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Editorial

Quality use of generic medicines

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Key words: drug industry, drug regulation, National Medicines Policy, consumers.

(Aust Prescr 2004;27:80–1)

The use of generic drugs has been steadily increasing internationally as a result of economic pressure on drug budgets.[1] Generic drugs provide the opportunity for major savings in healthcare expenditure since they may be substantially lower in price than the innovator brands. Prescribing drugs by their generic name and requesting pharmacists to dispense generic drugs are frequently suggested means for lowering the costs of health care. The practice of generic substitution is strongly supported by health authorities in many countries including Australia.[2]

Australia's National Medicines Policy aims to 'meet medication and related needs, so that both optimal health outcomes and economic objectives are achieved for Australians'.[3] In response to the rising cost of the Pharmaceutical Benefits Scheme (PBS), the Australian Government has introduced policies to encourage the use of generic drugs. Probably the most significant of these to date have been the Brand Premium Policy (1990) and the Brand Substitution Policy (1994).[4] Under the Brand Premium Policy, pharmaceutical manufacturers were allowed to set their own prices for the different brands of the same medicine. The PBS subsidy was determined by the lowest priced brand, the so-called 'benchmark brand'. Patients must pay the difference between the price of the dispensed drug and the benchmark brand. The Brand Substitution Policy allows pharmacists to substitute bioequivalent generic medicines without seeking advice from prescribers, unless otherwise indicated on the prescription.

Changes to prescribing software will further encourage the use of generics. Systems must now default to prescriptions allowing brand substitution. Doctors will still be able to select brand name drugs, but they will have to positively select for disallowing brand substitution. The government estimates that the change will save the government-funded PBS A$111 million over four years.[5] However, the potential for savings to the government through generic prescribing is limited because the government subsidy is linked to the 'benchmark' price.

The Australian Government has regulations to assure the quality, safety and efficacy of generic medicines. These include compliance with good manufacturing practice and the requirement that generic products must have demonstrated bioequivalence with the innovator brand, or the Australian market leader, before they can be listed on the PBS.[6]

The quality use of medicines is central to the National Medicines Policy. It requires the judicious selection of management options, the appropriate choice of necessary medicines, and their safe and effective use. Unfortunately, the introduction of generic medicines into the Australian marketplace has the potential for some negative effects on the quality use of medicines.

The main area of concern is the many 'generic brands' that are available through the PBS. Pharmaceutical companies are permitted to assign brand names to their products in Australia so there is the possibility for consumers to be confused if they receive different brand names of the same drug. A common example of this is ranitidine tablets where there are currently

In this issue…

With the Olympics approaching it is timely to revisit the issue of drugs in sport. Peter Fricker therefore guides us through the latest anti-doping code.

While diuretics can cause problems for athletes, they are still an important treatment for hypertension. Fiona Turnbull and Bruce Neal discuss the evidence that these drugs are as effective as ACE inhibitors.

Like hypertension, type 2 diabetes is a common problem in Australia. Almost all patients with type 2 diabetes will eventually require insulin, so Jencia Wong and Dennis Yue have provided practical advice on how to start insulin.

The use of warfarin is also increasing in the community. While there are benefits, Marija Borosak, Shin Choo and Alison Street remind us that these must be weighed against anticoagulation's adverse effects.

Warfarin is one of the drugs which does not have interchangeable brands. Azmi Hassali, Kay Stewart and David Kong discuss some of the other issues surrounding brand substitution and the use of generic drugs.

Fig.1

Some of the brands of ranitidine 150 mg available on the Pharmaceutical Benefits Scheme

Key

1 Ranihexal (Hexal)
2 Ranitidine BC (Biochemie)
3 Rani2 (Alphapharm)
4 Ranoxyl (Douglas)
5 Ranitidine (GenRx)
6 Zantac (GlaxoSmithKline)
7 Ausran (Sigma)

nine brands available (Fig.1). In some cases, the appearance of the drugs differs, adding to the problem of different brand names for the same drugs. Confusion could be greatly reduced if generic names of the drugs were required to be more prominent on the label than the 'brand' names.

From the consumers' point of view, the main advantage of generic drugs is that they have the opportunity to choose cheaper brands with savings to themselves as individuals and as taxpayers. This argument is not always as compelling as it may seem, as consumers may have beliefs or experiences that assume higher priority in their decision-making. Some of the quotes we have obtained from our own research into patients' perceptions of generic medicines show that factors other than money alone influence consumer choice.

> 'Well, I believe in sticking to what you are used to, if it is doing its job … I know the doctor, I feel safe with my doctor.'

> 'Well, for a lot of people it is alright … I've got a sister who is on the generic brand and she doesn't have any side effects but I do, so I can't take them. It doesn't matter if my tablets are a few dollars dearer.'

To achieve optimal outcomes, consumers must not only receive appropriate treatment, but also have the knowledge and skills to use it to best effect. Health professionals have a vital role to play in promoting quality use of medicines through good treatment choices, good communication with consumers, and collaboration with each other. Explaining about low cost brands may help to reduce confusion. While healthcare professionals are ultimately responsible for implementing the best therapeutic options for their patients, consumers should be included in the decision-making so that their beliefs and wishes can be taken into consideration. The following quotes from the consumers in our study clearly illustrate that the consumers are keen to receive information from their healthcare providers about their medicines.

> 'I wouldn't just swap to a generic medicine without talking. I like to talk to my doctors and my pharmacist about it because I have got very complicated needs in terms of medication.'

> 'I'm a great believer in consumer participation because I believe that you get as much information (as you can) and get it from the appropriate people … I mean it is silly to go to a friend rather than my nephrologist. I consider all the information they are giving me and then balance it all to make a decision … hopefully an informed decision.'

Achievement of optimal health outcomes and economic objectives requires participation, not just regulation.

Acknowledgement

We wish to acknowledge all the consumers who participated in our qualitative research entitled 'Perceptions of generic medicines by consumers' which was conducted with the help of the Department of Pharmacy Practice, Victorian College of Pharmacy, Monash University, Melbourne and the Chronic Illness Alliance, Victorian Branch, in 2003.

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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.

Calcium

Editor, – I refer to the article 'Calcium supplementation: the bare bones' by J.D. Wark and C. Nowson (Aust Prescr 2003;26:126–7). I would like to ask on what information they base their assertion that calcium citrate is more expensive than calcium carbonate.

Calcium carbonate (Caltrate) and calcium citrate (Citracal) are both on the Pharmaceutical Benefits Scheme and their regulated price is identical.

These two products are largely prescribed on concession scripts for an identical cost, and are also regularly bought by consumers at an equal retail price of about $12.

How then, can calcium citrate be more expensive?

David Haworth
Pharmacist
Kirrawee, NSW

Professor J. Wark, one of the authors of the article, comments:

It is true that the price of a 120-tablet pack of Citracal is the same as a 120-tablet pack of Caltrate. However, the former contains 250 mg elemental calcium while the latter contains 600 mg. This makes Citracal a substantially more expensive source of calcium, even if one accepts that it has somewhat better oral bioavailability than Caltrate (which is not a consistent finding in the literature). It is worth emphasising that consumers and prescribing doctors alike should check the elemental calcium content of supplements.

Off-label prescribing

Editor, – Craig Patterson and Brian Foster make some strong statements in Letters to the Editor (Aust Prescr 2003;26:51–2). Will pharmacists also be 'hung out to dry' and 'subjected to a compensation claim' for off-label dispensing?

I think it would be timely for *Australian Prescriber* to help clarify the situation with regard to off-label prescribing. The Australian Medicines Handbook uses the terms 'marketed indications' and 'accepted indications'. Do the professional indemnity organisations have an opinion here? Has the Therapeutic Goods Administration had any more recent thoughts than the (1992) reference quoted by Craig Patterson?

If I prescribe sodium valproate for prevention of migraine when other treatment has failed, use pethidine in the epidural space for obstetric analgesia or give ketorolac intravenously for post-operative pain control, where do I stand?

A survey in Sydney showed 26% of prescription medicines were used for off-label indications.[1] Other studies have shown that in the USA 9.2% of 500 medicines were for off-label use[2], in one UK specialist palliative care unit 25% of prescriptions affecting 66% of their patients were for off-label use, and in European audits between 39 and 55% of prescriptions were for off-label use.[3]

It would seem that Craig Patterson's washing line will need many clothes pegs!

The issue of using the Pharmaceutical Benefits Scheme to supply a drug outside the restrictions for authority prescribing is much clearer: it is a breach of the National Health Act. It would however be salutary for health professionals to know what penalties the Act provides for even when the prescription is written in good faith.

