafinil is contraindicated in pregnancy and not recommended during lactation based on previous animal studies with modafinil showing fetal effects and excretion in breast milk.

Armodafinil significantly improved the ability of patients to stay awake for longer than a placebo. However, this was only by a matter of minutes in sleep latency tests. Although rare, fatalities relating to armodafinil, including from serious skin reactions, have occurred. Psychiatric symptoms can also be a problem. As armodafinil may produce euphoric effects, prescribers should be aware of its potential for abuse.

T manufacturer provided the AusPAR

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The Transparency Score (T) is explained in 'New drugs: transparency', Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration (www.fda.gov) and the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-austpar.htm).

Blinatumomab

Aust Prescr 2016;39:223
http://dx.doi.org/10.18773/austprescr.2016.081
First published 10 October 2016

Approved indication: acute lymphoblastic leukaemia

Blincyto (Amgen)
glass vials containing 38.5 micrograms powder for reconstitution
Australian Medicines Handbook section 14.2.1

Blinatumomab is indicated for adults with Philadelphia chromosome-negative relapsed or refractory acute lymphoblastic leukaemia. It is a dual-action antibody that binds to CD19 expressed on all B cells (including acute lymphoblastic leukaemia cells) and CD3 on T cells. When these molecules are bound at the same time, the drug acts as a bridge between the T and B cells. This interaction activates the T cells and causes them to produce cytolytic proteins and inflammatory cytokines which kill normal and malignant B cells.

Blinatumomab is thought to be catabolised. Its mean half-life is 2.1 hours. The drug is not expected to affect cytochrome P450 enzymes but drug interaction studies have not been done.

Approval of this drug is based on one main study of 189 patients.[1] This was an open-label phase III trial with no comparator. Enrolled patients had relapsed or refractory disease with a bone marrow blast count of at least 10%. At baseline, over two-thirds of patients had a blast count of 50% or more. Blinatumomab was administered by continuous infusion in four-week cycles followed by a two-week treatment-free interval. Patients received the drug for a median of 42 days. Those with more rapidly progressing disease were given dexamethasone before treatment to reduce the incidence of severe cytokine release syndrome.

The primary outcome of the trial was a complete response (5% or less blasts in bone marrow, no evidence of disease and full recovery of peripheral blood counts) or a complete response with a partial recovery of blood counts, within the first two treatment cycles. After treatment, 33% of patients had a complete response, 10% had a complete response with a partial recovery of blood counts and 48% did not respond. The median overall survival of all participants was 6.1 months (95% confidence interval 4.2–7.5 months).[1]

In a safety cohort of 475 patients, adverse events were very common. The most serious events included infusion-related reactions (67% of patients), infections (63%), fever (60%), headache (34%), febrile neutropenia (28%), peripheral oedema (26%), nausea (24%), hypokalaemia (24%), constipation (21%), anaemia (20%), cough (19%), diarrhoea (18%), tremor (18%), neutropenia (18%), abdominal pain (17%), insomnia (15%), fatigue (15%) and chills (15%). Blood monitoring is recommended during treatment because of the haematological effects. Severe neurological events also occurred with blinatumomab and included encephalopathy, convulsions, speech disorders, confusion and problems with coordination and balance.

During the trial 23 patients died because of an adverse event. Fatalities were due to sepsis, pneumonias, and infections caused by *Fusarium*, *Aspergillus*, *Candida*, *Escherichia coli* and enterococci.[1] As patients are immunocompromised, live virus vaccines are not recommended during, and for at least two weeks before, treatment.

Blinatumomab comes with a boxed warning about life-threatening cytokine release syndrome and neurological toxicities, and reactivation of JC virus infection. Treatment should be stopped immediately if any one of these is suspected.

A third of patients with Philadelphia chromosome-negative relapsed or refractory acute lymphoblastic leukaemia had a complete response to blinatumomab. However, it is difficult to know how this benefit compares to conventional chemotherapy as there was no comparator in the trial. Serious adverse effects commonly occurred and were fatal for 12% of patients.

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The Transparency Score ([T]) is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration (www.fda.gov) and the European Medicines Agency (www.ema.europa.eu).

