Australian Prescriber

VOLUME 32 | NUMBER 5 | AN INDEPENDENT REVIEW | OCTOBER 2009

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Editorial

Extended prescribing rights – the UK experience

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Key words: drug utilisation, nurse prescribers, pharmacists.

(Aust Prescr 2009;32:118–9)

We are not doing too well with the prescribing of medicines in Britain. A recent review of the best evidence for the Royal Pharmaceutical Society of Great Britain (RPSGB)[1] found errors at each step of medicines use. There is an error rate of 7.5% in primary care prescribing, 2.6–5.2% of prescriptions are not taken to the pharmacy, and 3.3% of prescriptions are incorrectly dispensed. Non-adherence by patients with a chronic condition is 30–50%, and 72% of medicines are not reviewed for more than a year. Around 4–5% of hospital admissions are due to avoidable adverse events from medicines. On admission 58% of patients have discrepancies in their medicines and the inpatient prescribing error is 1.5–9.2%. After discharge and a subsequent prescription, around half of patients have unintentional discrepancies in their medicines. Following outpatient visits, 5% of prescribed items are not added to the general practitioners' records and doses are not recorded in 13% of consultations.[1]

Access to medicines is another issue; it is heavily controlled by regulation. Patients may suffer unnecessarily, or go long periods without treatment because they cannot get to a doctor who can write them the prescription they require.

The question is, could we improve prescribing quality and access for patients by extending prescribing rights to other professional groups – or would it make matters worse?

In this issue …

Renal disease reduces the production of erythropoietin by the kidneys. If patients then develop uraemic anaemia, Simon Rogers says they will benefit from treatment with a recombinant erythropoietin.

Renin is also produced by the kidney. Duncan Campbell and Karen Duggan explain how new drugs which inhibit renin can help in the management of hypertension.

The management of childhood coughs and colds may involve the use of over-the-counter medicines. Valerie Sung and Noel Cranswick question whether these products are of any benefit.

Iodine is found in over-the-counter antiseptics, but is rarely a cause of allergy. Connie Katelaris and William Smith also dismiss iodine as the cause of seafood allergy.

In answering this, we need first to differentiate, as has been done in the UK, between prescribing that follows a diagnosis and agreed clinical management plan (called, unhelpfully, supplementary prescribing in the UK) and the combined act of diagnosis and prescribing (called independent prescribing in the UK).

The drive to extend prescribing rights in the UK came predominantly from nurses. They conducted a large, politically adept campaign which was aided by the public's perceptions of nurses' skills, by role extension in the USA, and by examples of problems such as district nurses being unable to prescribe dressings when on a home visit. Pharmacists were more cautious, but their expertise in the management of medicines led to them being offered extended prescribing rights. Supplementary (originally called dependent) prescribing rights were introduced in 2003 and were followed by independent prescribing rights in 2006. The new prescribers work as part of a team with the doctor, in primary and secondary care, but they are legally responsible for their own prescribing. They have access to, and contribute to, the patient's medical records.

Supplementary prescribing by nurses and pharmacists has recently been evaluated jointly by the Universities of Sheffield, Nottingham, Flinders and South Australia.[2] The evaluation, which included primary and secondary care, is positive and provides interesting data. In 2007, after consultations around 20 minutes long, nurses prescribed 9.3 million items and pharmacists 64 883 items (around 1% of primary care prescribing). Of the pharmacists surveyed, most (60%) prescribed cardiovascular medicines while the largest category of nurse prescribing (46%) was for infections. Interviews found that health professionals generally liked supplementary prescribing and thought it safe. Case studies showed that patients found nurses and pharmacists easier to talk to than doctors. The main evaluation of independent prescribing, by Keele and Southampton Universities, is expected later this year.

If Australia widens the range of prescribers, it can avoid our errors and draw on our experiences of education (details of training can be found on the RPSGB website[3]). Currently nurses and pharmacists have common training, some of which, such as pharmacology, the pharmacists find very simple – separate training will probably work better. What is more, some nurses want specific prescribing skills and resent having to learn a

wider curriculum. The skills of the doctors providing training should also meet minimum standards. The doctors should be centrally funded for this role (at present in the UK nurses and pharmacists sometimes have to pay for themselves, or defer training until one of the small number of bursaries becomes available). In some states in the USA, pharmacists are certified by the same board as physicians, which aids local acceptability.

Overall, there is a clear rationale to extend prescribing rights. While it needs continued evaluation, where it has been introduced it seems to have improved access, been liked and, on the evidence of a small number of case studies, been effective. Extending prescribing rights is also logical. The burden of knowledge associated with medicines is vast and expanding, so it makes sense to share the task of prescribing while retaining an integrated system of care.

The role of the doctor is in a transition akin to that which theatre went through in the last century. The doctor's role has been like that of the great Victorian 'actor-managers' – controlling the whole show, making all the key decisions and being centre stage in the action. Medicine is getting too complex for that model to survive. Doctors should move to the equivalent of the theatre director of today. They can set direction, strategy and priorities, working with teams of colleagues, including non-medical prescribers.

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Conflict of interest: none declared

Letters

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

Warfarin pharmacogenetics

Editor, – Dr Martin has comprehensively reviewed the genetic and environmental factors contributing to the large inter-individual variability in warfarin requirements (Aust Prescr 2009;32:76–80). These factors explain about 50% of such variability which is quite impressive considering that for most drugs, 100% of the dose variability cannot be explained. It is very unlikely that additional genetic factors will be uncovered, as whole genome association studies have clearly identified CYP2C9 and VKORC1 genotype as the major genetic contributors to dosage requirements with a very small contribution by CYP4F2.[1] Other factors that need to be considered are drug-drug interactions, medication adherence, psychosocial factors and the less than optimal system of care for people prescribed warfarin.[2]

The Food and Drug Administration in the US refers to the genetic factors (CYP2C9 and VKORC1) which influence dosage requirements in the product information for warfarin, but Medicare and Medicaid will not pay for the genetic test (except as part of clinical trials) because of insufficient evidence of benefit. There is clearly a need for large scale prospective studies, including pharmacoeconomic studies, before any decisions are made to incorporate genetic testing into best practice guidelines.[3]

In Australia, the situation is complex as some pathology services already advertise the test, but there are no known large prospective multicentre trials being conducted to determine feasibility, interpretation, dosage recommendations and cost-benefit. It is timely that this be done so that Australia, with its different spread of ethnicities and diets, can contribute to the evidence and importantly, that Australian-based cost-benefit analyses and dosage recommendations can be made to determine whether or not warfarin genetic testing should become part of treatment guidelines.

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Prescribing in liver disease

Editor, – Tailoring treatment to the individual is the art of therapeutics and is supported by an increasing understanding of inter- and intra-individual variability (the science). Dose adjustment in liver impairment is difficult because a reliable predictor of hepatic drug clearance is lacking.[1] Drs Sloss and Kubler recently discussed the use of the Child-Pugh classification to guide dose adjustment in liver impairment (Aust Prescr 2009;32:32–5). This is a tool of last resort and there are several other factors that can and should be used to guide dosing.

If measures of clinical effects (desired and adverse) are available, these can be used to guide dosing. Firstly, many drugs have validated biomarkers of drug effect (for example INR for warfarin) or surrogate markers of clinical outcome (for example HIV viral load for antiretroviral treatment).[2] Similarly many drugs have concentration-related symptoms, for example pain for analgesics, or dry mouth and constipation for anticholinergics. Secondly, the concentration of some drugs can be easily measured. This is particularly valuable as therapeutic drug monitoring is available for many drugs with narrow therapeutic ranges, the drugs that prescribers are most concerned about in hepatic impairment. Immunosuppressants and anticonvulsants are examples of these.

We also recommend that prescribers consider the potential effect of liver impairment on the active drug moiety by changes in clearance (potentially decreased) and oral bioavailability (potentially increased). Pharmacokinetic variability due to hepatic impairment can be managed by considering clearance of the active moiety and first-pass metabolism in conjunction with monitoring drug effects, biomarkers, or concentrations.

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Editor, – Drs Sloss and Kubler discuss hepatic metabolism in a recent article (Aust Prescr 2009;32:32–5). They point out that, in phase I reactions, hydrolysis is very common. They go on to state that hydrolysis involves the addition of molecular oxygen. This sounds more like oxidation.

The term 'hydrolysis' refers to water and involves cleavage of a molecule with the addition of water, whether it is mediated by acid or base or by a hydrolase enzyme. Hydrolases are, in fact, like a particular type of transferase enzyme where water accepts the transferred group. So water is actually utilised and not created as stated in the article.

In the example given, acetylsalicylic acid (aspirin) reacts with water to form acetate (acetic acid) and the free phenolic salicylate, salicylic acid.

The aqueous nature of the body makes hydrolysis very probable. In fact, it is by confining easily hydrolysed intermediates within a hydrophobic enzyme active site that unique reactions can occur enzymatically that would be impossible in aqueous solution.

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Pitfalls in interpreting laboratory results

Editor, – I have read Dr Pat Phillips' article (Aust Prescr 2009;32:43–6) with interest. He points out that an individual's laboratory result may be abnormal for them, but still lie within the reference interval. This can occur when the individual's biological or 'intra-individual' variance is small compared with the 'inter-individual' or group variance. The 'index of individuality' – which is the ratio of the intra-individual coefficient of variation (CV_i) to the group CV (CV_g) – is used to estimate this variance. If the index is less than 0.6, the population-derived reference interval will not be of great use and the variable is said to show high individuality. If it is greater than 1.4 it should be useful.

The example used in the article on alkaline phosphatase is unfortunate, as this variable shows high individuality and the population reference interval is of limited value. For a variable such as ionised calcium, where the intra-individual variation is close to the inter-individual variation and therefore has a high index of individuality, it will be useful.

Another detail worth mentioning is that the appropriate CV for calculating the least significant difference is the combined intra-individual and analytical CV. This is obtained by squaring the respective CVs to obtain the variances, adding them and taking the square root to obtain the combined CV.

There is much published information on these sources of variation.[1,2] The possibility that individuals vary significantly in their intra-individual variances is recognised. Nevertheless

taking these combined values into consideration can be helpful, as Dr Phillips shows, in interpreting successive laboratory results in patients on treatment.

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Dr Pat Phillips, author of the article, comments:

I appreciate Dr Maserei identifying the 'index of individuality' as an objective way to tell when a test result may be within the relevant reference range (based on a group of people) but outside the individual's healthy range (which may be much narrower). This distinction can be clinically important. For example, a free T4 may be within the laboratory range (that is, normal) but be biologically high for the individual and associated with a suppressed or increased thyroid stimulating hormone. This is the pathophysiology of the real clinical syndromes 'subclinical' hyper- and hypothyroidism.