Roger Goucke
Head, Department of Pain Management
Sir Charles Gairdner Hospital
Perth

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3. The use of drugs beyond licence in palliative care and pain management. A position statement prepared on behalf of the Association for Palliative Medicine and the Pain Society. 2002. http://www.painsociety.org/pdf/drugs_doc.pdf [cited 2004 July 1]

Mr C. Patterson, one of the correspondents, comments:

Dr Goucke is right to highlight that off-label prescribing occurs extensively and, in certain populations such as children, this is through necessity. I am uncertain, however, that the potential increase in professional liability is widely recognised. Off-label prescribing would often be defended by the body of published evidence of an effect. My main point is that, in the gabapentin example, the pharmaceutical company was the voice goading this off-label prescribing, and doctors displayed good faith that what they were being told was true and accurate. Should the doctor find themselves in a legal dispute, that same voice would be strangely silent when it comes to supporting off-label use.

Management of acute gout

Editor, – In his excellent article 'Management of acute gout' (Aust Prescr 2004;27:10–3) Dr McGill mentioned that 'the acute attack is also an opportunity to assess and manage associated disorders such as obesity, excessive alcohol consumption, hypertension, hyperlipidaemia and renal insufficiency'. He went on to say that 'controlling these problems may prove to be of greater long-term benefit to the patient than controlling their hyperuricaemia', but he does not mention what part a diet low in purines plays, if any, in the long-term management of gout.

Charles Dickens' Mr Pickwick suffered from gout, which was portrayed as being related to his alcohol intake, and this remains the perception of many of our patients.

John A. Comerford
General practitioner
Newstead, Qld

Dr Neil W. McGill, the author of the article, comments:

Although patients may attribute acute attacks to dietary indiscretions, I am not aware of any study that has shown that a particular dietary event increases the likelihood of a gouty attack. With respect to the influence of diet on the chronic management of gout, hyperuricaemia is clearly associated with alcohol intake and obesity (3.4% of people below the 20th percentile and 11.4% of people above the 80th percentile for body weight are hyperuricaemic).

The effect of purines in the diet is complex and poorly understood. A prospective study of 47 150 men showed an increased risk of gout in association with the intake of meat and seafood, and a reduced risk with low-fat dairy foods. Total protein, animal protein and purine-rich vegetable intake were not associated with the risk of gout.[1] It would therefore appear sensible to recommend correction of obesity, a low alcohol intake, avoidance of high intakes of meat and seafood, and plenty of low-fat dairy products. However, it should be remembered that dietary intervention usually reduces the uric acid by a maximum of 15%, is often difficult to maintain and has never been prospectively shown to reduce the incidence of gout.

For patients with proven recurrent gout, especially those with tophi, erosions, persistent symptoms between attacks and renal impairment, encouraging lifelong compliance with hypouricaemic drug therapy is the most effective means of maintaining a healthy uric acid concentration and preventing disease progression.

Reference

1. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med 2004;350:1093-103.

Nitrofurantoin

Editor, –There has been some adverse publicity regarding the long-term use of nitrofurantoin. Some of my patients who require long-term prophylactic antibiotics, usually for urinary tract infection, are asking to come off this medication.

I find nitrofurantoin is a very useful antibiotic which is readily available (30 tablets with one repeat helps to ensure that patients do actually stay on it!). Nitrofurantoin is rapidly absorbed and rapidly excreted with high urinary concentrations and has good activity against Gram negative bacteria. It has a very low incidence of fungal problems especially vaginal candidiasis and a low incidence of gastrointestinal adverse effects.

It would be useful to know how these benefits can be weighed up against the risk of harm.

Tim Skyring
Urological surgeon
Figtree, NSW

Professor J. Turnidge, Infectious disease physician, comments:

Dr Skyring's letter highlights the dilemma faced by many practising clinicians: do I change my practice because of increasing reports of adverse reactions when the drug has a number of advantages?

He points out the significant benefits of nitrofurantoin and is rightly concerned that patients have been put off by recent publicity. For nitrofurantoin, the rates of adverse reactions are low, but some of these reactions are troublesome.

The reaction of most recent concern is peripheral neuropathy, although this problem has been known for many years. It is most likely in the elderly and others with reduced renal function. Of equal concern is immune-mediated hepatotoxicity, which most often resolves after cessation, but which can be fulminant. A third problem is pulmonary toxicity that can mimic pulmonary fibrosis.[1]

There are other serious reactions to nitrofurantoin, but the question remains as to whether they are more frequent than with other drugs used for prophylaxis against urinary tract infections, such as trimethoprim with or without sulfamethoxazole. Without a clear picture of the comparative toxicities of drugs taken over the longer term, it is not possible to make sensible recommendations about which drugs are favoured. The best way of dealing with the dilemma is to discuss the benefits and harms of **all** options with the patient. Dr Skyring should note that nitrofurantoin is still recommended in the current version of Therapeutic Guidelines: Antibiotic.

Reference

1. Pulmonary toxicity with long term nitrofurantoin. Aust Adv Drug React Bull 2004;23:15.

The anti-doping code in sport – update for 2004

Peter A. Fricker, Assistant Director (Technical Direction), Australian Institute of Sport, Canberra

Summary

The World Anti-Doping Agency has assumed responsibility for international doping control from the International Olympic Committee. It has revised, reformed and now presented a new World Anti-Doping Code, which became globally effective in January 2004. The World Anti-Doping Code contains the List of Prohibited Substances and Prohibited Methods. This list differs from its predecessor. Caffeine has been removed from the banned list, but a new category of 'specified substances' which may produce inadvertent positive tests has been added.

Key words: doping, anabolic steroids, stimulants, caffeine.

(Aust Prescr 2004:27:84–7)

Introduction

Over recent years, the World Anti-Doping Agency (WADA)* has worked with the International Olympic Committee (through its member national organisations) to produce a new World Anti-Doping Code (WADC).[1] This replaces previous lists of prohibited substances and methods.[2] The new Code has a number of implications for athletes, coaches and medical practitioners. Athletes are responsible for making sure that medications they take comply with the Code.

Prohibited substances

The rationale for determining whether or not a substance should be placed on the prohibited list is based on three criteria:

- potential to enhance sport performance
- actual or potential risk to health
- violation of the spirit of sport.

If two of these criteria are met, the substance is considered for inclusion on the prohibited list (see Box 1).

Anabolic agents

Of recent notoriety is tetrahydrogestrinone, a synthetic derivative, which has produced a number of positive doping tests among sprint and power athletes. Tetrahydrogestrinone was apparently provided to athletes as a supplement, and bears a similar history in this respect to nandrolone, which has often been identified in positive urine samples.

A positive doping test for testosterone still depends upon finding a urinary testosterone/epitestosterone ratio greater than six. Should an endogenous anabolic steroid be found in such a circumstance, further investigation is obligatory in order to determine whether the ratio is due to a physiological or pathological condition.

Other anabolic agents on the prohibited list include the beta agonists clenbuterol and zeranol.

Peptide hormones

The following peptide hormones are all prohibited, as are their mimetics and releasing factors (releasing hormones):

- erythropoietin
- growth hormone (hGH and insulin-like growth factor (IGF-1))
- chorionic gonadotrophin (HCG) – prohibited in males only
- pituitary and synthetic gonadotrophins (LH) – prohibited in males only
- insulin
- corticotrophins.

Beta agonists

All beta agonists (including their D- and L- isomers) are prohibited **except**:

- formoterol
- salbutamol
- salmeterol
- terbutaline.

Box 1

Examples of prohibited substances

Stimulants (but pseudoephedrine and caffeine have been removed from the list)

Narcotics

Cannabinoids

Anabolic agents

Peptide hormones

Beta agonists

Agents with anti-oestrogenic activity

Masking agents

Glucocorticosteroids

* An agency funded by the International Olympic Committee and, as at March 2004, by over 150 national governments.

The exempted drugs are only permitted by inhalation to prevent and/or treat asthma and exercise-induced bronchoconstriction. A medical notification is required for the athlete to compete. If the concentration of salbutamol in urine exceeds 1000 ng/mL, it will be considered an adverse analytical finding unless the athlete proves that the abnormal result was the consequence of the therapeutic use of inhaled salbutamol.

Masking agents

These agents can conceal the use of other substances and include diuretics, epitestosterone, probenecid and the plasma expanders, such as dextran and hydroxyethyl starch (see Box 2).

Glucocorticosteroids

Corticosteroids are prohibited when given orally, rectally or by intravenous or intramuscular administration. A medical notification is necessary for all topical applications, inhalational use, or intralesional or intra-articular injection.

Prohibited methods

The criteria for determining if a method of doping should be banned are the same as those for determining prohibited substances.