NEW DRUGS

Ocriplasmin

Aust Prescr 2016;39:224–5
http://dx.doi.org/10.18773/austprescr.2016.083
First published 10 October 2016

Approved indication: vitreomacular traction

Jetrea (Alcon)
vials containing 0.5 mg/0.2 mL concentrate for injection
Australian Medicines Handbook Appendix A

Vitreomacular traction is an age-related eye condition caused by vitreomacular adhesion. It is observed after vitreous detachment when part of the vitreous remains firmly attached to the centre of the retina. This pulls on the retina and distorts the macula. Oedema also occurs and holes in the macula can form. Symptoms include blurred or distorted vision, particularly with central vision.

Vitreomacular traction can be treated by surgery (vitrectomy). However, because of the risk of complications, such as infection, retinal detachment, haemorrhage and cataract, it is reserved for patients whose vision is seriously affected.

Ocriplasmin is a truncated form of the human enzyme plasmin and is produced by recombinant DNA technology. After intravitreal injection, it works by breaking down matrix proteins involved in the adhesion between the vitreous and the retina. Most of the drug is cleared from the eye within 30 minutes and is rapidly catabolised once it enters the systemic circulation.

The evidence for ocriplasmin's efficacy is based on two identical phase III trials.[1] People with symptomatic vitreomacular adhesion were randomised to a single 100 microlitre intravitreal injection of ocriplasmin 0.125 mg (n=464) or placebo (n=188). The primary outcome was resolution of vitreomacular adhesion (assessed by optical coherence tomography) 28 days after the injection. In a combined analysis of the studies, resolution of adhesions was more common in people who received ocriplasmin compared with those who received placebo (26.5% vs 10.1%). Improved vision at six months (defined as a gain of three or more lines on an eye chart) was also more common with ocriplasmin (12.3% vs 6.4%). In those with a macular hole at baseline, closure of the hole was more likely in the ocriplasmin groups than in the placebo groups – 40.6% (43/106) versus 19.6% (5/47). A subgroup analysis revealed that treatment was more likely to work in patients with milder disease who did not have an epiretinal membrane (37.4% vs 8.7%). Based on this finding, the National Institute for Health and Care Excellence in the UK recommends that ocriplasmin only be used in patients without a membrane (www.nice.org.uk/guidance/ta297).

Some patients underwent vitrectomy during the studies, usually for persistent vitreomacular adhesion. This was less common in people who received ocriplasmin than those who received placebo (17.7% vs 26.6%).

Ocular adverse events were very common in the trials, affecting 68.4% of those who received ocriplasmin and 53.5% of those who received placebo. The most common events with ocriplasmin were vitreous floaters (16.8%), conjunctival haemorrhage (14.6%), injection-related pain (13.5%), photopsia (11.8%) and blurred vision (8.6%). Serious adverse events included macular hole (5.2% – 24 people), retinal detachment (0.4% – 2 people) and reduced visual acuity (0.6% – 3 people).

Eyesight may get transiently worse in the week following treatment. There is also a risk of inflammation, infection, haemorrhage and raised intraocular pressure with intravitreal injection, so monitoring is important and patients should be encouraged to report any adverse effects. Administration of ocriplasmin in both eyes at the same time or repeat administration in the same eye is not recommended.

Exclusions from the trial included people with proliferative diabetic retinopathy, neovascular age-related macular degeneration, retinal vascular occlusion, aphakia, high myopia, uncontrolled glaucoma, a macular hole over 400 micrometres in diameter, a history of retinal detachment or vitreous haemorrhage, recent eye surgery or eye injection. Ocriplasmin is not recommended in these conditions. There is limited experience in people with non-proliferative diabetic retinopathy, uveitis and eye trauma. Benefit was not found in a study of ocriplasmin in children scheduled for vitrectomy, so paediatric use is not recommended.

Although ocriplasmin is better than placebo at resolving vitreomacular adhesions, only about a quarter of patients benefited in the trials. Ocriplasmin is more likely to work in people who do not have an epiretinal membrane and it is not recommended for people with macular holes larger than 400 micrometres. Complications after the injection are not uncommon and ocriplasmin should be administered by an experienced ophthalmologist.

[T] manufacturer provided the product information

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The Transparency score (T) is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA (www.fda.gov) and European Medicines Agency (www.ema.europa.eu).