Unfortunately, the only measure of result variability given by most laboratories is the laboratory reference range, which includes many components of variability as well as that occurring within one individual. In these situations, one has little choice and must interpret the individual result in the context of the general laboratory range.

However, when interpreting sequential results in one individual, one does not consider the laboratory reference range but the total variability within that individual (CV_i). I suggested that the least significant change should be considered a true signal of biological change over and above the background 'noise' of variability and is approximately $2CV_i$.

The major point was that when interpreting laboratory results, one is trying to identify a clinical signal against the background variability. For single results the only information about the background variability is the laboratory reference range, but for sequential results the appropriate measure of variability is the variability within the individual and the least significant change.

Subsidised medicines for Aboriginal and Torres Strait Islander people

Since August 2006, the Pharmaceutical Benefits Scheme (PBS) has been including new listings specifically for the treatment of common conditions in Aboriginal and Torres Strait Islander people. Some listings are medicines new to the PBS, while others vary the restrictions for prescribing existing PBS items. For the most up-to-date information on relevant PBS-subsidised items, and their conditions for prescribing, see the current list in the fact sheet at www.pbs.gov.au.

A new listing is nicotine replacement therapy for nicotine dependence.

The items in the box are available as 'Authority PBS prescriptions'. For more information about PBS access by Aboriginal and Torres Strait Islander people, send an email to pbs-indigenous@health.gov.au

For changes to this list and other listings, readers can subscribe to news alerts from the PBS at www.pbs.gov.au/html/healthpro/subscription/manage

Authority PBS listings as at 1 August 2009

Treatment of a fungal or a yeast infection

1. Bifonazole cream (1%)
2. Clotrimazole lotion (1%)
3. Ketoconazole cream (2%) and shampoo (1%, 2%)
4. Miconazole nitrate (2%) as cream, powder, lotion and tincture
5. Nystatin cream (100 000 units per g)
6. Terbinafine cream (1%)

Prophylaxis of thiamine deficiency

7. Thiamine tablet (100 mg)

Treatment of whipworm infestation

8. Albendazole tablet (200 mg)

Treatment of chronic suppurative otitis media

9. Ciprofloxacin ear drops (0.3%)

Treatment of a dermatophyte infection where topical treatment has failed

10. Terbinafine tablet (250 mg)

Nicotine replacement therapy

11. Nicotine transdermal patch (releasing approximately 15 mg over 16 hours)

Cough and cold remedies for children

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Summary

Over-the-counter cough and cold remedies for children under two years of age have recently been rescheduled to prescription-only. This will mean that doctors and pharmacists will encounter more consultations for such medicines. These drugs are no longer recommended in children because of the lack of efficacy and reports of serious adverse events.

Key words: children, over-the-counter medicines.

(Aust Prescr 2009;32:122–4)

Introduction

Upper respiratory tract infections are common in children and it is not surprising that cough and cold symptoms can be a major burden to many families. Until recently, over-the-counter (OTC) cough and cold remedies were widely available in Australia, and extensively used in young children. They include antitussives, antihistamines, expectorants and decongestants (Table 1). However, since September 2008 cough and cold medicines for children under two years have been rescheduled to S4 to become prescription-only. The USA and the UK introduced similar restrictions in response to reports of adverse effects, accidental overdoses and lack of evidence of their efficacy for acute and chronic cough in children.

This change in the scheduling of these medicines will result in more consultations, and doctors and pharmacists should be aware of the potentially serious adverse effects of these medicines. It is important to have a sound approach to providing symptomatic relief to children with cough and colds.

Cough in children

Cough is a reflex response to mechanical, inflammatory and chemical irritation of the tracheobronchial tree. It is a normal mechanism for the maintenance of a healthy respiratory system.

Diagnosis

When a child presents with cough or cold symptoms, the most important first step is to make the correct diagnosis and exclude serious pathology. Most causes of cough are self-limiting and do not require investigations. A detailed history and physical examination are most important, followed by specific investigations only when clinically indicated.

Causes of cough

Management of a cough should be directed at the underlying cause. Cough that is accompanied by other upper respiratory tract infection symptoms, such as rhinorrhoea and sore throat, is usually due to viral infections and is rarely bacterial. If such a cough lingers, it may be a postinfective cough. A barking or brassy cough may suggest croup or tracheomalacia. Cough accompanied by respiratory distress suggests pneumonia or bronchiolitis. Asthma may present as nocturnal cough, while cough that disappears when the child is asleep may suggest a psychogenic cause.

A coughing infant or child with paroxysms of cough may have pertussis. Suppurative lung disease should be considered if the cough is most vigorous in the morning. If there is a temporal association with feeding or with positioning, gastro-oesophageal reflux should be considered.

The presence of a foreign body should be suspected after an acute episode of choking, while aspiration may occur in children with hypotonia or pharyngeal incoordination. Chlamydia trachomatis is an uncommon but serious cause of cough that should be considered especially if the infant has conjunctivitis or whose mother has evidence of chlamydial infection. Structural anomalies causing cough are usually associated with other symptoms such as stridor or cyanosis.

Symptomatic treatments for colds and cough

Cough and cold symptoms can cause significant distress to children and their families, and this is reflected in the vast array of OTC medications marketed over the years. Most cough and cold remedies are a combination of antitussives, antihistamines, expectorants and decongestants. Table 1 lists their reported actions, common adverse effects and more serious adverse reactions.

Efficacy in children under two years

Data on the efficacy of cough and cold medicines in children under two years old are extremely limited. There is no reliable evidence to recommend their use in this age group.

Table 1

Common cough and cold remedies *

Drug type	Reported actions	Common adverse effects	Serious adverse reactions
Antitussives			
Pholcodine	Centrally acting opioid derivative; directly suppresses medullary cough centre	Dizziness, sedation, nausea	Opioid dependence, potential abuse, serotonin syndrome, lethargy, stupor, aspiration
Dextromethorphan	Narcotic analogue; directly suppresses medullary cough centre		
Antihistamines Diphenhydramine Brompheniramine Chlorpheniramine	Histamine H_1-receptor antagonists; prevent histamine-induced reactions in cells of the respiratory tract, gastrointestinal tract and blood vessels	Sedation, headache, dizziness, nervousness, restlessness, irritability, palpitations	Hallucinations, seizures, central nervous system depression, cardiovascular collapse, apnoea, death, anticholinergic effects
Decongestants Pseudoephedrine Phenylephrine	Sympathomimetic drugs, adrenergic receptor agonists; produce vasoconstriction within the respiratory tract mucosa, and cause increased heart rate and cardiac contractility	Nervousness, restlessness, insomnia, trembling, headache, anxiety	Tachycardia, palpitations, dysrhythmias, hypertension, hallucinations, agitation, central nervous system depression, seizures
Expectorants Guaifenesin Ipecacuanha	Expectorants; promote the expulsion of mucus and other materials from the respiratory tract	Drowsiness, dizziness, headache, rash – these rarely occur at therapeutic doses	Nausea/vomiting, abdominal pain, nephrolithiasis
Mucolytics Bromhexine	Oral mucolytics; loosen and thin bronchial secretions by reducing surface tension and viscosity of mucus	Dizziness, headache, rash – these rarely occur at therapeutic doses	Nausea/vomiting, abdominal pain, diarrhoea

* information modified from references 14 and 15

Note: these drugs are commonly sold as combination products

Efficacy in children over two years

There have been numerous trials of cough and cold drugs in older children. A Cochrane review in 2008 found that treatments were no more effective than placebo for acute cough in children. The review included two trials with antitussives, two with antihistamines, two with antihistamine-decongestants and one trial with antitussive/bronchodilator combinations. One trial favoured active treatment with mucolytics over placebo.[1]

Another Cochrane review of three randomised controlled trials found that antihistamines had uncertain efficacy for prolonged non-specific cough (more than four weeks) in children compared to placebo.[2] The two larger trials showed no significant difference in symptom improvement. The smaller study indicated that cetirizine, a second generation antihistamine, was significantly more efficacious than placebo in reducing chronic cough in children with seasonal allergic rhinitis.[2]

In another Cochrane review, there was insufficient evidence to determine whether OTC medicines were beneficial for cough when given as an adjunct to antibiotics for acute pneumonia in children and adults.[3] Similar results were found in a review of nasal decongestants for the common cold in children.[4]

Non-drug treatments

There are limited data on the use of non-pharmacological therapies for cough and colds. Nasal saline drops are effective in chronic rhinosinusitis[5], but there is limited evidence on their efficacy in the common cold. Steam and vapour are not recommended due to lack of efficacy data and the potentially serious adverse effect of burns. There is no evidence to show that physiotherapy is effective for cough other than when secondary to suppurative lung diseases. Cochrane reviews do not support the use of complementary medicines such as echinacea, vitamin C or zinc in the treatment of cough and colds.[6] A randomised controlled trial showed that honey was effective in children with cough[7], however there were many limitations to this study. In addition, ingestion of honey has been associated with infantile botulism and should not be used in children under one year.

Why not prescribe cough and cold medicines?

Although the majority of trials analysed in the Cochrane reviews did not report adverse events, it is well known that cough and cold products in children are a major cause of unintentional

drug overdoses[8], and are associated with sudden infant deaths.[9] A recent report estimated that 7091 children under 12 years of age have been treated for adverse drug events in 63 emergency departments in the USA over two years.[10] Adverse reactions to drugs contained in cough and cold medicines have also been reported in Australia (www.tga.gov.au/ndpsc/record/rr200706.pdf).

The potential for adverse effects is high, firstly because until recently there was no regulation for dosing of such drugs in young children, and secondly because these medicines are often administered by multiple caregivers. In October 2008, the US Food and Drug Administration advised against the use of OTC cough and cold products in infants and children under two years of age, and recommended caution in children aged 2–11 years due to the risk of potentially life-threatening adverse effects.[11] These were described in the context of overdose or the use of multiple similar preparations. The Therapeutic Goods Administration made the same announcements in April 2008.[12] A recent recommendation in the UK advises that cough and cold medicines should not be used in children under six years.[13]

Recommendations for managing coughs and colds

After excluding or treating the more serious underlying causes of cough, parents should be offered non-pharmacological advice on symptomatic treatment of coughs and colds. The first step is to explain the aetiology of symptoms and the mechanism of cough, and provide realistic information on the expected time-course of symptoms. Reassure parents that symptoms usually improve spontaneously and they have the option of continuing medical reviews.