Enhancement of oxygen transfer

This includes blood doping and the use of products that enhance the uptake, transport and delivery of oxygen. Examples include erythropoietin, modified haemoglobin products, perfluorochemicals, and efaproxiral (RSR13).

Pharmacological, chemical and physical manipulation

These techniques are intended to alter the integrity and validity of specimens collected in doping control tests. They include catheterisation of the bladder, urine substitution and/or tampering, inhibition of renal excretion and alterations of testosterone and epitestosterone concentrations.

Gene doping

This is defined as the non-therapeutic use of genes, genetic elements and/or cells that have the capacity to enhance athletic performance. (The Code anticipates the possible future use of genetic engineering in sport.)

Box 2

Masking agents

Diuretics – promote excretion of urine

Epitestosterone – used to correct an altered testosterone/epitestosterone ratio

Probenecid – blocks excretion of anabolic agents

Plasma expanders – alter red cell parameters such as haemoglobin and haematocrit (used in the detection of erythropoietin abuse)

Substances and methods prohibited in and out of competition

Prohibited substances include:

- anabolic agents
- peptide hormones
- beta agonists (clenbuterol, and salbutamol >1000 ng/mL in urine)
- anti-oestrogenic agents
- masking agents.

Prohibited methods include:

- enhancement of oxygen transfer
- pharmacological, chemical and physical manipulation
- gene doping.

Substances prohibited in particular sports

Under the new WADA Code, particular sports have identified particular substances they wish to prohibit only during competition periods. These substances include:

- alcohol
- beta blockers
- diuretics.

Specified substances

The prohibited list identifies substances which are particularly susceptible to unintentional violations of anti-doping rules because of their general availability in medicinal products, or because they are less likely to be successfully abused as doping agents. Consequently, a doping violation involving these specified substances **may** result in a reduced sanction (penalty) as noted in the WADA Code, provided the 'athlete can establish that the use of such a specified substance was not intended to enhance sport performance'.

Specified substances are:

- stimulants (ephedrine, L-methylamphetamine, methylephedrine)
- cannabinoids
- inhaled beta agonists (except clenbuterol)
- diuretics (except where prohibited in weight-classified sports and sports in which weight loss can enhance performance, such as ski jumping)
- glucocorticosteroids
- masking agents – probenecid
- beta blockers
- alcohol.

Caffeine

One major change from the previous regulations is the removal of caffeine from the banned list. A review of caffeine has deemed it to be performance enhancing at concentrations lower than those required to produce a positive test (urinary levels of 12 mg/L).[3]

As caffeine is widely available in a variety of foods and drinks it is easily used as a performance enhancing agent. Although caffeine will be monitored at competitions through urine testing, no action will be taken against athletes who show caffeine in their urine.

Medical notification

Medical notification relates to the use of substances which are not on the banned list, but are permitted for use under certain specified conditions. Notifiable substances are the beta agonists, formoterol, salbutamol, salmeterol and terbutaline, which are permitted for the treatment of asthma and exercise-induced bronchospasm.

Notification must be made by a medical practitioner on the athlete's behalf specifying the substance, the dosage, duration of treatment, and the diagnosis of asthma or exercise-induced bronchospasm. The athlete's national sporting organisation is to be notified well in advance of any competition (where the athlete may be tested by doping control). The onus is on the athlete to ensure that documentation is appropriate and timely.

Authorities should also be notified about the use of glucocorticosteroids when used by inhalation (for the treatment of asthma and/or allergic rhinitis), by injection (into joints, bursae or lesions – but not intravenously or by intramuscular injection), or as topical applications in the ear, the eye or on the skin. Notification is the responsibility of the athlete, and the sporting organisation must be notified of the details of the diagnosis, substance used, dosage, and duration of treatment.

Therapeutic use exemption

While medical notification is for substances permitted under certain conditions, therapeutic use exemption is for the therapeutic use of a substance or method which is on the prohibited list. In Australia, the Australian Sports Drug Medical Advisory Committee (ASDMAC) is the body which grants exemptions.

Should an athlete require treatment with a prohibited substance or prohibited method, a medical practitioner may apply to ASDMAC by way of its web site or by mail for a therapeutic use exemption (see Further information). The ASDMAC form specifies the relevant details which need to be provided – including athlete details, the medical condition(s) (with supporting evidence), treatment(s) being recommended (with dosages and duration of treatment) and other details as necessary. The decision to grant an exemption depends upon:

- the capacity of the treatment (substance or method) to enhance performance 'other than that which might be anticipated by a return to a state of normal health following the treatment of a legitimate medical condition'
- the lack of reasonable therapeutic alternatives
- the risk to the health of the athlete if the substance or method were to be withheld in the course of treatment.

In addition, the need for use of the substance or method cannot be a consequence in any way of prior non-therapeutic use of any prohibited substance or method.

In medical emergencies, such as hospital admission, whereby a prohibited substance or method is used appropriately, a therapeutic use exemption can be provided after the event. An application should be made as quickly as possible.

Conclusion

At first pass the WADA Code appears complex and somewhat confusing. However, the Code attempts to limit the opportunity to cheat by specifying prohibited substances in and out of competition, while allowing for the use of substances under certain conditions (notifiable substances), the use of banned substances for therapeutic purposes, and the recognition that some substances may produce inadvertent positive dope tests while not being used for performance enhancement (specified substances). It should also be recognised that many nutritional supplements contain banned substances and extreme caution should be taken to avoid inadvertent doping.

Finally, the concerns about drugs in sport and doping are not confined to young elite athletes – similar concerns should be held for any athlete who wishes to compete at any age.

References

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2. Fricker PA. Drugs in sport. Aust Prescr 2000;23:76-8.
3. Graham TE. Caffeine and exercise: metabolism, endurance and performance. Sports Med 2001;31:785-807.

Further information

World Anti-Doping Agency
http://www.wada-ama.org

The World Anti-Doping Code
http://www.wada-ama.org/docs/web/standards_harmonization/code/code_v3.pdf

The 2004 Prohibited list
http://www.wada-ama.org/docs/web/standards_harmonization/code/list_standard_2004.pdf

Australian Sports Drug Medical Advisory Committee (ASDMAC) – for Applications for therapeutic use exemption

PO Box 345
CURTIN ACT 2605
Fax: (02) 6206 0262
http://www.asdmac.org.au

Australian Sports Drug Agency (ASDA)
PO Box 345
CURTIN ACT 2605
http://www.asda.org.au
Phone: (02) 6206 0200
E-mail: asda@asda.org.au

Australian Sports Drug Agency (ASDA) Drugs in Sport Hotline – a confidential, free call service for athletes and their support staff that offers information on the status of Australian pharmaceutical medications and substances in sport
Phone: 1800 020 506

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 105)

1. Caffeine is a prohibited substance in elite sports.
2. The prescription of a topical corticosteroid should be notified to an athlete's sporting organisation.

Medicinal mishap

Ibuprofen and asthma

Prepared by Sally P.S. Yeung, Drug Information/Clinical Trials Pharmacist, Pharmacy Department, and Greta M. Palmer, Consultant, Department of Anaesthesia and Pain Management, Royal Children's Hospital, Melbourne

Case

A 17-year-old 47 kg male was admitted for an elective inguinal hernia repair. He had a past history of allergic rhinitis (no nasal polyps) and severe chronic asthma. Although he had been admitted to the intensive care unit three times previously, there had been no emergency presentations/admissions for 10 months. His asthma was well controlled with inhaled corticosteroids. The patient had no known allergies to any food or medications.

During a pre-operative consultation, the use of non-steroidal anti-inflammatory drugs (NSAIDs) for analgesia was discussed. The patient had no known prior exposure to NSAIDs or aspirin.

Surgery progressed unremarkably and postoperatively the patient was given one oral dose of 500 mg ibuprofen. Within 15 minutes he became distressed and complained of feeling 'tight' in the chest. Eight puffs of inhaled salbutamol via spacer were given immediately but the patient's respiratory symptoms continued to worsen over the next hour. He required high dependency care with nine doses of nebulised salbutamol and three doses of intravenous salbutamol, in conjunction with intravenous steroids (two doses of 8 mg dexamethasone six hourly). The patient recovered within six hours of the ibuprofen dose and was discharged home the following day after a dose of oral prednisolone (50 mg).

Comment

Aspirin-induced asthma is a distinct clinical syndrome. It is a recognised condition in adults[1,2] but is considered rare in children.[2] There are no tests to identify this syndrome in patients with asthma and the diagnosis is usually established only by observations or by direct re-challenge with aspirin.[2] Cross-sensitivity with other NSAIDs is possible as the syndrome is thought to be related to the inhibition of cyclo-oxygenase enzymes.[1,2] A history of rhinitis is also consistent with the syndrome.