NEW DRUGS

Sacubitril/valsartan

Aust Prescr 2016;39:226–7
http://dx.doi.org/10.18773/austprescr.2016.080
First published 19 September 2016

Approved indication: chronic heart failure

Entresto (Novartis)
24.3/25.7 mg, 48.6/51.4 mg, 97.3/102.8 mg film-coated tablets
Australian Medicines Handbook section 6.3.4

This product is a fixed-dose combination of sacubitril and valsartan and comes in three strengths. It is indicated for people with heart failure who have a reduced ejection fraction. The combination is given in place of an ACE inhibitor or other angiotensin receptor antagonist, with other drugs for heart failure.

The combination is designed to simultaneously inhibit neprilysin (sacubitril) and the renin–angiotensin system (valsartan).[1] Neprilysin is an enzyme that degrades vasoactive substances such as bradykinin and natriuretic peptides. By inhibiting neprilysin, sacubitril increases the concentration of these peptides which promotes vasodilation, an increased glomerular filtration rate and anti-fibrotic and anti-hypertrophic effects.

The combination of sacubitril and valsartan (49/51 mg increased to 97/103 mg twice daily) has been compared to the ACE inhibitor enalapril (10 mg twice daily) in a large phase III trial in patients with chronic systolic heart failure (PARADIGM-HF).[2] The average left ventricular ejection fraction of participants was 29% and most had New York Heart Association class II or III symptoms. Before enrolment, patients were already taking an ACE inhibitor or angiotensin receptor antagonist and most were also on a beta blocker. During a run-in period, all patients received enalapril for two weeks. If tolerated, they were then given sacubitril/valsartan for a further 4–6 weeks. Only patients who could tolerate both products were randomly switched to sacubitril/valsartan or enalapril. They were then followed for a median of 27 months.

There were fewer cardiovascular deaths and hospitalisations due to worsening heart failure in patients receiving sacubitril/valsartan than in those receiving enalapril. This was reflected in the primary outcome which was a composite of the two outcomes (see Table).[2] All-cause mortality and scores on a validated symptom questionnaire were also lower with the combination than with enalapril. However, the rate of decline in renal function or new-onset atrial fibrillation was not significantly different between study treatments.[2] The trial was stopped prematurely because of the observed benefit of sacubitril/valsartan over enalapril.

Drug intolerance was common during the trial. During the run-in period, just over 10% of participants (1138/10 513) discontinued because of an adverse event to one of the study treatments. After randomisation, a similar proportion discontinued sacubitril/valsartan because of an adverse event.[2] The most common events relating to the combination included hypotension (17.61%), hyperkalaemia (11.61%) renal impairment (10.14%) and cough (8.78%).

Hypotension was more common with sacubitril/valsartan than with enalapril (17.61% vs 11.97%). The risk of it occurring is higher in older age (≥75 years), low baseline systolic blood pressure, renal disease, use of high-dose diuretics, diarrhoea and vomiting. Blood pressure should be monitored at baseline and during dose titration. If hypotension persists despite adjusting the dose of other treatments (e.g. diuretics), reduce the sacubitril/valsartan dose or temporarily discontinue.

Renal function should be checked before and during treatment, especially in those with renal artery stenosis. Decrease or interrupt the sacubitril/valsartan dose if renal function declines.

Because of the risk of hyperkalaemia, serum potassium should be monitored and treatment

Table **Efficacy of sacubitril/valsartan compared to enalapril in chronic heart failure**

Outcome	Sacubitril/valsartan 97/103 mg twice daily	Enalapril 10 mg twice daily
Composite primary outcome: death from cardiovascular causes or hospitalisation from worsening heart failure	21.5% (914/4187)	26.5% (1117/4212)
Death from cardiovascular causes	13.3% (558/4187)	16.5% (693/4212)
Hospitalisation from worsening heart failure	12.8% (537/4187)	15.6% (658/4212)

Source: Reference 2

should not be started if concentrations are more than 5.4 mmol/L. Hyperkalaemia is more likely to occur in patients with severe renal impairment, diabetes, hypoaldosteronism or on a high potassium diet.

Neprilysin is involved in the clearance of amyloid-beta. Increased concentrations were found in the cerebrospinal fluid of healthy adults taking sacubitril/valsartan. The clinical relevance of this is currently unknown.