Children with upper respiratory tract symptoms may benefit from adequate hydration and rest, together with symptomatic relief with analgesia, if required. If requests are made for the prescription of cold and cough remedies, parents should be given adequate information on the lack of evidence for their efficacy and the potential for significant adverse effects. Parents should also understand that such remedies will not change the course of their child's illness.

Cough and cold medicines must be avoided in children under two years and should not be recommended in children of any age, particularly those with neurological disorders, seizures, hypotonia, heart disease and those at risk of respiratory depression. Doctors and pharmacists should work together to avoid recommending the use of cough and cold remedies for children.

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Conflict of interest: none declared

'Iodine allergy' label is misleading

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Summary

'Iodine allergy' is not an accurate label for patients who have had allergic reactions to iodinated radiological contrast media or iodinated antiseptics. Allergy to seafood has nothing to do with iodine content as it is caused by specific immunoglobulin E to proteins. Seafood allergy is not a specific risk factor for reactivity to iodinated radiological contrast media, but a history of any moderate or severe allergic disorder confers a slight increase in risk. Patients with a previous history of allergy to radiological contrast media are at highest risk of a reaction. In some cases the risk of an allergic reaction to contrast media can be reduced by premedication, but, if previous reactions were severe, contrast media will usually remain contraindicated.

Key words: anaphylaxis, contrast media, seafood allergy.

(Aust Prescr 2009;32:125–8)

Introduction

The term 'iodine allergy' is used frequently and usually refers to a history of an allergic reaction to iodinated radiological contrast media or possibly a contact allergy to povidone-iodine. A misconception has arisen that allergy to seafood is caused by the iodine content of fish and shellfish. In a survey of patients presenting to a paediatric clinic because of suspected seafood allergy, 92% of the parents or patients believed that it was iodine in seafood that was the cause of the allergy.[1]

As a result, a history of seafood allergy is frequently considered to be a contraindication to the use of iodinated radiological contrast media. In a recent survey of radiologists and cardiologists in the USA, over 50% said that a history of seafood or shellfish allergy was sought before the administration of contrast media. One-third of the radiologists and 50% of cardiologists stated that they would withhold contrast media or recommend premedication if there was a history of sensitivity to seafood.[2] Anecdotally, this is also often the case in Australia.

There is significant misunderstanding and confusion regarding seafood allergy, contrast media sensitivity and the role of iodine. This is clinically important because patients may be denied useful procedures unnecessarily, while true risk factors may not be given due consideration resulting in the correct risk management procedures not being undertaken.

Dietary sources of iodine

Iodine is an element which is present in many body tissues. It is an essential trace mineral required for thyroid hormone synthesis. Ingested iodine is converted in the gut to iodide, the ionised form of iodine. There are many dietary sources of iodine including iodised salt, fish, vegetables, meat and iodates used as preservatives in bread.

Potassium iodide

Potassium iodide is used to prevent the uptake of radioactive iodine by the thyroid gland following exposure in a radiation emergency. The effectiveness of potassium iodide as a specific blocker of radioactive iodide uptake is well-established. When used for prophylaxis in Poland after the Chernobyl disaster, it reduced the incidence of thyroid cancers below the expected rate. Potassium iodide is also used in smaller quantities to iodise table salt.

Theoretically it is not possible to be allergic to elemental iodine or simple iodide salts (such as potassium iodide). Indeed no true allergy or anaphylaxis to iodine has been reported. Iodine itself can cause non-allergic adverse reactions such as iododerma (a rare acneiform or ulcerative eruption related to iodide ingestion) or iodide mumps (salivary gland swelling due to iodide overload from contrast media infusion in those with renal insufficiency).

Iodinated antiseptics

Some topical antiseptics contain povidone-iodine which is a complex of polyvinylpyrrolidone (povidone, PVP) with iodine. Povidone is a polymer similar to dextran and it acts as a carrier that delivers complexed diatomic iodine, which is bactericidal, directly to the bacterial cell surface. Povidone-iodine may cause allergic contact or irritant dermatitis, however this is rare. When patch testing has been conducted, positive reactions may be seen with povidone-iodine, but not iodine or potassium iodide solution. Although povidone itself is considered not to cause contact hypersensitivity, some of its non-iodinated copolymers (PVP-eicosene, PVP hexadecane) have been reported to cause contact dermatitis.

Systemic reactions to povidone-iodine are rare, but there are several case reports of generalised urticaria and even anaphylactic shock. These cases have the characteristics of IgE-mediated reactions and in one case specific IgE against povidone was found. There are also reports of anaphylaxis from povidone alone without iodine. Two of the cases of povidone-iodine anaphylaxis showed positive allergy tests with povidone alone. The conclusion is that in these rare cases, the allergy is against povidone and the iodine probably plays no role.

Drugs

Iodine is present in some drugs such as amiodarone. Although hypersensitivity to amiodarone is a contraindication to its further use, there is no evidence that iodine is directly involved in allergic reactions to this drug. Hypersensitivity to other iodine-containing compounds should not be considered a contraindication to amiodarone.

Seafood allergy

Allergy to seafood (fish, crustaceans and molluscs) has nothing to do with iodine content. It is caused by specific IgE against allergenic proteins including, but not limited to, parvalbumins in fish and tropomyosins in crustaceans and molluscs. Cross-reactive allergy within each of these three groups of animals is common, but is less common between the groups. (Those allergic to prawns are often allergic to crab, but those allergic to crustaceans are not usually allergic to fish.) While it is true that seafood may contain relatively high levels of iodine compared with other foods, the allergenic proteins are not iodinated and seafood allergy does not depend on the iodine content of the seafood.

Contrast media

Radiocontrast materials are tri-iodinated benzoic acid derivatives that in solution contain a small amount of free iodide. Non-idiosyncratic reactions to radiocontrast media are due to direct toxic or osmolar effects. The only adverse effect of contrast material that can convincingly be ascribed to free iodide is iodide mumps and other manifestations of iodism.

Idiosyncratic (including allergic) reactions

Immediate and non-immediate hypersensitivity-type reactions after contrast media are not common. However, contrast media are frequently used (estimated at 70 million administrations worldwide per year[3]) and often in large volumes so reactions are an important problem. Immediate reactions consist of allergic-type manifestations such as pruritus, erythema, urticaria, angioedema and anaphylaxis. Non-immediate (more than one hour after administration) reactions are predominantly cutaneous and consist of urticaria, angioedema, maculopapular rash or rarely, more severe reactions such as Stevens-Johnson syndrome.[3]

Iodinated contrast media were formerly hypertonic and ionic solutions, whereas newer products are closer to isosmolarity and are non-ionic. The incidence of hypersensitivity-like reactions is much lower with non-ionic, low-osmolar contrast media. Anaphylaxis has been estimated to occur at a frequency of 0.1–0.4% with ionic and 0.02–0.04% with non-ionic contrast media.[2] In the case of hyperosmolar and ionic contrast media, the predominant mechanism of the reaction is thought to be a direct non-immunological effect on mast cells and basophils or activation of the complement system. Severe reactions are associated with elevation of histamine and mast cell tryptase in the same way as allergic anaphylaxis. These reactions to contrast media were previously termed 'anaphylactoid', but the term 'nonallergic anaphylaxis' is now preferred.

There is growing evidence that a proportion of the rare cases of anaphylaxis to non-ionic contrast media is IgE-mediated, in other words, a true allergic anaphylaxis. Some research suggests that intradermal testing or *in vitro* IgE detection might be useful in these cases, but this is an evolving area. The role of the iodine atom (as a part of the iodinated molecular complex) in these cases is unknown. It is known, however, that none of 23 patients with documented contrast sensitivity reacted to subcutaneous sodium iodide.

Risk factors for hypersensitivity

A number of studies have shown that while patients with an allergy to seafood are at a slightly greater risk of reacting to contrast media, seafood allergy is not a specific risk factor. It is food allergy in general which increases the risk, as does severe hay fever or asthma, indicating that the atopic state is the risk factor, not seafood allergy itself. A large case-control study established that the presence of cardiovascular disease, asthma and the use of beta-blockers were risk factors for severe reactions. Although the odds ratio for anaphylaxis is between 7 and 20, the absolute risk in these patients remains relatively low.[4] The presence of these risk factors alone should not be sufficient to contraindicate administration of contrast media, but should signal caution. The only substantial risk factor for severe immediate reactions to contrast media is a history of a previous severe reaction, but this may be a relative or absolute contraindication (see Table 1). Systemic mastocytosis is theoretically another significant risk factor. Whether these risk factors apply equally to ionic and non-ionic contrast media is not established, but non-ionic contrast media have a lower incidence of reactions in all of these cases.

Risk factors for non-immediate reactions are an elevated serum creatinine, a history of drug allergy or contact hypersensitivity, and previous non-immediate reactions. There is no evidence that previous non-immediate reactions to contrast media increase the risk of anaphylaxis to contrast media.

A history of contact allergy to iodinated antiseptics is not a specific contraindication to the administration of contrast media,

Table 1

Management of patients having contrast media

Risk factors	Management
None	Routine procedure*
Severe food allergy Moderate–severe asthma Significant cardiovascular disease Beta blocker use	Close observation High-level preparedness Use non-ionic low-osmolarity contrast media if not routine
Previous mild–moderate immediate reaction to contrast media	Premedication (see box) Close observation High-level preparedness Use non-ionic low-osmolarity contrast media if not routine
Previous mild–moderate non-immediate cutaneous reaction to contrast media	Premedication (see box) Use non-ionic low-osmolarity contrast media if not routine†
Previous anaphylaxis to contrast media	Contrast media probably contraindicated‡
Previous severe non-immediate cutaneous reaction to contrast media (e.g. vasculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis)	Contrast media contraindicated‡

* Always be prepared to treat unexpected allergic reactions (see Emergency management of anaphylaxis in the community: wall chart. Aust Prescr 2007;30:115)
† Risk of anaphylaxis probably not increased
‡ Suggest consult immunologist

Premedication

Cetirizine 10 mg
Prednisolone 25 mg
Ranitidine 150 mg
} repeat after 12 hours

This regimen is given on the day before and on the day of the procedure. It is also given on the day after the procedure if there is a history of delayed reaction.

but may slightly increase the risk of a non-immediate reaction to the same degree as any other contact hypersensitivity. A history of anaphylaxis to povidone-iodine does not contraindicate the use of contrast media because the structure of povidone, with or without iodine, is not similar to that of contrast media and cross-reactivity has not been demonstrated.