Our patient's asthma exacerbation was probably due to ibuprofen as the reaction occurred within 15 minutes of ingestion, symptoms peaked at 45 minutes and there were no symptoms during anaesthesia or in the immediate post-anaesthesia recovery period.

Conclusion

It is important to ask patients with asthma, or their parents, about all non-prescription medications as many people will not associate asthma with the use of aspirin or other NSAIDs, or be aware of the risk of taking these medications. Patients who are aspirin sensitive or at risk can be counselled about the risk of asthma exacerbation and the appropriate selection of analgesics. This advice becomes even more important with the recent relaxation of the scheduling of NSAIDs, increasing their availability without prescriptions.

References

1. Fahrenholz JM. Natural history and clinical features of aspirin-exacerbated respiratory disease. Clin Rev Allergy Immunol 2003;24:113-24.
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Editor's note:

The Adverse Drug Reactions Advisory Committee has received three other reports of similar adverse reactions to ibuprofen in children.

Warfarin: balancing the benefits and harms

Marija Borosak, Haematology Registrar, Pathology Department, Shin Choo, Senior Pharmacist, Department of Pharmacy, and Alison Street, Associate Professor and Head, Haematology Unit, The Alfred Hospital, Melbourne

Summary

The benefits of warfarin therapy are substantial in the prevention of arterial and venous thrombosis, and in the primary and secondary prevention of stroke related to non-rheumatic atrial fibrillation. The major risk of warfarin is bleeding, which can cause significant morbidity or mortality. If the bleeding risk is high then alternatives to therapeutic doses of warfarin may be considered, although their efficacy may be suboptimal and may not eliminate the risk of bleeding. Constantly review the patient's circumstances in order to weigh up the benefits and harms of treatment with warfarin.

Key words: anticoagulation, haemorrhage, thromboembolism.

(Aust Prescr 2004;27:88–92)

Introduction

Anticoagulation with warfarin significantly reduces the morbidity and mortality related to arterial and venous thromboembolism. For many patients the benefit is clear and the risk of harm is acceptable, so anticoagulation is indicated.

Almost 1.9 million out-of-hospital prescriptions for warfarin were dispensed in 2001. The cost to the Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS) of warfarin for the same period was $8.3 million. From Health Insurance Commission statistics coagulation tests numbered 2.5 million in the same year at a cost of $29.4 million. Most of these tests are for routine monitoring of warfarin therapy. There are therefore many patients taking warfarin, but the decision to use the drug and accept the adverse effects requires constant review.

Before prescribing warfarin, the risk of bleeding should be evaluated and discussed with each patient

Indications for warfarin therapy

There are published recommendations, with supporting levels of evidence, for warfarin therapy.[1,2] The major indications are for prophylaxis and treatment of venous thromboembolism and its extension, for example pulmonary embolism. Warfarin is also indicated for the prophylaxis of non-rheumatic atrial fibrillation in association with risk factors, particularly previous thromboembolism (transient ischaemic attack or ischaemic stroke), diabetes and hypertension. Warfarin is not indicated in patients with lone atrial fibrillation who are less than 60 years of age with no risk factors.

One of the most frequent indications for anticoagulation is reducing the risk of stroke associated with non-rheumatic atrial fibrillation, particularly in the elderly. The prevalence of atrial fibrillation approximately doubles with each advancing decade of age. Non-rheumatic atrial fibrillation is found in approximately 15% of all stroke patients.[3,4] The average stroke rate among patients with atrial fibrillation is 5% per annum. With the ageing population stroke prevention in atrial fibrillation will continue to be a significant management issue.

Contraindications to warfarin therapy

Contraindications to warfarin are any localised or general physical condition or personal circumstance in which the hazard of haemorrhage might be greater than the potential clinical benefit of anticoagulation. These include:

- haemorrhagic tendencies and blood dyscrasias
- recent or contemplated surgery of the central nervous system or the eye
- traumatic surgery resulting in large open surfaces.

Warfarin is contraindicated if the patient is unwilling or unable to comply with monitoring due to cognitive impairment, alcoholism, psychosis or problems with accessing services.

In the major interventional trials studying the efficacy of warfarin for stroke reduction in atrial fibrillation, patients considered at excessive risk of bleeding were excluded (Table 1). These exclusion criteria resulted in the recruitment of a fit group with only a very small sub-group of very elderly people, so there are inherent problems in extrapolating the study results into everyday practice.

Pregnancy

Warfarin is contraindicated during pregnancy, particularly during organogenesis (weeks 6–12). The risk of fetal bleeding remains throughout pregnancy due to the immature fetal liver.[2] Warfarin is not normally prescribed at any stage during pregnancy in Australia.

Table 1

Exclusion criteria used in the major intervention trials of anticoagulation for patients with atrial fibrillation [13,19]

Bleeding disorder or abnormal coagulation at baseline
Recent stroke or transient ischaemic attack (previous two years)
Uncontrolled hypertension (> 180/100 mmHg)
Active bleeding
Haemorrhagic retinopathy
History of intracranial haemorrhage
Use of non-steroidal anti-inflammatory drugs
Chronic alcohol abuse
Risk of gastrointestinal bleeding (active peptic ulcer disease, positive faecal occult blood testing, known oesophageal varices)
Planned surgery or invasive procedure
Pregnancy or breastfeeding
Psychiatric disorder or dementia
Expected poor compliance
Limited life expectancy
Significant renal dysfunction (creatinine > 0.25 mmol/L)
Platelet count < 100 x 10^9/L

Patients were also excluded if they refused to participate or if their doctor considered the risk of anticoagulation was too great.

Harm:benefit analysis in prescribing warfarin (Fig. 1)

The risk of major bleeding in the atrial fibrillation intervention trials was 1–4% per year, with an intracranial bleeding rate of 0.2–0.5% per year. The fatality rate mirrored the intracranial bleeding rate.[5] In observational studies of ambulatory patients the risk of major bleeding is 4–9% per annum.[6,7]

Major determinants of warfarin-induced bleeding include the intensity of anticoagulation, patient characteristics, the concomitant use of drugs that interfere with haemostasis, and the length of therapy.[5] Before prescribing warfarin the risk of bleeding should be evaluated and discussed with each patient.[8]

Intensity of anticoagulation and duration of therapy

The risk of bleeding increases dramatically when the International Normalised Ratio (INR) exceeds 4.0.[9,10] An INR greater than 4.0 is probably the most important risk factor for intracranial haemorrhage, independent of the indication for warfarin.[5]

The risk of major bleeding is greatest in the first month of therapy (3%) and decreases with time to 0.8% per month for the remainder of the first year and to 0.3% per month thereafter.[7]

Patient characteristics

Age

Atrial fibrillation is an increasingly important cause of stroke as patients get older. In the Framingham study the incidence of stroke due to atrial fibrillation increased from 1.5% for those aged 50–59 years to 23.5% for those aged 80–89 years.[11] The prevalence of atrial fibrillation in those over 80 years old reaches approximately 10%.[12]

The results of studies conflict on whether age is an independent risk factor for bleeding. Advanced age is not itself a contraindication to warfarin. Studies in atrial fibrillation support the ongoing benefit of anticoagulation with increasing age. Warfarin therapy reduces the risk of ischaemic stroke in patients with non-rheumatic atrial fibrillation from 7.4% to 2.3% per year.[13]

Age is, however, a risk factor for more unstable prothrombin time results. For every 10-year increase in age there is a 15% increase in the risk of anticoagulation having to be suspended because of a raised INR.[14]

Comorbidities and medication

Conditions associated with an increased risk of bleeding during warfarin therapy include treated hypertension, cerebrovascular disease, serious heart disease, renal insufficiency and malignancy.[5] Over time a person's comorbidities and medications accumulate. These increase the potential for interactions with warfarin.