Angioedema was found to be a serious adverse event with previous combination therapies that inhibit neprilysin and the renin–angiotensin system simultaneously.[3] Although rare in the PARADIGM-HF trial, angioedema was more common with sacubitril/valsartan than with enalapril (0.5% vs 0.2%).[2] If angioedema occurs, treatment should be permanently stopped. Sacubitril/valsartan is contraindicated in patients with a history of angioedema with an ACE inhibitor or other angiotensin receptor antagonist, and in those with hereditary angioedema.

Concomitant use of an ACE inhibitor is contraindicated because of the risk of angioedema. A washout period of 36 hours is recommended before sacubitril/valsartan is initiated in patients switching from an ACE inhibitor. Angiotensin receptor antagonists should not be taken with sacubitril/valsartan.

Sacubitril/valsartan has numerous other drug interactions. Co-administration of potassium-sparing diuretics may lead to increased serum potassium. Use of non-steroidal anti-inflammatory drugs may increase renal impairment, and there is a theoretical risk of lithium toxicity with concomitant use. Other drugs that may interact with the combination include aldosterone antagonists, frusemide, rifampicin, cyclosporin, ritonavir, metformin, statins and sildenafil.

Following oral administration, the combination dissociates into sacubitril and valsartan, and sacubitril is metabolised to the active metabolite (LBQ657) by esterases. Steady-state drug concentrations are reached after three days of twice daily dosing. Up to 68% of sacubitril (mainly as LBQ657) and 13% of valsartan are excreted in the urine with the rest excreted in the faeces. The elimination half-lives of sacubitril, LBQ657 and valsartan are 1.4, 11.5 and 9.9 hours.

The recommended starting dose of sacubitril/valsartan is 49 mg/51 mg twice daily. A lower starting dose (24 mg/26 mg) should be considered in patients not currently taking an ACE inhibitor or angiotensin receptor antagonist, or who have risk factors for hypotension such as those aged 75 years and over or with low systolic blood pressure. A lower dose is also recommended for patients with severe renal impairment or moderate hepatic impairment. Valsartan is more bioavailable in this formulation than in other valsartan products. This should be considered for patients switching over to this formulation.

The drug is contraindicated in patients with severe hepatic impairment, biliary cirrhosis and cholestasis. It should also not be used in pregnancy.

The combination of sacubitril and valsartan lowered the risk of death or hospitalisation due to worsening heart failure compared to enalapril in a large phase III trial. However, the enalapril dose (20 mg/day) in the trial was at the lower end of the recommended dose (20–40 mg/day) in Australia. This raises the question of whether it was a valid comparator. Another concern about the trial design was that many patients discontinued because they could not tolerate the drug during the run-in period and after randomisation so the patients that completed the trial may not be representative of the general population of patients with heart failure. Patient monitoring is very important, particularly when treatment is initiated and during dose titration and when there is a change in the patient's other medicines. Before starting this drug in patients switching from an ACE inhibitor, there should be a washout period of at least a day to reduce the risk of angioedema.

T T manufacturer provided additional useful information

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The Transparency Score (T) is explained in 'New drugs: transparency', Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration (www.fda.gov) and the European Medicines Agency (www.ema.europa.eu).

NEW DRUGS

Ulipristal acetate

Aust Prescr 2016;39:228–9
http://dx.doi.org/10.18773/austprescr.2016.082
First published 10 October 2016

Approved indication: emergency contraception

EllaOne (MS Health)
30 mg tablets
Australian Medicines Handbook section 17.1

Ulipristal acetate is another option for preventing pregnancy after unprotected sex. Levonorgestrel is effective for emergency contraception if it is taken within 72 hours. If a women presents after this time the only option is a copper intrauterine device (IUD). This can be used up to five days after unprotected intercourse. As IUD insertion is a medical procedure there has been research into an alternative option for presentations after 72 hours.

Ulipristal is a progesterone receptor modulator. By binding to the progesterone receptor it stops the surge in luteinising hormone which occurs before ovulation. Ulipristal will therefore either inhibit or delay ovulation.

The 30 mg tablet is rapidly absorbed. A second tablet is only needed if vomiting occurs within three hours. Ulipristal has a terminal half-life of 32 hours. Its metabolism involves cytochrome P450 3A4. The concomitant use of inducers of this enzyme, such as phenytoin and carbamazepine, is not recommended as these drugs will reduce the plasma concentration of ulipristal and may reduce its efficacy.