Using contrast media in patients with risk factors

When preparing a patient for a procedure using contrast media, risk factor assessment should include asking about severe food allergy, drug allergy, asthma, cardiovascular disease or beta blocker use and previous reactions to contrast media. Management strategies in the presence of these risk factors might include:

- close observation and preparedness to treat a reaction
- giving low-osmolarity non-ionic contrast media (if this is not yet routine)
- premedication (see box).

There are a number of case reports of premedication failing to prevent subsequent anaphylaxis[5], so in some cases contrast media should be avoided. Other diagnostic tests may be more suitable.

Conclusion

There is little evidence to support iodine as a cause of allergic reactions. Any reactions to substances containing iodine are probably caused by other parts of the molecule. The term 'iodine allergy' is therefore misleading.

Seafood allergy is not caused by the iodine contained in fish, crustaceans and molluscs. A history of seafood allergy does not therefore specifically contraindicate the use of iodinated contrast media. Each patient should be assessed for factors which increase the risk of a reaction to contrast media and managed according to the severity of the risk.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 143)

1. Seafood allergy is caused by the iodine content of fish.
2. Beta blockers reduce the risk of a hypersensitivity reaction to iodinated contrast media.

Patient support organisation

Anaphylaxis Australia

Anaphylaxis Australia supports and helps people affected by anaphylaxis and food allergies to manage their everyday lives while minimising the risk to their health and wellbeing. As a charitable non-profit organisation, it aims to raise public awareness and provides advocacy and education, for example through parents, schools and workplaces.

Anaphylaxis Australia has information on its website and offers support in all states. It has many educational resources for sale including DVDs, books, action plans, and medication and training accessories. There are also information packs for health professionals. Doctors can order free brochures for their patients.

Mailing address	PO Box 3182 ASQUITH NSW 2077
Web	www.allergyfacts.org.au
Phone	1300 728 000 (02) 9482 5988 for administration and orders only
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Managing the anaemia of chronic kidney disease

***Simon D Roger**, Renal Physician, Gosford Hospital, New South Wales*

Summary

Anaemia is a common manifestation of chronic kidney disease, especially when the glomerular filtration rate falls below 30 mL/min. It is important to exclude other causes of anaemia such as iron and other haematinic deficiencies, chronic inflammation, malignancy and drugs. After reversible causes of anaemia are excluded, supplementary erythropoietin (epoetin) can be considered when the patient's haemoglobin concentration falls below 100 g/L. Patients treated with epoetin often require supplements of oral or intravenous iron to maintain adequate iron stores during the correction and the maintenance phases of management. The main adverse effect of epoetin use is the development or worsening of hypertension. Care must also be taken not to overshoot the target haemoglobin of 110–120 g/L, as this can be associated with a prothrombotic tendency.

Key words: darbepoetin alfa, epoetin alfa, epoetin beta, erythropoietin, iron.

(Aust Prescr 2009;32:129–31)

Introduction

Erythropoietin is a hormone made predominantly within the peritubular cells of the kidney. It acts on the bone marrow, stimulating erythropoiesis. Erythropoietin also controls apoptosis (programmed cell death) of mature red blood cells. Renal disease reduces erythropoietin production.

The management of anaemia in chronic kidney disease has been revolutionised by the development of recombinant human erythropoietin (epoetin).[1] Many of the symptoms that had been ascribed to chronic kidney disease such as fatigue, lethargy, somnolence and shortness of breath, which all impact unfavourably on quality of life, were resolved or markedly improved when anaemia was corrected.[2] Before the development of epoetin, uraemic anaemia was managed by recurrent blood transfusions, with the risk of iron overload and viral infection (hepatitis B and C and HIV).

Uraemic anaemia

Although uraemic anaemia can be present when the glomerular filtration rate is above 30 mL/min, it is more prevalent when the rate falls below 30 mL/min (stages four and five chronic kidney disease). Patients with diabetic nephropathy or analgesic nephropathy (who took Bex, Vincent's or APC powders during the 1950s and 1960s) tend to be more anaemic than patients with other causes of chronic kidney disease. In contrast, patients with adult-onset polycystic kidney disease often maintain their haemoglobin concentrations as renal failure progresses.

Uraemic anaemia is characterised by relative erythropoietin deficiency. Chronic inflammation or infection, malignancy and hyperparathyroidism always need to be considered, but iron deficiency is the most common cause of reversible anaemia in patients with chronic kidney disease. Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers may reduce endogenous erythropoietin levels and contribute to anaemia in these patients. However, these effects are outweighed by their renoprotective benefits.

Iron deficiency is common in chronic kidney disease because of the widespread use of antiplatelet drugs (aspirin and clopidogrel), and a possible uraemic platelet defect, enhancing gastrointestinal blood loss.[3] Endoscopy should be considered to exclude gastrointestinal lesions. Haemodialysis patients are also exposed to heparin at least three times per week to prevent clotting on dialysis and a certain amount of blood is lost in the artificial kidney during each haemodialysis session.

Diagnosis of iron deficiency

If the patient has a low haemoglobin, iron studies are indicated. Serum ferritin is a marker of iron stores but can be elevated as an acute phase reactant, similar to C-reactive protein and erythrocyte sedimentation rate. Transferrin saturation reflects iron availability in the bone marrow. Both measurements are needed to assess iron status accurately. Serum iron is subject to diurnal variations in concentration and is not a useful marker of iron status in chronic kidney disease.

There is a chronic inflammatory state in patients with chronic kidney disease so the normal ranges for serum ferritin and transferrin saturation do not apply. Absolute iron deficiency cannot be excluded unless the ferritin is greater than 100 microgram/L or the transferrin saturation greater than 20%.

Treatment of iron deficiency

In patients who do not require dialysis, iron deficiency is managed with oral iron. The main adverse effects from oral iron include diarrhoea or other gastrointestinal upsets. The only oral iron tablets subsidised by the Pharmaceutical Benefits Scheme (PBS) are iron fumarate with folic acid. Some patients cannot tolerate oral iron and require admission for an intravenous infusion of iron polymaltose (500 mg). Iron polymaltose should not be injected intramuscularly because of the risk of tattoo or neuropraxia. Iron sucrose (100 mg) may be administered by slow intravenous injection.

When is treatment with supplementary epoetin considered?

If the patient does not respond to iron, and other causes of anaemia have been excluded, epoetin can be considered. It is expensive, but the PBS subsidises supplementary epoetin when the patient's haemoglobin concentration falls below 100 g/L. However, this subsidy does not consider comorbidities. Tailoring the use of epoetin to patients' underlying comorbidities makes sense because, for example, patients with chronic obstructive pulmonary disease would have higher baseline haemoglobins than the general population.

The target haemoglobin values have been studied in patients who have haemodialysis and in those who do not. The results have been disappointing when the target haemoglobin has been greater than 130 g/L.[4,5] Higher haemoglobin concentrations are associated with an increased risk of thrombotic events such as clotting in the arteriovenous fistulae used for haemodialysis access. These trials have led expert groups to recommend a target haemoglobin of 110–120 g/L for most patients.[6] Nevertheless, some prescribers may individualise epoetin dosages to achieve higher haemoglobin concentrations according to the patient's background functional status and other illnesses. Iron therapy continues, if required, depending on the results of blood tests.

Which supplementary epoetins are available?

Since the original epoetin alfa was released, there have been different molecular modifications including increased numbers of sialic acid residues, carbohydrate moieties or pegylation. These modifications increase the half-life of the epoetins and reduce the dosage frequency. All currently available epoetins correct anaemia to the same extent. The choice is dictated by the preferred frequency and route of administration (subcutaneous or intravenous).

All epoetins are subject to degradation if not refrigerated. Care must be taken when transporting epoetin from hospital or community pharmacies to the patient's home.

Epoetin alfa

This epoetin was released onto the Australian market in 1989. It has been extensively studied in trials since then. Originally it was given three times per week, but can be extended to weekly administration. Several years ago over 200 patients worldwide developed pure red cell aplasia secondary to the development of anti-erythropoietin antibodies. This manifested as severe transfusion dependent anaemia because the injected epoetin and any native erythropoietin were destroyed by these antibodies.

Epoetin beta

This epoetin has a similar pharmacological profile to epoetin alfa. Recently it has been shown to be less painful than darbepoetin alfa when injected subcutaneously.[7]

Darbepoetin alfa

This product has a much longer duration of action than the epoetins. The dosing schedule can be extended to monthly administration during the maintenance phase in patients who do not need dialysis. Whether the drug is administered intravenously or subcutaneously makes no difference to its efficacy in maintaining haemoglobin concentrations.

Methoxy polyethylene glycol-epoetin beta

This product has not as yet been released in Australia. It is a pegylated epoetin with a different mode of receptor activation. This further extends the dosing interval so that it can be administered monthly during either the correction or maintenance phase irrespective of whether or not the patient is having dialysis.

Biosimilar epoetin alfa

A biosimilar is a product which is similar to a biological medicine that has already been approved by the regulatory agencies but whose patent has typically expired. Biopharmaceuticals are far more complex than traditional chemical drugs in their structure, methods of production and modes of action. Biosimilar products are therefore similar but not identical to the innovator product. This is in contrast to generic medicines, which have the same chemical structure as the original medication. Biosimilar epoetins have been released in Europe and other countries now that the original patents have expired.[8] These drugs are produced with more modern production techniques than the innovator products and so may result in lower prices.

Other drugs

There are multiple new drugs currently under development or in clinical trials. These are peptides which stimulate the erythropoietin receptor through different mechanisms.

Hematide has an amino acid sequence that is unrelated to erythropoietin or to any other known naturally-occurring human proteins. It should therefore not cause pure red cell aplasia, the haematological disorder that can be induced by treatment with

other erythropoiesis stimulating agents. Its advantages include monthly administration, relatively uncomplicated chemical synthesis, greater stability than currently marketed products, and storage at room temperature.

What monitoring needs to be undertaken?

During the correction phase of anaemia, blood pressure should be monitored monthly and the haemoglobin concentration every 4–6 weeks. Hypertension is associated with a rapid rise in haemoglobin from baseline so the target rate of rise is 10 g/L/month. Iron studies should be checked at least once every two months, but this recommended frequency of monitoring has not been subject to clinical trial verification. Consultation with nephrology services is required during the correction phase, but monitoring of haemoglobin in the maintenance phase is often undertaken by general practitioners. In this setting, the frequency of haemoglobin monitoring can be extended to every 2–3 months, with iron studies every three months.