The INR becomes unstable with the introduction, change in dose or suspension of many common drugs such as antibiotics. Warfarin and aspirin combinations are associated with a high frequency of bleeding, even when combined with 'low intensity' warfarin therapy.[5]

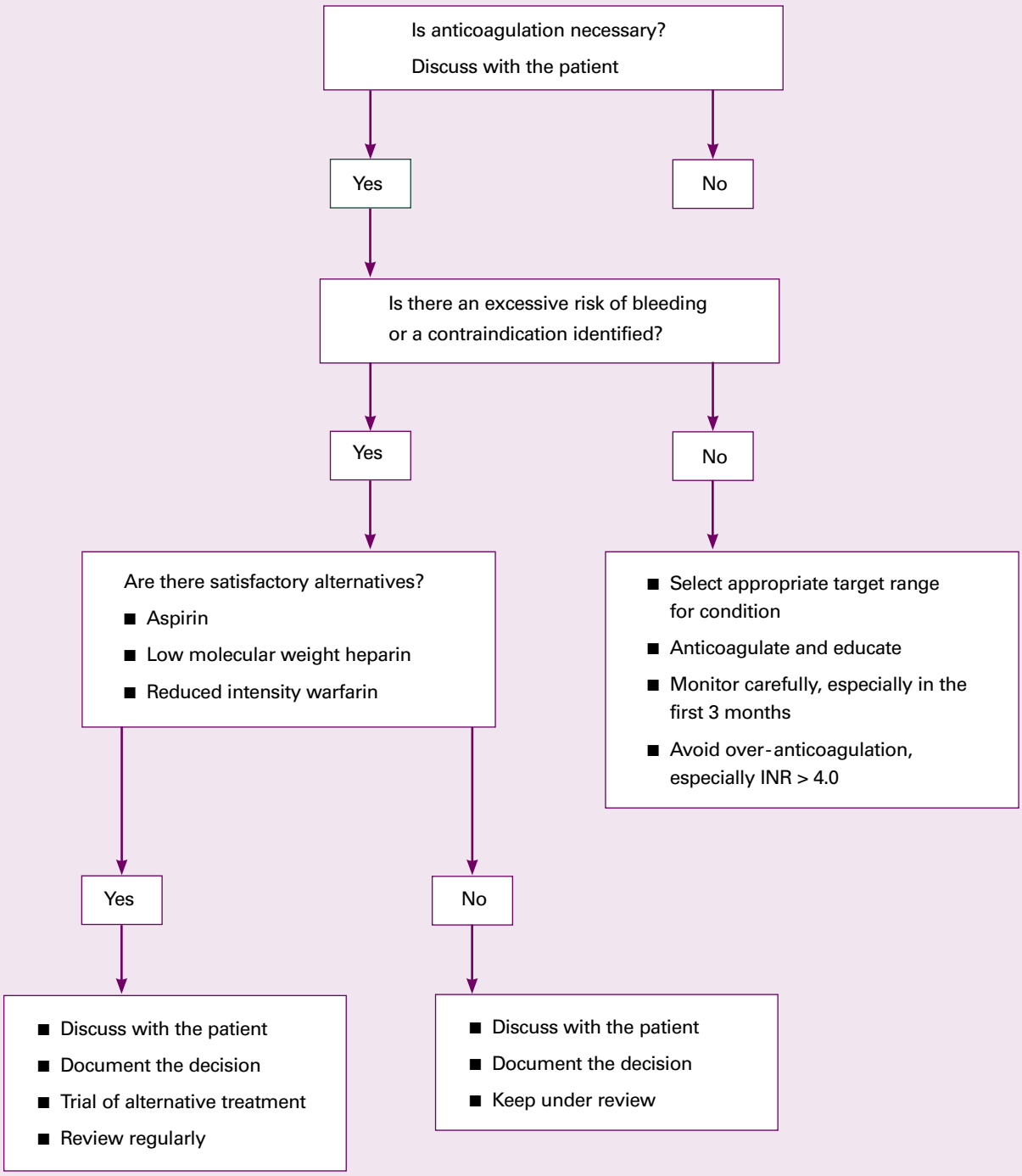
Some herbal preparations and large quantities of vitamin K-rich foods can also interfere with warfarin.[15] Many such interactions are unpredictable so the INR should be checked within a few days of any change. Poor nutrition results in a relative deficiency of vitamin K and increased sensitivity to warfarin. A temporary dose reduction and increased monitoring are essential during an acute illness.

Falls

Patients should be assessed for their risk of falls and possible causes. Where a cause is identified and reversible, for example postural hypotension, and can be ameliorated by a change in medication, anticoagulation can be maintained although careful monitoring of the patient is essential. If the falls continue then the patient should be reviewed and alternatives to warfarin considered.

Fig. 1

Defining the indication for anticoagulation therapy



A decision analysis model of the risks of central nervous system bleeding found that the propensity to fall is not a contraindication to the use of antithrombotic drugs (especially warfarin) in the elderly person with atrial fibrillation.[16] However, approximately 1 in 10 falls causes major injury, including fractures, and people who fall are much more likely to suffer other serious morbidity. There is insufficient evidence to know whether those who fracture a bone while on warfarin suffer greater morbidity and mortality.

There are factors that contribute to the risk of falls that may also have an impact on the ability to adhere to warfarin therapy and monitoring. These include cognitive and sensory impairment as well as poor mobility due to gait, balance and foot problems. Often the general practitioner will be aware of other problems in addition to falls that preclude the safe and reliable use of anticoagulation.

Change in patient status

Each new diagnosis, treatment or major change in the patient's condition, particularly with concomitant poor diet, requires a further assessment of the risks and benefits of oral anticoagulation. The goals of therapy need constant review and possible revision, particularly when anticoagulation is used for long-term prophylaxis as, for example, in atrial fibrillation. An emphasis on 'perfect' primary prevention may be inappropriate when the patient only has a limited life expectancy.

Gastrointestinal bleeding

A similar analytical model has also been used to balance the risk of stroke and gastrointestinal bleeding in older patients with atrial fibrillation.[17] For those with a significant risk of upper gastrointestinal bleeding or lower risks of stroke, warfarin is not clearly the optimal antithrombotic therapy. An 80-year-old with a baseline risk of stroke of 4.3% per year, who is concurrently taking a non-steroidal anti-inflammatory drug, has no difference in predicted outcomes with warfarin, aspirin or no treatment (quality-adjusted life-years of 7.44 for warfarin, 7.39 for aspirin and 7.21 for no treatment).[17]

What are the alternatives to oral anticoagulation?

If the target INR carries too high a risk of bleeding with the usual doses of warfarin, consider if the patient will benefit from other strategies.

Aspirin

When warfarin is contraindicated in patients with atrial fibrillation, aspirin should be given as it confers a 42% risk reduction compared to placebo.[13] This is inferior to warfarin and still increases the risk of bleeding (major bleeding rate of 1.4% per year[13]).

Reduced intensity regimens

Moderately sub-therapeutic levels of anticoagulation (INR 1.6–1.9) may still reduce the risk of stroke in patients with non-rheumatic atrial fibrillation[18] although a minimum INR of 2.0 is required if there is a history of prior stroke or recent transient ischaemic attack.[19] However, there is conflicting evidence about the efficacy and safety of reduced intensity regimens.

Previous studies of fixed low doses of warfarin showed low rates of major bleeding.[5] A more recent study of long-term, low intensity treatment with warfarin (INR target 1.5–2.0) for the prevention of recurrent thromboembolism also found low rates of major haemorrhage[6], while other research reported no difference in bleeding risk.[20] Another study has found that reduced intensity regimens result in more frequent strokes, that are more severe and lead to greater mortality, than regimens which aim for an INR greater than 2.0. This study found the stroke rate was no better than with aspirin and the bleeding complications were greater.[21] These findings suggest that the target INR should be at least 2.0.

Low molecular weight heparin

An alternative to warfarin is the extended use of low molecular weight heparin for venous thromboembolism. If there are problems with compliance or with recurrent wild fluctuations in the INR, low molecular weight heparin can be administered under supervision. It is important to measure renal function as accumulation occurs with renal impairment, particularly when the creatinine clearance falls below 30 mL/min.

Discontinuation of warfarin

Warfarin therapy should be discontinued when the risk of bleeding outweighs the potential benefit. Any decision to discontinue warfarin should only be made after discussion with the patient or carer. Once the decision is made the relevant clinical carers should be informed, and the reasoning and the harm:benefit analysis should be clearly identified and documented. This decision should be subsequently reviewed if clinical or social circumstances alter.

Future directions

New oral anticoagulants, particularly the oral direct thrombin inhibitors, appear promising. They are currently being evaluated for a variety of thrombotic disorders including atrial fibrillation.

Note

Two case studies accompany the electronic version of this article on the *Australian Prescriber* web site www.australianprescriber.com

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 105)

3. Old age is a contraindication to warfarin therapy.
4. The risk of bleeding increases dramatically with INR values above 4.0.

Starting insulin treatment in type 2 diabetes

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Summary

Almost all patients with type 2 diabetes will eventually fail to respond adequately to oral hypoglycaemic drugs and will require insulin therapy. A regimen of bedtime intermediate-acting insulin in combination with daytime oral drugs is acceptable to patients, simple to start and results in rapid improvement in glycaemic control. It can be started safely in general practice and is the most practical way of implementing insulin in the face of a worldwide epidemic of type 2 diabetes.

Key words: metformin, sulfonylureas, thiazolidinediones.