A double-blind trial compared ulipristal and levonorgestrel in women presenting within 72 hours of unprotected intercourse. Efficacy was assessed in 775 women who took ulipristal 50 mg and in 774 who took two doses of levonorgestrel 0.75 mg. Pregnancy occurred in 0.9% of the ulipristal group and 1.7% of the levonorgestrel group. The difference was not statistically significant and met the criteria for non-inferiority.[1]

This trial used a formulation which differs from what will be used in Australia. However a 30 mg dose of ulipristal has been compared with levonorgestrel in women presenting within five days. Efficacy was assessed in 941 women given ulipristal and 958 given levonorgestrel. The pregnancy rates in women who presented within 72 hours were 1.8% with ulipristal and 2.6% with levonorgestrel. There were 203 women who took emergency contraception between 72 and 120 hours after unprotected sex. The three pregnancies that occurred were in the levonorgestrel group.[2]

Both trials showed that ulipristal was non-inferior to levonorgestrel. Combining the results of the two trials seems to show an advantage for ulipristal (see Table).[2]

Another study reported on the efficacy of ulipristal 30 mg in 1241 women who took it 48–120 hours after unprotected sex. The pregnancy rate was 2.1%. There were 548 women who were treated 72–120 hours after sex. Their pregnancy rate was 1.8%.[3]

The most frequent adverse effects of ulipristal and levonorgestrel are nausea, headache and dysmenorrhoea. There may be intermenstrual bleeding and the next period may be earlier or later than expected. When ulipristal was not effective few women continued with the pregnancy. Data are only available on two women who continued to term. One had a normal live birth and the other had a baby with optic nerve hypoplasia. Ulipristal is excreted in breast milk.

While the evidence shows that ulipristal reduces the risk of pregnancy after unprotected sex, its efficacy will depend on the menstrual cycle. It will be less effective if ovulation has already occurred. If the woman has symptoms of pregnancy or her period is late, pregnancy should be excluded before prescribing ulipristal. After treatment, women are recommended to use a barrier method of contraception until their next period.

Table **Efficacy of ulipristal and levonorgestrel for emergency contraception**

Time after unprotected sex	Pregnancies per patient population	
	Ulipristal	Levonorgestrel
0–24 hours	5/584 (0.9%)	15/600 (2.5%)
0–72 hours	22/1617 (1.4%)	35/1625 (2.2%)
0–120 hours	22/1714 (1.3%)	38/1731 (2.2%)

Source: Reference 2

T T manufacturer provided additional useful information

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The Transparency Score (T) is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the European Medicines Agency (www.ema.europa.eu) and the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-austpar.htm)..

NEW DRUGS

Ulipristal acetate

Aust Prescr 2016;39:230-1
http://dx.doi.org/10.18773/austprescr.2016.091

Approved indication: fibroids

Esmya (Vifor Pharma)
5 mg tablets
Australian Medicines Handbook section 17.1.3

Ulipristal acetate is a progesterone receptor modulator that has previously been approved as a postcoital contraceptive.[1] As progesterone promotes the growth of uterine fibroids, blocking its receptor may reduce their size. The dose used for this indication can inhibit ovulation and lead to amenorrhoea which will be of benefit to women who have heavy menstrual bleeding related to their fibroids.

Treatment should begin in the first week of a menstrual period. The single daily dose is rapidly absorbed. There is extensive metabolism involving cytochrome P450 3A4. Ulipristal should therefore not be taken with inducers of this enzyme, such as carbamazepine, phenytoin and St John's wort, or with inhibitors such as erythromycin. The half-life of ulipristal is about 38 hours with most of the metabolites being excreted in the faeces. No studies have been done in women with impaired hepatic or renal function.

The approval of ulipristal for the treatment of fibroids appears to have been mainly based on four trials (see Table).[2-5] PEARL I and II were short term while PEARL III and IV studied repeated courses of treatment.