Conclusion

Anaemia is common in patients with chronic kidney disease. Other causes of anaemia should be excluded. Iron deficiency should be corrected, but if the haemoglobin falls below 100 g/L, treatment with a recombinant epoetin should be considered. This will correct the uraemic anaemia and maintenance therapy will be required once the target haemoglobin has been achieved. If epoetin is stopped, the haemoglobin falls back towards baseline. Correcting the anaemia can improve the patient's quality of life.

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Dr Roger has served on advisory boards/speakers bureaus for Janssen-Cilag, Hoffman-La Roche, Amgen and Vifor. In addition, he has undertaken clinical trials in anaemia/iron management for Takida, Sandoz and the above companies.

Self-test questions

The following statements are either true or false
(answers on page 143)

3. Serum ferritin concentrations may be increased by chronic kidney disease.
4. Iron deficiency in patients with chronic kidney disease is due to erythropoietin deficiency.

Renin inhibitors – mechanisms of action

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Summary

Renin inhibitors are antihypertensive drugs which block the first step in the renin-angiotensin system. Their mechanism of action differs from that of angiotensin converting enzyme inhibitors and angiotensin receptor antagonists, but like these drugs, renin inhibitors interrupt the negative feedback effects of angiotensin II on renin secretion. This increases renin concentrations which may attenuate the inhibition of the renin-angiotensin system by these therapies. Renin inhibitors may interfere with measurements of renin in plasma.

Key words: aliskiren, antihypertensives, hypertension.

(Aust Prescr 2009;32:132–5)

Introduction

Drugs that inhibit the renin-angiotensin system, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists, have proven value for the treatment of hypertension, heart failure and renal disease. They reduce the rates of death, myocardial infarction and stroke in a broad range of patients at high risk, but do not control the blood pressure in all cases. This led to research into inhibiting the renin-angiotensin system at its first step – the production of angiotensin I.

Physiology

Renin is an enzyme produced from the inactive protein, prorenin. The release of renin from the juxtaglomerular cells of the kidney is controlled by several mechanisms. These include the sympathetic nervous system, salt and fluid balance, blood pressure, and negative feedback by angiotensin II. Renin cleaves circulating angiotensinogen to form angiotensin I (Fig. 1). This inactive decapeptide is subsequently cleaved by ACE to produce the octapeptide angiotensin II. Although other bioactive angiotensin peptides are produced from angiotensin I and II, angiotensin II is the main bioactive angiotensin peptide.

Two different receptors mediate the actions of angiotensin II. These are the type 1 (AT_1) and the type 2 (AT_2) receptors (Fig. 1). Stimulation of the AT_1 receptor increases arterial tone and aldosterone secretion. Angiotensin II therefore plays an essential role in blood pressure, and fluid and electrolyte homeostasis. However, this role is much diminished in people consuming a Western diet with an excessive salt content. In these people, even 'normal' concentrations of angiotensin II may play a role in hypertension and in cardiovascular and renal disease.

Angiotensin-(1-7), a heptapeptide, is a metabolite of angiotensins I and II. Both angiotensin-(1-7), acting through its own receptor, and angiotensin II, acting on the AT_2 receptor, may counterbalance some of the effects of angiotensin II stimulating the AT_1 receptor.

The kidney is not the only organ which produces prorenin, and a receptor which binds renin and prorenin has been discovered. The physiological roles of the (pro)renin receptor are unknown, but high concentrations of prorenin predict microvascular complications of diabetes.

Inhibitors of the renin-angiotensin system

The therapeutic benefits of inhibiting the renin-angiotensin system are attributed primarily to reduced stimulation of the AT_1 receptor. This can be achieved by either reducing angiotensin II concentrations or blocking the AT_1 receptor, although other mechanisms may contribute (Table 1).

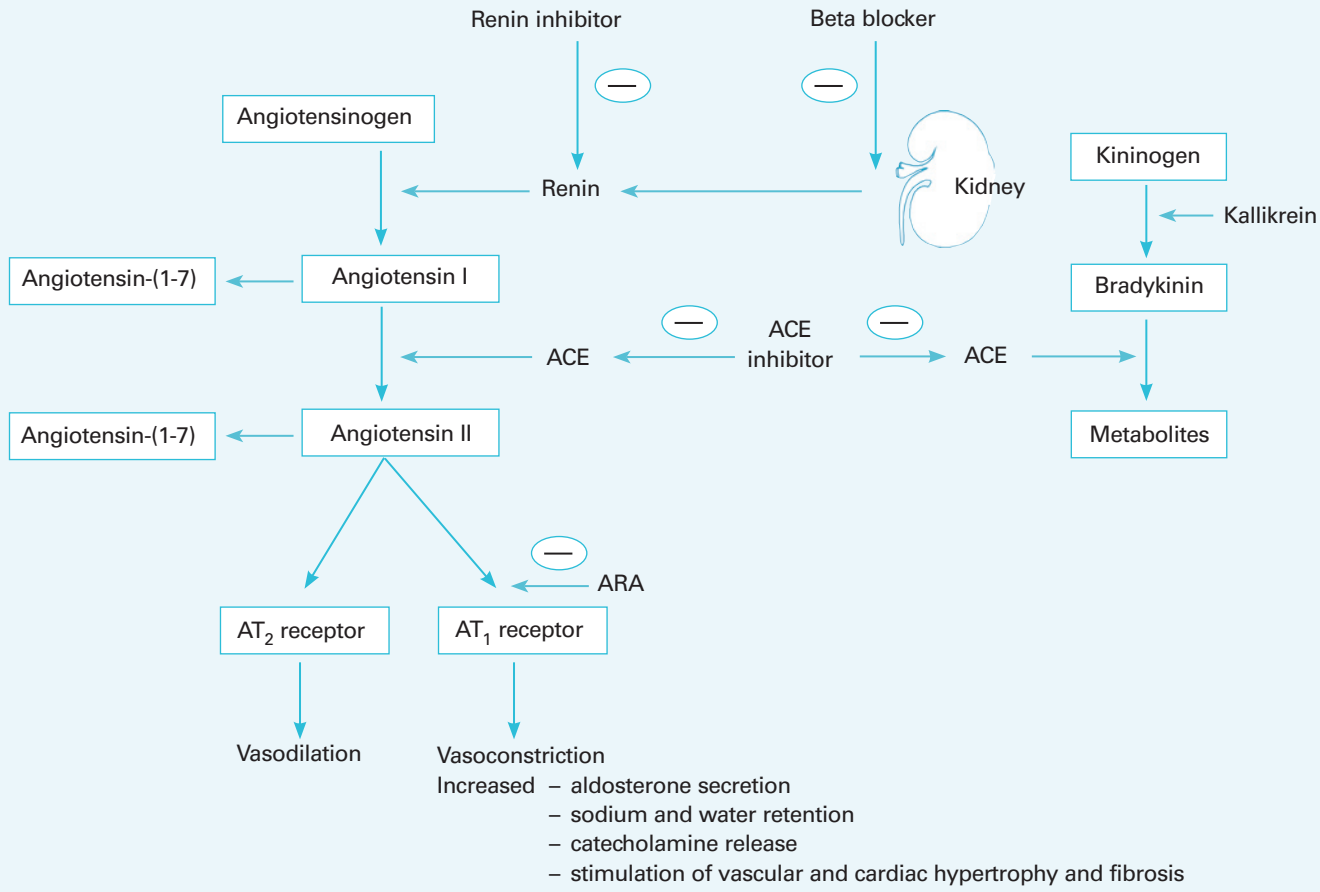
Beta blockers inhibit renin release from the kidney and were the original renin-angiotensin system inhibitors. Reduced renin release leads to reduced concentrations of angiotensin I and II, which may contribute to the benefits of beta blockade in heart failure.[1]

In contrast to beta blockers, ACE inhibitors, angiotensin receptor antagonists and renin inhibitors cause an increase in renin release. This is because by reducing AT_1 receptor stimulation they interrupt the negative feedback-mediated regulation of renin release. The combination of an ACE inhibitor, angiotensin receptor antagonist or renin inhibitor with another drug from these groups, or with a diuretic, markedly amplifies the increase in renin concentrations. The increase in renin concentrations may be as much as 100-fold, which then offsets the inhibition of the renin-angiotensin system by these antihypertensive drugs. This may attenuate any reduction in blood pressure.

ACE inhibitors, angiotensin receptor antagonists and renin inhibitors have different effects on the concentrations of angiotensin peptides and bradykinin (a vasodilator) (Table 1).

Fig. 1

Mechanisms of action of renin inhibitors



The renin-angiotensin system can be inhibited by angiotensin converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor antagonists (ARA), renin inhibitors and beta blockers. Also shown is the role of ACE in bradykinin metabolism. ACE also metabolises angiotensin-(1-7).

— inhibitory action

Table 1

Effects of renin-angiotensin system inhibitors on renin, angiotensin and bradykinin concentrations, and on AT_1 and AT_2 receptor stimulation

	Beta blocker	ACE inhibitor	ARA	Renin inhibitor
Renin concentrations	↓	↑	↑	↑
Renin activity	↓	↑	↑	↓
Angiotensin II concentrations	↓	↓	↑	↓
Angiotensin I concentrations	↓	↑	↑	↓
Angiotensin-(1-7) concentrations	↓	↑	→	↓
Bradykinin concentrations	?	↑	↑	?
AT_1 receptor stimulation	↓	↓	↓	↓
AT_2 receptor stimulation	↓	↓	↑	↓

ACE angiotensin converting enzyme
ARA angiotensin II type 1 receptor antagonist
↑ increase
↓ decrease
→ no change
? uncertain

Renin inhibitors reduce the concentrations of all angiotensin peptides, and their effect on bradykinin concentrations is under investigation.

ACE inhibitors block the conversion of angiotensin I to angiotensin II and the metabolism of angiotensin-(1-7). They reduce angiotensin II concentrations and increase the concentrations of angiotensin I and angiotensin-(1-7). In addition, because ACE contributes to bradykinin metabolism, ACE inhibitors increase bradykinin concentrations[2], which may contribute to the therapeutic benefits of ACE inhibition.

Angiotensin receptor antagonist therapies block AT_1, but not AT_2, receptors. This blockade leads to increased renin concentrations and consequently increased angiotensin II concentrations. This causes increased stimulation of the AT_2 receptor. Angiotensin receptor antagonists also increase bradykinin concentrations.[3] Stimulation of the AT_2 receptor and increased bradykinin concentrations may contribute to the clinical effects of angiotensin receptor antagonist therapy.