(Aust Prescr 2004;27:93–6)

Introduction

The emerging epidemic of type 2 diabetes, coupled with finite health resources, requires the treatment of hyperglycaemia to be simple and efficiently managed. Type 2 diabetes is a progressive disease and eventually almost all patients will require insulin to maintain good glycaemic control. Knowing when and how to start insulin in general practice is central to the optimal management of type 2 diabetes.

The need to start insulin therapy in a newly diagnosed patient with type 2 diabetes is relatively uncommon. It should be considered when there is considerable weight loss, severe symptoms of hyperglycaemia or the presence of significant ketonuria. Many of these patients can be converted back to oral drugs once glycaemic control has been established and there is some recovery of pancreatic β cell function.

A more common problem is when and how to commence insulin in patients with type 2 diabetes who are in 'secondary failure'. The term secondary failure refers to the 'failure' of oral hypoglycaemic drugs to maintain glycaemic control. The United Kingdom Prospective Diabetes Study (UKPDS)[1] clearly showed that most people with type 2 diabetes will experience progressive pancreatic β cell dysfunction, despite excellent control. The secondary failure rate in this study was 44% after six years of diabetes. Since the time of the UKPDS, targets for glycaemic control have become increasingly stringent so secondary failure of oral hypoglycaemic drugs now occurs much sooner and is almost invariable.

The younger, the sooner, the better

The key to when to start insulin is to identify the appropriate glycated haemoglobin (HbA1c) target for an individual patient. Despite the promulgation of various 'guidelines', there is no single HbA1c concentration which suits everyone. For example, the younger patients already on maximal oral therapy and as much lifestyle modification as they can manage, would benefit greatly in the long term from early introduction of insulin, even if their HbA1c is only minimally elevated (e.g. 7%). The important point here is the **early** introduction of insulin, as the lifetime risk of complications for young patients is great. On the other hand, older patients who are not symptomatic and have no microvascular complications such as retinopathy, can be allowed to remain in 'secondary failure' at an HbA1c of 8–9%. In these patients, prognosis is governed mainly by macrovascular disease, which is not greatly influenced by glycaemic control.

New oral drugs or insulin?

Traditionally metformin plus a sulfonylurea has been the mainstay of oral treatment. Patients understandably often want to know whether they should try adding a third drug or begin insulin. The addition of acarbose can usually only decrease the HbA1c by 0.5% at best, so one would only consider its use if a slight improvement in control is needed. Repaglinide and sulfonylureas should not be used in combination, as they are both insulin secretagogues. The response to therapy with a thiazolidinedione (pioglitazone or rosiglitazone) can be more profound with improvements in HbA1c of 1–2%. The decision whether to start insulin or to add a thiazolidinedione would depend on factors such as patient acceptance, coexisting conditions (thiazolidinediones are contraindicated in oedematous states and heart failure) and access to medicines. At this stage it matters less which drug or 'pathway' is used, but more that the patient's glycaemic target is reached.

Sometimes it is necessary to let patients try triple oral drug therapy. If nothing else, it serves to convince them that insulin is indeed necessary. In this situation, it is important not to delay insulin therapy for more than a few months. A trial of triple therapy for two months should be sufficient to assess whether it is likely to be effective or not.

Choice of insulin regimen: the combined oral drug and insulin approach

Many patients and practitioners procrastinate as insulin treatment is erroneously considered to be risky and difficult.

However, the regimen used routinely in our clinic is safe and easy to start.[2] In our opinion this regimen can be started in general practice. The regimen consists of a combination of intermediate-acting insulin before bed, while continuing maximum oral drug therapy during the day.

What to do with the oral drugs?

The patient is asked to remain on all the oral hypoglycaemic drugs that they are currently taking. The only exceptions are:

- if the patient is taking supra-maximal doses of any of the oral drugs, they are reduced to what is recommended in the product information
- if the patient is suffering from the gastrointestinal adverse effects of metformin, it is reduced to a dose which is tolerated
- if the patient is taking three oral hypoglycaemic drugs including acarbose, the acarbose is stopped as its adverse effects usually outweigh its advantage.

Although the oral drugs have 'failed' in the situation of 'secondary failure', they are still exerting considerable hypoglycaemic effects. Clinical studies have shown that if either the sulfonylurea or metformin are stopped altogether, then each needs to be replaced by an extra 20–30 units of daily insulin. In other words, the insulin dosage would need to exceed about 60 units a day before improvement in glycaemic control could occur. This would require a more aggressive insulin regimen and titration, making the process of starting insulin much more difficult. If a thiazolidinedione has been used, this could be continued initially at least, as it may also contribute an insulin sparing effect.

How much insulin and at what time?

For practical purposes, the patient can always be commenced on 10 units of intermediate-acting insulin, given just before bedtime and as late as possible. This timing allows the insulin to exert its maximum action just before dawn (a time of higher insulin resistance) rather than at 2–3 a.m. when it is most likely to cause hypoglycaemia. If the patient is very nervous or reluctant and it is imperative to minimise the risk of hypoglycaemia, however small, then a slightly lower dosage can be used to get the process underway and to gain the patient's confidence. Patients who have symptoms of hyperglycaemia can start at a higher dose of insulin, but this would rarely need to exceed 20–25 units.

The bedtime dose of insulin is best given as isophane insulin. Currently in Australia, there is only one brand of human isophane insulin available. When it becomes generally available, insulin glargine will probably become the basal insulin of choice as its 'flatter' and longer action make it more suitable for this purpose.[3]

What to tell patients on the day they start insulin?

Although everyone has different information needs, comprehensive information given when starting insulin may confuse many patients. They may not remember the more important messages and some may even be scared away from insulin treatment altogether. Our practice is to concentrate on teaching patients how to inject the insulin subcutaneously into the abdomen, using devices such as the FlexPen or InnoLet which are extremely user-friendly and can be taught in a matter of minutes.

The day patients start insulin is also not an ideal time for detailed dietary advice. We only emphasise the need to have regular meals and snacks (including one before bed) containing carbohydrates.

At this stage of diabetes, most patients would be familiar with glucose monitoring and should be asked to perform this. As adjustment of insulin dosage in this regimen is primarily dependent on the morning fasting blood glucose concentrations, testing at this time point is the first priority and should be included every day. For some patients who cannot test their blood glucose for various reasons, it may be necessary to commence insulin without such monitoring and rely on blood glucose monitoring at the doctor's office and HbA1c concentration to make dose adjustments.

Hypoglycaemia is the only risk in starting insulin therapy and however much this risk is minimised, it cannot be completely eliminated. How much to inform patients about it is a difficult question. Too much detail would incur the risk of scaring a reluctant patient away from the correct treatment, but not enough would open the door to medical litigation. This dilemma is of course not unique to commencing insulin and each doctor must make a decision with individual patients. It is reassuring that in patients with type 2 diabetes, hypoglycaemia due to insulin is usually not severe.

How to titrate insulin dosage and monitor progress?

A major feature of this regimen is that insulin is added to existing treatment. Glycaemic control should therefore improve immediately and for practical purposes, should not deteriorate. This means that the dose of insulin can be increased relatively slowly, minimising the risk of hypoglycaemia. As described originally, the regimen[2] increased the insulin dosage by 4 units a day if the fasting blood glucose exceeded 8 mmol/L on three consecutive days and by 2 units a day if it exceeded 6 mmol/L. We tend to do it slightly slower and adjust insulin dosage according to these glucose thresholds every 1–2 weeks. The slower pace helps to gain the patient's confidence and reduces the risk of hypoglycaemia. This titration regimen is of course not 'cast in stone' and there are ongoing trials that are exploring the best options.

After 2–3 months, the patient is likely to be on about 30 units of insulin each day and maximum oral drug therapy. Measuring the HbA1c concentration after this interval helps to quantify the

new level of glycaemic control and further increases in insulin dosage can be made accordingly. There is generally a reduction in HbA1c of about 2% and an increase in body weight of several kilograms. If these changes are not evident, one should consider the possibility that the patient has not been taking the insulin regularly or someone unfamiliar with the regimen has reduced or stopped one or more of the oral hypoglycaemic drugs.

In our experience, after about 6–12 months, a further increase in insulin dosage, according to HbA1c concentration, is required. The final daily insulin requirement is about 50–60 units and is higher in those with obesity, higher initial concentrations of HbA1c, and elevated hepatic enzymes which are surrogate measures of fatty liver and insulin resistance.

The advantages of the combined oral drug and insulin regimen

The literature often addresses the question of whether combined oral drug and insulin treatment provides better glycaemic control than insulin alone. This is in a sense a meaningless question because the answer would depend on how much insulin was used. We favour the combined regimen because glycaemic control begins to improve from the day insulin is started. The titration of insulin dosage can be gradual and therefore relatively safe, in an outpatient setting.