Single three-month course

PEARL I enrolled women with anaemia as a result of heavy periods related to fibroids. These women were planning to have surgical treatment. There was a placebo group of 48 women, while 96 were randomised to take ulipristal 5 mg and 98 to take ulipristal 10 mg. After 13 weeks, bleeding was significantly reduced in more than 90% of the women taking ulipristal compared with 19% of the placebo group. Amenorrhoea was reported by 73% of the women taking ulipristal 5 mg and by 82% of those taking 10 mg. Only 6% of the placebo group had amenorrhoea. MRI showed that the median total fibroid volume had decreased by 21% with ulipristal 5 mg and by 12% with 10 mg while there had been a 3% increase in the volume measured in the placebo group.[2]

PEARL II enrolled 307 women with heavy bleeding who were eligible for surgical treatment of their fibroids. In this trial daily ulipristal was compared to monthly injections of leuprorelin, an agonist of gonadotrophin-releasing hormone. After 13 weeks, bleeding had been controlled in 90% of the women who took ulipristal 5 mg and 98% of those taking 10 mg. It was also controlled in 89% of the women given leuprorelin. These differences showed ulipristal was not inferior to leuprorelin, but leuprorelin had a greater effect on fibroid size. The total volume of the three largest fibroids in each patient was reduced by a median of 36% with ulipristal 5 mg, 42% with ulipristal 10 mg and by 53% with leuprorelin.[3]

Repeated courses

In PEARL III 209 women with heavy bleeding and at least one fibroid took open-label ulipristal 10 mg for three months. This was followed by double-blind treatment with norethisterone or a placebo for 10 days. The women could then opt to repeat this regimen up to three times giving a total of up to four courses. The primary outcome of the study was amenorrhoea. This was achieved by 79% of the women after the first course of ulipristal. Among the 107 women who had four courses of treatment, 90% had amenorrhoea. The three largest fibroids, seen on ultrasound scans, shrunk by a median of 45% after one course and 72% after four courses. In the women who took norethisterone, menstruation resumed more rapidly and blood loss was less than in the placebo group.[4]

PEARL IV had a similar study population and also had amenorrhoea as a primary end point. The 451 women were randomised to take ulipristal 5 mg or 10 mg in 12-week courses. The interval between each course

Table **Efficacy of ulipristal in women with fibroids**

Trial	Total number of patients	Duration of treatment	Proportion of patients with amenorrhoea after treatment			
			Ulipristal 5 mg	Ulipristal 10 mg	Placebo	Leuprorelin
PEARL I[2]	242	13 weeks	73%	82%	6%	–
PEARL II[3]	307	13 weeks	75%	89%	–	80%
PEARL III[4]	209	Four 12–week courses (107 women)	–	90%	–	–
PEARL IV[5]	451	Four 12–week courses (291 women)	63%	73%	–	–

depended on the timing of menstruation. At the end of each of the first two treatment courses 62% of the women taking 5 mg and 73% of those taking 10 mg had amenorrhoea.[6] For patients who completed the protocol of four treatment courses the corresponding figures were 63% and 73%. After four treatment courses the three largest fibroids seen on ultrasound had reduced in volume by around 72% in both groups.[5]

Safety

The common adverse effects of ulipristal include headache, nausea and abdominal pain. The actions of ulipristal may cause some women to experience hot flushes. In the comparison with leuprorelin approximately 25% of the women taking ulipristal had at least one hot flush compared with 65% of those taking leuprorelin.[3] Ulipristal causes changes in the endometrium. This is one reason for having intermittent courses of therapy. An annual ultrasound is recommended. If there is persistent thickening of the endometrium, a biopsy may be indicated to exclude malignancy. Some women will develop ovarian cysts.

Although ulipristal at the recommended dose will suppress ovulation in most women, others will still be at risk of pregnancy. A non-hormonal contraceptive is recommended during treatment. If pregnancy occurs there is little information about the effects of ulipristal on the fetus. It is contraindicated in pregnancy and lactation.

The effect of repeated courses on fertility is uncertain. For most women menstruation resumes within a month of stopping ulipristal.[4,6]

Conclusion

The role of ulipristal will be determined by each patient's problems. While surgery will remove fibroids, this may not be appropriate for women planning a future pregnancy. It is possible that ulipristal could reduce the size of the fibroids to enable less invasive surgery. For women who do not want surgery more research will be needed on repeated courses of ulipristal.

Although a 10 mg dose was studied in the trials (see Table), 5 mg is the approved dose in Australia.

T T manufacturer provided additional useful information

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The Transparency Score (T) is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the European Medicines Agency (www.ema.europa.eu) and the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-austpar.htm)..

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Postal The Editor
Australian Prescriber
PO Box 104
DEAKIN WEST 2600

Telephone (02) 6202 3100

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