Renin inhibition differs from ACE inhibitor therapy because it reduces angiotensin I and angiotensin-(1-7) concentrations. It differs from angiotensin receptor antagonist therapy because there is reduced stimulation of the AT_2 receptor.

Clinical pharmacology of renin inhibitors

Several renin inhibitors were abandoned because of problems in development. Aliskiren is the first renin inhibitor for which we have extensive information about clinical pharmacology. Other renin inhibitors in clinical development are likely to have different pharmacologies.

Aliskiren is a competitive renin inhibitor which binds to the active site of the enzyme. It is a rather hydrophilic molecule with high aqueous solubility.[4] The distribution volume of intravenously administered aliskiren is 135 L in normal volunteers, indicating extensive tissue uptake of the drug.[5] The absorbed fraction of orally administered aliskiren is approximately 5%. This low oral bioavailability is compensated for by a long plasma half-life of 34–41 hours, and steady-state plasma aliskiren concentrations are achieved after 5–8 days of daily dosing.[6] Approximately 90% of the drug is excreted unchanged in the faeces.[7] The long plasma half-life and very low urinary excretion (< 1%)[6,7] suggest extensive binding of the drug to plasma proteins.[5]

Protein binding accounts for the discrepancy between the concentration of aliskiren required for 50% inhibition of pure renin and that for inhibition of renin in plasma. The concentration (IC_{50}) required was 0.6 nmol/L for pure renin versus 10–14 nmol/L for renin in human plasma.[5] This suggests that more than 90% of plasma aliskiren is bound to plasma proteins. Extensive binding of aliskiren to plasma proteins reduces the 'free' concentration of aliskiren available to inhibit renin. This, together with the several-fold increase in renin concentrations, accounts for the modest and transient reduction of plasma angiotensin concentrations during aliskiren therapy.[6] Long-term therapy failed to significantly reduce plasma aldosterone concentrations, although aliskiren did reduce urinary aldosterone excretion.[6]

Effect of renin inhibitors on renin measurement

Renin is measured in the investigation of hypertension. There are two methods – activity assays and immunoassays.[5] Activity assays measure angiotensin I produced by renin cleavage of plasma angiotensinogen. Immunoassays measure renin concentrations in plasma. Renin inhibitors have different effects on the two methods of renin measurement. Renin inhibitors reduce plasma renin activity, although the reduction in plasma renin activity is attenuated by the rise in renin concentrations. By contrast, renin immunoassay measures both active renin molecules and renin molecules that are inhibited by the renin inhibitor. Consequently, renin immunoassay shows increased renin concentrations because of the increased release of renin that occurs during treatment with a renin inhibitor.

Renin inhibitor therapy can interfere with renin activity assays and immunoassays in other ways. The renin activity assay may overestimate renin inhibition because displacement of the inhibitor from plasma proteins during the assay causes greater inhibition of renin activity *in vitro* than was present *in vivo*. During immunoassay, renin inhibitors may cause an artefactual increase in the amount of renin molecules measured as the drug binds to, and causes unfolding of, the prosegment of plasma prorenin. This unfolding causes prorenin to be recognised by the renin immunoassay.

The clinician who wishes to screen for primary aldosteronism or who wishes to investigate hypertensive conditions with high renin concentrations such as renal artery stenosis, in a patient receiving renin inhibitor therapy, needs to cease this therapy for at least two weeks. This allows for clearance of the renin inhibitor before samples are taken for measurement by either activity assay or immunoassay.

Conclusion

Renin inhibitors represent an alternative strategy for inhibiting the renin-angiotensin system. They have a mechanism of action different from that of ACE inhibitors and angiotensin receptor antagonists. Whether renin inhibitors offer therapeutic benefits beyond those provided by ACE inhibitor and angiotensin receptor antagonist therapies will require their direct comparison in clinical outcome studies.

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Dr Campbell holds a Senior Research Fellowship from the National Health and Medical Research Council (NHMRC), and has received research grants from the NHMRC and the National Heart Foundation. He has had research contracts with Solvay and Novartis and has been on an advisory board for Novartis.

Self-test questions

The following statements are either true or false (answers on page 143)

5. Renin inhibitors act at angiotensin II receptors.
6. Renin inhibitors increase the plasma concentration of renin.

Experimental and clinical pharmacology

Clinical implications of renin inhibitors

***Karen Duggan**, Chair, National Blood Pressure and Vascular Disease Advisory Committee, and formerly Director, Hypertension Service, Sydney South West Area Health Service*

Summary

Direct renin inhibition lowers blood pressure by an effective blockade of the renin-angiotensin system. Aliskiren is the first renin inhibitor to be marketed for the treatment of hypertension. At currently available doses it lowers blood pressure to a similar degree as other antihypertensive drugs. Used in combination with thiazides, angiotensin converting enzyme inhibitors, angiotensin receptor antagonists or calcium channel blockers, aliskiren has improved blood pressure control with no appreciable increase in adverse events. Aliskiren has an adverse effect profile comparable to placebo, but its long-term effects are unknown.

Key words: aliskiren, antihypertensives, hypertension.

(Aust Prescr 2009;32:135–8)

Introduction

Hypertension is one of the commonest reasons for general practitioner attendances. Less than 25% of those who are diagnosed attain their recommended blood pressure targets, while some studies place this figure as low as 7%. Although much of this failure to control blood pressure can be attributed to therapeutic inertia, the adverse effects of antihypertensive drugs also contribute. These adverse effects often limit the doses at which antihypertensive drugs can be used. This problem has prompted the ongoing search for more efficacious drugs with fewer adverse effects. One such group of drugs is the direct renin inhibitors which are currently undergoing clinical trials. The first of the drugs to be marketed is aliskiren.

Prorenin and the renin receptor

The discovery of the renin receptor provided a new role for renin, that of a profibrotic agent in its own right. It was subsequently found that the renin receptor also binds

prorenin so it is now termed the (pro)renin receptor. Prorenin is the inactive protein which is converted to renin. Clinically, the incidence of microvascular complications in diabetes is positively associated with prorenin concentrations.

When renin is bound to the (pro)renin receptor, conversion of angiotensinogen to angiotensin I is increased fivefold and there is activation of mitogen stimulated protein kinase which causes fibrosis. As the (pro)renin receptor is present on mesangial cells, renin may be implicated in accelerating glomerular damage and renal failure.

Direct renin inhibitors

Direct renin inhibition has long been a therapeutic aspiration because of the substrate specificity of renin compared with that of angiotensin converting enzyme (ACE). ACE has actions in addition to the formation of angiotensin II.

Early renin inhibitors were peptide analogues of angiotensinogen. They acted by competitively displacing angiotensinogen from the active site of renin. The first synthetic renin inhibitors, enalkiren and remikiren, had low efficacy and very low bioavailability. Further developments have addressed these deficits. Structural modifications have improved bioavailability and efficacy has been improved by making the inhibitory process non-competitive. Non-competitive inhibition means that in addition to stopping the conversion of angiotensinogen to angiotensin I, the stimulation of mitogen activated protein kinase is also prevented.

Aliskiren

While not yet marketed in Australia, aliskiren is available overseas in doses of 75 mg, 150 mg and 300 mg. Doses of 600 mg and 640 mg were also studied but have not been marketed, possibly as a consequence of the plateauing of the dose-response curve above 300 mg. The bioavailability is better than that of remikiren and enalkiren, but remains relatively low. Studies using radiolabelled aliskiren show that only 5% of an oral dose is absorbed. Absorption is rapid with maximal concentrations being reached after 1–3 hours.

In plasma, aliskiren circulates unchanged and is excreted via the biliary route with less than 1% being excreted in the urine. Aliskiren has a long half-life and is therefore suitable for once-daily dosing. The predicted long duration of action has been confirmed in a number of studies using ambulatory blood pressure monitoring.

Efficacy

In patients with hypertension, aliskiren lowered blood pressure more than placebo. The maximum effect was seen after a few weeks of treatment.

Trials of once-daily aliskiren have shown it to be as effective as angiotensin receptor antagonists and ACE inhibitors.

Reductions of the order of 11 mmHg in systolic and 9 mmHg in diastolic blood pressure have been found with aliskiren 150 mg once-daily. The 300 mg dose was associated with decreases of 16 mmHg in systolic and 12 mmHg in diastolic blood pressure. Head-to-head studies over periods ranging from 48 hours to eight weeks have demonstrated equivalent blood pressure reductions for aliskiren 150 mg and irbesartan 150 mg, valsartan 160 mg and enalapril 20 mg. Aliskiren 300 mg is similar to losartan 100 mg.

Many of the trials have focused on changes in the components of the renin-angiotensin system, for example, plasma renin activity is reduced by aliskiren, but increased by losartan. This escape in plasma renin activity and increase in plasma angiotensin II concentrations, which occurs with both angiotensin receptor antagonists and ACE inhibitors, is avoided during treatment with aliskiren. All trials have shown sustained reductions in plasma renin activity and angiotensin II concentrations with aliskiren therapy. It is hoped that this sustained reduction in plasma renin activity may provide better end-organ protection as fibrosis secondary to renin stimulation of mitogen activated protein kinase will be prevented.

Safety and tolerability

In all trials to date, the adverse effect profile of aliskiren in doses up to 300 mg per day has been comparable to that of placebo or of angiotensin receptor antagonists. The most commonly reported adverse effects were fatigue, headache, dizziness and diarrhoea. In contrast, the higher dose of 600 mg per day was associated with an increased incidence of diarrhoea (9.6% vs 1.2% placebo). Unlike the ACE inhibitors, aliskiren does not appear to be associated with cough or angioedema, and in combination with ACE inhibitors aliskiren has been reported to reduce cough.[1]

Although aliskiren is excreted via the biliary route, liver disease did not affect the pharmacokinetics after single dose administration. It has been suggested that dose reductions in patients with concomitant hepatic impairment will not be needed.[2]

As yet no clinical data are available to assess the effects of aliskiren on renal function and plasma potassium concentrations in patients with renal impairment, renal artery stenosis or heart failure. One study in diabetes mellitus found that rates of discontinuation for hyperkalaemia were similar to those of the ACE inhibitor ramipril.

Plasma renin concentrations increase as a consequence of treatment with aliskiren although plasma renin activity and angiotensin II concentrations remain low. Theoretically this could lead to rebound hypertension on sudden withdrawal, but in practice this has not occurred. Blood pressure rises gradually after aliskiren is withdrawn.