The alternative is to stop the oral drugs abruptly. In this scenario, insulin needs to be given at least twice daily and the dose needs to be quickly titrated upward to 70–80 units per day, or glycaemic control may actually deteriorate. This 'insulin alone' regimen is obviously possible, but requires more patient contact, making it less user-friendly for both doctors and patients. All too commonly, we have witnessed deterioration in glycaemic control when both oral drugs were stopped and not replaced with sufficient insulin.

In our experience, it is easier to persuade patients to undertake combined oral drugs and insulin treatment. They are often comforted by the knowledge that they only need to take insulin once, in the privacy of their own home and without a great deal of disturbance to their daytime routine. When they are familiar with insulin injections they become accepting of a more intensive insulin regimen, should this be required.

When to stop oral hypoglycaemic agents?

Sometimes patients develop frequent daytime hypoglycaemia on combined treatment. When this happens, the sulfonylurea dosage should be reduced or ceased if necessary. Apart from this and in the absence of contraindications (such as renal failure or allergy), there is no good evidence that oral hypoglycaemic drugs must be stopped at any stage and our policy is to continue them while glycaemic control remains satisfactory. Most diabetes specialists would support the continuation of metformin indefinitely, because it increases insulin sensitivity. Others advocate stopping the sulfonylurea after insulin treatment is established, an attitude based more on philosophy than real need. Some patients may wish to reduce the number of tablets they take especially when they are already on multiple medications for blood pressure and lipid control. There is nothing wrong with reducing one or more of the oral hypoglycaemic drugs once they are established on insulin therapy, as long as it is recognised that the dose of insulin needs to go up, by an average of 20–30 units per day for each withdrawn drug, to maintain the same degree of glycaemic control.

When to introduce more complex insulin regimens?

In some patients, fasting blood glucose concentrations may be quite acceptable and yet HbA1c remains significantly elevated. In this situation, a second dose of insulin is needed, usually given in the morning before breakfast. A small starting dose of medium-acting insulin in the order of 6–12 units would be reasonable.

Other patients who are at the more insulin-deficient end of the type 2 diabetes spectrum (these patients can be recognised by their relatively lean body weight and younger age) may be better starting on a twice-daily insulin regimen. The insulin sparing effects of oral hypoglycaemic drugs (and therefore the simplification of insulin titration) would still be present in this situation.

Handy hints

The inevitable need for insulin therapy in most patients is best discussed early in treatment when the need for insulin therapy is not imminent. This message should be continuously reinforced as it helps to set expectations and eases the transition to insulin later on.

Giving practice injections of saline at the time when insulin therapy is being considered may help to allay the anxiety surrounding the injection process. This helps the patients' acceptance of therapy. Diabetes educators can be an additional ongoing source of support and information for your patient, at this time of change.

Conclusion

We are confronting the prospect of having to treat more than one million patients with diabetes in Australia. It will soon be untenable for general practitioners to send all their patients requiring insulin to specialists or diabetes clinics to have this implemented and monitored. The regimen of giving an insulin injection before bed to complement the use of maximum oral hypoglycaemic drugs for patients with diabetes in secondary failure, is easy and safe to implement in general practice as the first step of introducing insulin treatment.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 105)

5. In lean young patients with type 2 diabetes, insulin therapy should be delayed as long as possible.
6. Oral hypoglycaemic drugs should be stopped when a patient with type 2 diabetes starts insulin.

Patient support organisation

Diabetes Australia

Diabetes Australia is a federation of twelve organisations – the eight State and Territory Associations of Diabetes Australia, the Australian Diabetes Society, the Australian Diabetes Educators Association, the Kellion Diabetes Foundation and The Diabetes Research Foundation – Western Australia.

The State and Territory associations (see below) and their shopfronts provide ongoing support as well as products, services, information and education for people with diabetes and their families.

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Medicinal mishap

Tramadol and hyponatraemia

Prepared by Robin Hunter, Rehabilitation Physician, Brighton, Vic.

Case

A 76-year-old woman with a past history of hypertension, compression fracture of the lumbar vertebrae, diverticulitis and leg cramps was admitted to hospital with a Colles' fracture. Her usual medications were perindopril 2 mg in the morning, quinine sulfate 300 mg at night, ranitidine 300 mg at night, calcium carbonate at night and risedronate 5 mg daily. Her sodium on admission was 135 mmol/L.

The fracture was reduced under an arm block and she was commenced on tramadol 50 mg four times daily for pain control.

The patient was transferred to a rehabilitation hospital nine days later. On admission, her sodium was mildly reduced at 129 mmol/L. Her sodium continued to drop over the following seven days, despite fluid restriction, to 122 mmol/L. Her other electrolytes were within normal limits. Clinically she was euvolaemic. Serum osmolality was low at 256 (280–300), suggesting inappropriate antidiuretic hormone (ADH) secretion. Tramadol was ceased and her sodium returned to normal over four days.

Comment

Tramadol is an analgesic which stimulates the same receptor as morphine and other opioids.[1] It also inhibits noradrenaline and serotonin reuptake potentially resulting in increased concentrations of serotonin and noradrenaline.

It has been well documented that selective serotonin reuptake inhibitors (SSRIs) cause hyponatraemia (defined as a sodium concentration less than 135 mmol/L) particularly in the elderly, females and in the initial stage of therapy.[2,3] This is thought to be due to increased serotonin levels stimulating the release of vasopressin (ADH).[4] Vasopressin causes fluid retention resulting in expansion of extra cellular volume and lowered sodium levels.

Tramadol, by increasing serotonin levels, may result in hyponatraemia through a similar mechanism.

I have had four elderly patients who have taken tramadol for pain control after fractures and have developed hyponatraemia, which has been corrected on cessation of tramadol. One of these cases occurred when tramadol was added to a patient already on citalopram, an SSRI.

Recommendations

Tramadol use should be reviewed and, if possible, the dose reduced or the drug ceased altogether after 48–72 hours. Sodium concentrations should be monitored when prescribing tramadol particularly in the elderly and those taking other medications, such as SSRIs and diuretics, which also predispose to hyponatraemia.

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Editor's note:

The Adverse Drug Reactions Advisory Committee has received 14 reports of hyponatraemia in patients taking tramadol.

Resolving the differences between ACE inhibitors and diuretics – ALLHAT and ANBP2

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Summary

The protective effects of blood pressure reduction are clear. However, the choice of antihypertensive drug is less clear. Two trials comparing the effects of ACE inhibitors and diuretics have produced apparently conflicting conclusions. The US Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial reported that diuretic therapy was probably better, while the second Australian National Blood Pressure study suggested that ACE inhibitor-based regimens were superior. On balance, it appears that differences in the design and conduct of these two trials probably explain the differing results. Neither trial provides really compelling evidence for the preferential selection of one drug over the other. Achieving good blood pressure control is probably far more important than the drug with which that control is achieved.

Key words: antihypertensives, hypertension, cardiovascular disease.

(Aust Prescr 2004;27:98–101)

Introduction

The benefits of effective blood pressure reduction are well established, although the best means of achieving these benefits is less clear. Substantial data are now available from trials of diuretics, beta blockers, ACE inhibitors, calcium antagonists and angiotensin receptor blockers. However, if clinical trials report seemingly conflicting results, what do we believe? The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[1] and the second Australian National Blood Pressure study (ANBP2)[2] appear to have created exactly this dilemma.

ALLHAT and ANBP2

ALLHAT was a very large, North American trial in which around 42 000 people with hypertension were randomised to take either an ACE inhibitor, a diuretic, a calcium antagonist or an alpha adrenergic blocker. The alpha blocker arm of the study was terminated early after an interim analysis showed an excess of major cardiovascular events compared with the diuretic arm. This left around 33 000 people in the remaining three arms. About 24 000 were included in the ACE inhibitor versus diuretic comparison.

The ANBP2 study was a much smaller trial of around 6000 older hypertensive Australians. They were randomised to receive either ACE inhibitor- or diuretic-based treatment.

The main characteristics of each trial are shown in Table 1. In each trial, numbers of cardiovascular events in each treatment group were compared after a mean follow-up of 4–5 years. Both trials compared the outcomes of treatment with diuretics or ACE inhibitors.