Aliskiren is contraindicated in pregnancy. It is unknown if the drug is excreted in breast milk.

Drug interactions

Aliskiren undergoes no significant metabolism, in particular it is not metabolised by cytochrome P450, and it has relatively low plasma protein binding. As a consequence aliskiren could be predicted to cause few adverse drug interactions. The limited number of pharmacokinetic studies have supported this prediction. In healthy volunteers aliskiren was found to have no detectable effect on the pharmacokinetics of warfarin, acenocoumarol, digoxin, lovastatin, atorvastatin, metformin, pioglitazone, fenofibrate, isosorbide-5-mononitrate, celecoxib or cimetidine, but did reduce frusemide concentrations.[3–6]

Patients who have been taking high doses of diuretics may become salt or volume depleted. This may cause symptomatic hypotension when they start taking aliskiren.

Combination therapy

In various studies aliskiren has been used in combination with thiazide diuretics (hydrochlorothiazide), ACE inhibitors (enalapril, ramipril), angiotensin receptor antagonists (irbesartan, losartan, valsartan), beta blockers (atenolol) and dihydropyridine calcium channel blockers (amlodipine). In each study there has been no increase in adverse outcomes compared with monotherapy, and in all instances blood pressure control has been improved. In particular, no significant changes in plasma potassium were seen in combination with ACE inhibitors or angiotensin receptor antagonists, although the patient groups studied and reported on to date have been those with essentially normal renal function. The numbers in these trials have been relatively small and predictions about preferred therapeutic combinations cannot be made.

Prevention of end-organ damage

Aliskiren is highly specific for human renin. This limits the usefulness of animal studies in predicting the protective effect of renin inhibitors on organs such as the heart and kidney. Studies in transgenic hypertensive rats which develop malignant hypertension, heart failure and renal failure show that aliskiren lowers blood pressure to that of non-transgenic rats as well as preventing heart and renal failure.

Small short-term clinical trials have addressed the effects of aliskiren on cardiac hypertrophy, brain natriuretic peptide and diabetic renal disease. ALLAY, which was powered only to show non-inferiority, demonstrated similar effects of aliskiren and losartan on left ventricular mass index at nine months.[7] ALOFT demonstrated a decrease in brain natriuretic peptide when aliskiren was added to therapy with an ACE inhibitor or angiotensin receptor antagonist, but the study was not powered to show a benefit.[8] AVOID showed a decrease in albuminuria when aliskiren was added to losartan compared with placebo.[9] Further insights will have to await completion of large postmarketing clinical trials.

Conclusion

Aliskiren is the first of the renin inhibitors to be approved in Australia. In short-term studies aliskiren has reduced blood pressure to a similar extent as other antihypertensive drugs. It has been well tolerated in these studies, but its long-term safety is unknown. The role of aliskiren in therapy will be unclear until clinical trials report on outcomes such as cardiovascular mortality.

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Conflict of interest: none declared

Medicinal mishap

Atropt – Azopt substitution

*Prepared by **Catherine Dunlop**, Ophthalmologist, Newcastle, NSW*

Case

A 50-year-old female fitness instructor was referred for management of raised intraocular pressures. Gonioscopy revealed bilateral narrow angles so she was treated with bilateral peripheral iridotomies.

Topical medication was also required to achieve the desired intraocular pressures. Latanoprost caused irritable red eyes, and beta blockers were avoided because of a history of asthma. The patient was able to tolerate brinzolamide, a carbonic anhydrase inhibitor, with the brand name of Azopt.

The patient filled the second month's prescription in the late afternoon at her busy local pharmacy. This computer-generated script was for Azopt 1% twice a day to both eyes.

Noticing a different red top on the bottle, the patient checked the name was correct on the pharmacy label, which obscured the manufacturer's label on the bottle. She thought the red-topped bottle must be a 'generic brand'. She used the drops in both eyes that night.

In the morning, the patient telephoned complaining of bilateral large pupils, glare intolerance while driving to work and blurred vision in both eyes. She also mentioned her new red topped bottle. On examination, her pupils were fixed and dilated. The optic discs showed no pulsation or haemorrhages, and her vision corrected to normal in both eyes. The intraocular pressures were within the normal range and the peripheral iridotomies were patent.

After the drops were stopped, the patient's main problem was glare while driving. She was able to work as there was little reading involved. After five days, the glare and blur had significantly improved.

Comment

The patient had instilled Atropt, a brand of atropine. Using this anticholinergic drug in a patient with narrow angles in the anterior chamber can precipitate angle-closure glaucoma. Atropine causes irreversible dilatation of the pupil. The dilated peripheral iris then blocks the angle, causing high intraocular pressure, ischaemia of the optic nerve head and possible blindness.

Narrow angles are more common in Asian eyes[1] and older Caucasian eyes, secondary to cataract development. There is an increasing risk of asymptomatic narrow angles being present in our population. Reversible dilating drops, such as tropicamide for fundoscopy, still need to be used cautiously in patients who have had laser treatment. Laser iridotomies may not remain patent.

Azopt and Atropt eye drops are unfortunately similar in name. I have several thoughts which may help avoid this potentially blinding mix-up:

1. These drops are stored alphabetically. Is it possible to move one to another area?
2. The trade names are made up. Similar names should be detected by regulatory authorities before marketing. (Horse-racing officials veto horses' names which are similar!)
3. Labels are stuck over the drug company label. Why can't the dispensed labels be transparent over the manufacturer's label and opaque for the instructions on the free tag? In this way, both patients and doctors can read the manufacturer's label.
4. Presbyopia is an annoying condition. It is the inability to see small print clearly. The potentially dangerous aspect of this condition is that initially the vision is clear, except in dim light and when the person is tired or stressed. At these times the vision is not really clear. In this example, z and tr are in the same part of the word and are the only different letters. The initial and last letters are the same. Health professionals may function accurately most of the time, but they should be aware that clear vision is essential all the time. Adequate lighting in the area the drugs are held would also help.

Conclusion

Health professionals can confuse drugs with similar brand names. This exposes patients to unnecessary harm. In the case of Atropt and Azopt the confusion can blind the patient. There is less chance of confusing the generic names, but if brand names are used the prescription should be clearly written and carefully read when dispensed.

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Comment by Ian D Coombes, Senior Pharmacist, Safe Medication Practice Unit, Queensland Health, Brisbane

Serious adverse events secondary to the error of selecting and dispensing a similar sounding drug are not uncommon. The author raises a number of logical and sensible suggestions on how to reduce the risk of this error recurring.

Strategies to reduce similar errors have been identified by medication safety bodies nationally and internationally:

- Generic prescribing reduces the risk of the similar sounding brand names. In this case brinzolamide would be less likely to be confused with atropine.

- Tall man letters are 'uppercase letters that are used within a drug name to highlight its primary dissimilarities with look-alike drug names', for example AZopt and ATRopt. Several studies have shown that using tall man lettering can make similar drug names easier to distinguish, and that fewer selection errors are made when tall man letters are used.[1]
- Bar coding of all medications. Pharmaceutical Defence Limited recommends the use of scanners in the dispensing process and it is either compulsory in Pharmacy Acts (in Victoria) or included in Regulations. The use of a computer to scan the medication bar code after selection to confirm that the product selected is what was intended, before completing the process and providing medication to patients, can significantly reduce the risk of drug selection errors.[2]
- Over-labelling of a manufacturer's label can be addressed by attaching the label so that it is only attached to a small area and 'flagged' or doubled over so that the dispenser and patient can still see the product's name.
- The role of the patient or carer as a 'defence' is critical and patients should be encouraged to ask and check whenever something is presented that does not look, sound or appear familiar.[3]

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Book review

Therapeutic Guidelines: Dermatology. Version 3.

Melbourne: Therapeutic Guidelines Limited; 2009. 335 pages. Price $39, students $30, plus postage. Also available in electronic formats as eTG complete.

***Subana Amirthanandan**, Academic General Practice Registrar, Department of General Practice, University of Sydney, Westmead Hospital, Sydney*

The third edition of Therapeutic Guidelines: Dermatology provides a valuable resource for general practitioners, general practice registrars and other doctors-in-training. The book is well organised into disease categories covered in succinct chapters, facilitating its use as a quick reference guide for busy medical professionals.

The chapter on 'getting to know your drugs' is a concise summary of the numerous available prescribed and over-the-counter medicines used in current practice. Helpfully, it outlines the most suitable therapeutic preparation to use (for instance ointments, gels, lotions) for a particular skin disease.

The skin disorders commonly encountered in practice by the target medical audience are covered in thorough detail. The chapters on acne, psoriasis, dermatitis, hair disorders and nail disorders comprise stepwise treatment plans based on best practice guidelines that are easy to follow, while also providing an appropriate refresher summary on pathogenesis and classification. In keeping with the times, a chapter is dedicated to the ever evolving discipline of cosmetic dermatology, delivering relevant insights into the therapeutic options available in this field.

A limitation of the book is the absence of visual images. Dermatology is to a considerable extent a visual science and accordingly, the inclusion of a set of images to illustrate a number of the conditions would have been useful. Although the guidelines do not seek to fill the role of a dermatological atlas, visual aide memoires for less commonly encountered, unusual or frequently misdiagnosed disorders would have been a beneficial addition. The chapter on dermatological emergencies, blistering disorders and connective tissue disorders in particular, could have benefited from such a visual approach.

Overall, the book is a worthy addition to the therapeutic guidelines library. It is sufficiently detailed and offers a methodical approach for the management of dermatological disorders. I would recommend it as a valuable resource to the readers of *Australian Prescriber*.

Medicinal mishap

Possible acute hepatotoxicity from oral clindamycin

Prepared by Sanjaya Senanayake, Infectious Diseases Specialist, The Canberra Hospital

Case

A 52-year-old woman presented feeling giddy and generally unwell. She complained of episodic upper abdominal pain and headaches.

The patient had a past history of pulmonary embolism and was taking warfarin. She was also taking phenytoin to prevent seizures and long-term amoxycillin for cerebral abscesses. This infection had been slow to resolve so 36 hours before her presentation, clindamycin 450 mg three times daily had been added to her treatment.

Physical examination was unremarkable and her warfarin and phenytoin concentrations were in the therapeutic range. The woman's liver function had been normal before starting clindamycin but was now abnormal:

- alanine aminotransferase 340 U/L (normal range 5–40 U/L)
- aspartate aminotransferase 855 U/L (normal range 5–40 U/L)
- gamma-glutamyl transferase 524 U/L (normal range 12–43 U/L)
- alkaline phosphatase 159 U/L (normal range 30–150 U/L)
- lactate dehydrogenase 714 U/L (normal range 100–230 U/L).

The patient's bilirubin, albumin and alpha-fetoprotein concentrations were normal. Serology for hepatitis B and hepatitis C infection was negative. Apart from a previous cholecystectomy, the liver and biliary tree were normal on a CT scan.

Clindamycin was ceased, but no other changes were made to her drugs. Three days after stopping clindamycin, her symptoms had resolved and her liver function tests were almost back to baseline values.

Comment

Clindamycin is a lincosamide antibiotic with antibacterial activity against anaerobes, protozoa and Gram-positive bacteria, including community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). Oral doses have a high bioavailability. Probably for these reasons, clindamycin is widely used. Most clinicians are aware that up to 20% of patients taking clindamycin will experience diarrhoea[1], however hepatotoxicity is less well recognised. Reversible subclinical transaminitis is not uncommon with parenteral clindamycin, however acute symptomatic hepatotoxicity with oral clindamycin is rare. Only one case has been published recently[2], the remaining few coming from the 1970s.[3,4] The recent case occurred with low-dose oral clindamycin while the earlier cases involved parenteral clindamycin. Hepatotoxicity resolved in all cases after stopping clindamycin, but unlike our patient the resolution took several weeks. Liver biopsies showed mixed hepatocellular and portal damage.[2,3] The hepatotoxicity is probably idiosyncratic since patients with underlying liver disease who were given clindamycin had no exacerbation of liver dysfunction.[5]

In summary, acute hepatotoxicity is a rare complication of clindamycin that may be seen more often with its increasing use. Clinicians should have a low threshold for checking liver function in their patients, particularly if they become unwell while taking clindamycin.

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New drugs

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

Arsenic trioxide

Phenasen (Phebra)

10 mL vials containing 10 mg/10 mL

Approved indication: acute promyelocytic leukaemia

Australian Medicines Handbook Appendix A

Acute promyelocytic leukaemia is a subtype of acute myeloid leukaemia. There is a translocation of chromosomes 15 and 17 resulting in the expression of abnormal proteins. It is currently treated with regimens containing all-*trans*-retinoic acid. The persistence of an abnormal transcript, promyelocytic leukaemia-retinoic acid receptor-alfa (PML-RARα), after chemotherapy predicts relapse. Relapses can be managed with chemotherapy, but the toxicity is high so alternatives are needed.

The active ingredient in a traditional Chinese medicine used to treat leukaemia was found to be arsenic trioxide. Chinese researchers therefore tried a purified solution of arsenic trioxide in the treatment of relapsed acute promyelocytic leukaemia. The percentage of blast cells in the bone marrow was reduced to less than 5% in 14 of 15 patients. These complete responses were obtained after a median of 38 days treatment with arsenic trioxide.[1]

An American study then tried arsenic trioxide in 12 patients with relapsed disease. Although one patient died the others all had a complete response after a median of 33 days. In eight patients PML-RARα was no longer present after two courses of treatment.[2]

A multicentre study enrolled 40 patients during their first or second relapse. There was a complete response, confirmed by bone marrow examination in 34 patients. In 25 patients the PML-RARα transcript was no longer present after treatment. Overall survival at 18 months was estimated to be 66%.[3]

The recommended regimen of arsenic trioxide for relapsed disease is a daily intravenous infusion until there is bone marrow remission. Three to six weeks after induction therapy is completed, 25 doses of arsenic trioxide are given in a consolidation regimen which can last for up to five weeks.

The infusion is given over 1–2 hours. Pharmacokinetic information is limited, but arsenic trioxide is thought to be metabolised in the liver and excreted in the urine.

As the clinical trials only involved small numbers of patients, safety data are limited. All patients will experience some drug-related adverse events. Common complaints are oedema, fever, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Hypokalaemia, hyperglycaemia and hypocalcaemia are also frequent. In the multicentre study of arsenic trioxide, 25% of the patients developed symptoms suggestive of acute promyelocytic leukaemia differentiation syndrome. This presents with fever, weight gain, dyspnoea, pulmonary infiltration and pleural or pericardial effusions. It requires urgent treatment with high doses of intravenous steroids. Arsenic prolongs the QT_c interval on the ECG so patients have an increased risk of arrhythmia. It is therefore important to monitor the patients for electrolyte abnormalities which may contribute to potentially fatal arrhythmias.

Arsenic is a carcinogen. It also suppresses the production of normal blood cells so blood counts and coagulation should be checked twice a week.

Patients with relapsed promyelocytic leukaemia are likely to respond to arsenic trioxide. If remission has not occurred within 60 days the patient is unlikely to respond. The published clinical trials have not compared arsenic trioxide with other approaches to treating relapsed disease. The optimum use of arsenic trioxide with other treatments needs further study to see if the high response rates translate into improved long-term survival.

T manufacturer provided only the product information

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Etoricoxib

Arcoxia (Merck Sharp & Dohme)

30 mg, 60 mg and 120 mg tablets

Approved indications: analgesia, gout, osteoarthritis

Australian Medicines Handbook section 15.1.1

Etoricoxib is a non-steroidal anti-inflammatory drug which mainly inhibits the cyclo-oxygenase-2 enzyme (see 'COX-2

inhibitors', Aust Prescr 2000;23:30–2). By reducing the synthesis of inflammatory mediators, etoricoxib can modify the pain response.

Acute gout presents with pain and inflammation. Etoricoxib has therefore been studied in the early treatment of acute gout in a double-blind trial involving 150 patients. The patients were randomised to take indomethacin 50 mg three times a day or a once-daily dose of etoricoxib 120 mg for eight days. Both drugs reduced pain and swelling with no significant differences in efficacy. Overall, there was no significant difference in adverse events, but etoricoxib caused fewer drug-related adverse effects.[1]

Etoricoxib is also approved for use in primary dysmenorrhoea and postoperative dental pain. A single dose of 120 mg provides similar analgesia to ibuprofen 400 mg and naproxen 550 mg.

The early studies of etoricoxib in osteoarthritis used a dose of 60 mg daily. This dose was found to have the maximum efficacy in a six-week dose-ranging trial involving 617 patients with osteoarthritis of the knee.[2] In a 12-week study of 501 patients with osteoarthritis of the hip or knee, etoricoxib 60 mg reduced pain significantly more than placebo. Its efficacy was similar to that of naproxen 500 mg twice daily.[3]

Two longer-term studies also compared etoricoxib 60 mg daily with naproxen 500 mg twice daily. Almost 1000 patients were randomised to take etoricoxib, naproxen or a placebo for 12 weeks. This was followed by a 40-week comparison of etoricoxib and naproxen and then an 86-week extension study. The active drugs were significantly better than placebo in the first 12 weeks. After 52 weeks there was no significant difference between etoricoxib and naproxen. The reduction in pain was maintained over the whole 138 weeks of the studies.[4]

Following the withdrawal of rofecoxib in 2004, there has been increased concern about the adverse effects of COX-2 inhibitors. Although 60 mg is a more effective dose[2], the recommended dose of etoricoxib for osteoarthritis has been reduced to 30 mg daily. This dose was used in a trial which compared the drug with placebo or ibuprofen 800 mg three times daily for 12 weeks. The 528 patients in the study had osteoarthritis of the knee or hip. The active drugs had comparable efficacy, but were significantly better than placebo. Most of the benefit was achieved by the second week of treatment.[5]

Although COX-2 inhibitors were expected to have fewer serious gastrointestinal complications than other non-steroidal anti-inflammatory drugs, abdominal pain can be a reason for people stopping treatment with etoricoxib. After 40 weeks of treatment, 8.5% of the patients discontinued etoricoxib 60 mg because of drug-related adverse events (11.4% of the naproxen group discontinued). Common adverse effects included dyspepsia, epigastric discomfort, heartburn and hypertension.[4] In the study of etoricoxib 30 mg, only 3.3% of the patients discontinued because of drug-related adverse events, compared with 9% of the ibuprofen group.[5]

Data from long-term comparisons of etoricoxib and diclofenac have been used to investigate cardiovascular and gastrointestinal safety. These studies involved more than 34 000 patients over the age of 50 years with rheumatoid arthritis or osteoarthritis. They took diclofenac 75 mg twice daily or 50 mg three times a day, or etoricoxib 60 mg or 90 mg daily. The mean duration of treatment was approximately 18 months. Thrombotic events, such as myocardial infarction and stroke, affected 468 of the patients taking diclofenac and 495 of those taking etoricoxib. This difference is not statistically significant.[6] Upper gastrointestinal events occurred in 246 patients taking diclofenac and in 176 taking etoricoxib. This statistically significant advantage for etoricoxib was mainly accounted for by uncomplicated ulcers. Etoricoxib did not significantly reduce the rate of complications such as perforation and bleeding.[7]

Active peptic ulceration is a contraindication to etoricoxib as are vascular disease, heart failure and uncontrolled hypertension. Treatment should be stopped if hepatic dysfunction develops.

Etoricoxib is well absorbed and does not have to be taken with food. It is almost completely metabolised with most of the metabolites appearing in the urine. The long half-life enables once-daily dosing. Etoricoxib is contraindicated in patients with severe renal or hepatic impairment.

Caution is also advised if etoricoxib is considered for patients who are also taking drugs that are known to potentially interact with non-steroidal anti-inflammatory drugs. These drugs include ACE inhibitors, diuretics, oestrogens and lithium. Etoricoxib may also increase the effect of warfarin.

If etoricoxib is used for acute pain, the daily dose should not exceed 120 mg. This can only be used for a maximum of eight days.

Australian guidelines do not support long-term use of non-steroidal anti-inflammatory drugs or COX-2 inhibitors in osteoarthritis. Etoricoxib should be used at the lowest dose for the shortest possible time. If a patient's arthritic pain does not improve within a few weeks, the drug should be stopped. Although etoricoxib has been studied in rheumatoid arthritis, it is not approved for this condition.

T manufacturer provided only the product information

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Correction

New drugs, Aust Prescr 2009;32:112-5.
The brand name for eculizumab is Soliris.

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

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

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

Answers to self-test questions

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

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Typesetting
Barnes Desktopping and Design

Printed in Australia by
Blue Star Print Group, ACT
22 Pirie Street FYSHWICK ACT 2609

Published by
National Prescribing Service Limited (NPS), an independent organisation for Quality Use of Medicines funded by the Australian Government Department of Health and Ageing

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Print Post Approved PP349181/00151 • ISSN 0312-8008