Main findings (Table 2)

In ALLHAT, the primary outcome was coronary heart disease and the trial found no difference in the incidence of events between the ACE inhibitor group and the diuretic group. However, for the secondary outcomes, the risks of stroke (15% lower relative risk,

Table 1

Characteristics of ALLHAT and ANBP2 trials

Characteristics	ALLHAT	ANBP2
Study design	Randomised double-blind	PROBE
Number of participants	33 357	6083
Study population/ setting	North America ≥ 55 years Hypertension and one other CVD risk factor	Australia 65–84 years Hypertension only
Intervention	Diuretic v calcium antagonist v ACE-I	Diuretic v ACE-I
Median follow-up	4.9 years	4.1 years
Baseline characteristics		
Mean age	67 years	72 years
Women	47%	51%
Ethnicity	35% African-American	95% 'white'
Baseline BP	146/84	168/91
Diabetes	36%	7%
Coronary heart disease	25%	8%
Blood pressure goals	< 140/90	140/80

ACE-I ACE inhibitor
CVD cardiovascular disease
PROBE Prospective, Randomised Open with Blinded Endpoint assessment

Table 2

Main findings for ACE inhibitor versus diuretic in ALLHAT and ANBP2 [1,2]

	ALLHAT	ANBP2
Primary outcome	*Fatal CHD or non-fatal MI*	*CVD events or death from any cause*
ACE inhibitor	11.4 events/100 people/6 years	56.1/1000 people/year
Diuretic	11.5 events/100 people/6 years	59.8/1000 people/year
	No difference (Relative risk 0.99 CI 0.91–1.08)	No difference (Hazard ratio 0.89 CI 0.79–1.00)
Secondary outcomes	*Stroke*	*Stroke*
ACE inhibitor	6.3 events/100 people/6 years	9.2 events/1000 people/year
Diuretic	5.6 events/100 people/6 years	8.8 events/1000 people/year
	Higher risk with ACE inhibitor (Relative risk 1.15 CI 1.02–1.30)	No difference (Hazard ratio 1.02 CI 0.78–1.33)
	Heart failure	*Heart failure*
ACE inhibitor	8.7 events/100 people/6 years	5.6/1000 people/year
Diuretic	7.7 events/100 people/6 years	6.4/1000 people/year
	Higher risk with ACE inhibitors (Relative risk 1.19 CI 1.07–1.31)	No difference (Hazard ratio 0.9 CI 0.71–1.14)
	Combined CVD	*Combined CVD (first event)*
ACE inhibitor	33.3 events/100 people/6 years	33.7/1000 people/year
Diuretic	30.9 events/100 people/6 years	37.1/1000 people/year
	Higher risk with ACE inhibitor (Relative risk 1.10 CI 1.05–1.16)	Lower risk with ACE inhibitor (Hazard ratio 0.9 CI 0.77–1.01)
		Myocardial infarction (first event)
ACE inhibitor		4.7/1000 people/year
Diuretic		6.7/1000 people/year
		Lower risk with ACE inhibitor (Hazard ratio 0.68 CI 0.47–0.98)
Achieved blood pressure	2 mmHg higher systolic blood pressure with ACE inhibitor	No difference between treatments

CHD coronary heart disease
CVD cardiovascular disease
MI myocardial infarction
CI 95% confidence interval

95% CI* 2–30%), heart failure (19% CI 7–31%) and combined cardiovascular events (10% CI 5–16%) were all lower in those taking diuretics. In other words, aside from myocardial infarction for which there was no apparent difference, diuretics seemed to be superior to ACE inhibitors.

The ANBP2 trial reported an 11% (0–21%) reduction in the risk of its primary outcome (any cardiovascular event or death from any cause) in favour of the ACE inhibitor group compared to the diuretic group. In terms of the secondary outcomes, there was a 32% (1–53%) greater reduction in the risk of non-fatal myocardial infarction with ACE inhibitor therapy compared to diuretic therapy. There were corresponding trends towards greater reductions in the ACE inhibitor group for heart failure and other cardiovascular events. Overall therefore, ACE inhibitors seemed to be superior to diuretics, however, for both primary and secondary outcomes, differences between treatment groups in cause-specific fatal and nonfatal events were only seen in men.

Findings with respect to diabetes

The risk of developing type 2 diabetes in the ALLHAT trial was 40% higher with diuretic therapy than with ACE inhibitor therapy. However, the longer-term clinical relevance of this observation is not known. In the diabetic sub-group of ALLHAT, there was no difference between ACE inhibitors and diuretics for any of the cardiovascular outcomes, except for heart failure. There was a 20% reduction in the risk of heart failure with diuretic therapy compared with ACE inhibitors, irrespective of

* CI confidence interval

whether the patients had diabetes or not. ANBP2 has not yet reported findings with respect to diabetes.

Why do the study results appear to be in conflict?

At first glance, the two studies appear to reach opposite conclusions, that is, the ALLHAT findings favour diuretics whereas the ANBP2 findings favour ACE inhibitors. However, when comparing the studies, one needs to consider the ways in which systematic differences between the trials and random variation about the estimates of effect might affect the validity of this conclusion. Two particular differences between ALLHAT and ANBP2 were the blood pressure reductions that were achieved in the randomised groups and the ethnicity of the study populations.

Target blood pressure

In both trials, doctors aimed to achieve similar target blood pressures by first using the drugs under investigation and then adding other antihypertensives as required. In ANBP2 the blood pressure reductions were almost identical in each group. However, in ALLHAT, the systolic blood pressure at follow-up was 2 mmHg higher in the ACE inhibitor group compared with the diuretic group. While small, a 2 mmHg lower systolic blood pressure would, on the basis of epidemiology, be expected to result in an approximately 10% lower stroke risk and a 7% lower coronary risk.[3] The smaller benefits of ACE inhibitors observed in ALLHAT might therefore be attributable to the less effective blood pressure control achieved in this group.

Ethnicity

ALLHAT included a large proportion (over one-third) of African-Americans, while most patients in ANBP2 were white. Subsidiary analyses suggested that the increased risk in those receiving an ACE inhibitor in ALLHAT might have been partly attributable to less effective blood pressure control with ACE inhibitors (4 mmHg higher at follow-up) among black patients. This is an observation which has been reported elsewhere.[4]

Design

The two trials differed in study design. In ANBP2, the PROBE (Prospective, Randomised Open with Blinded Endpoint assessment) design meant that general practitioners were aware of the assignment of study drugs and were free to choose the most appropriate second-line drug to achieve blood pressure control.

In ALLHAT, not only were physicians blind to treatment assignment, but they were also restricted, by protocol, to using potentially less favourable combinations of drugs. Sub-optimal combinations are a further possible explanation for the follow-up differences in blood pressure in the two randomised groups.

Power

The differences in the size of the trials and the numbers of events observed produced markedly different levels of precision about the estimates of effect obtained in each study. No previous trial of antihypertensive therapy has approached the size of ALLHAT which recorded nearly 5000 deaths, 3000 coronary events and more than 1500 strokes. The large study size increased the power to detect differences between the treatments as evidenced by the tight confidence limits around the estimates of effect.

Relative to ALLHAT, ANBP2 was small, and had greatly reduced power to reliably detect the differences between the treatments and to examine the effects on cause-specific outcomes or in patient sub-groups. For every outcome reported in ANBP2 the confidence intervals were considerably wider than those for ALLHAT. In almost every case the confidence intervals in ANBP2 substantially overlapped the estimates of effect identified in ALLHAT.

How different are the results?

Overall, the findings of ALLHAT and ANBP2 are probably not as divergent as they might at first seem. The differences are likely to be explained by the systematic differences between the studies and uncertainty about the point estimates of effect. Certainly, for coronary heart disease, the evidence for superiority of one drug over the other is very weak. For stroke and heart failure, there is some evidence from ALLHAT that a greater benefit was achieved with diuretic therapy. However, this is probably explained by the greater reduction in blood pressure seen in patients taking diuretics.

Conclusion

The ANBP2 versus ALLHAT debate highlights the need for clinicians to consider the most reliable evidence for the relative benefits of different blood pressure lowering regimens. Overviews or meta-analyses that combine results of individual studies can serve exactly this purpose. A collaboration comprising the investigators of large trials of blood pressure lowering drugs (the Blood Pressure Lowering Treatment Trialists' Collaboration) has conducted such overviews.

The first cycle of results from these overviews showed that treatment with any of the commonly used antihypertensive drugs reduced the overall risk of major cardiovascular events and that all regimens were broadly comparable.[5] The second cycle of results from the collaboration, based on data from more than 160 000 patients, provides more definitive evidence about the effects on individual outcomes such as stroke, ischaemic heart disease and heart failure.[6]

On the basis of the evidence available to date, good blood pressure control appears to be far more important than whether or not it is achieved with an ACE inhibitor or a diuretic.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 105)

7. Thiazide diuretics are as effective as ACE inhibitors in reducing overall mortality in patients with hypertension.
8. Treatment with thiazide diuretics is associated with significantly more strokes than treatment with ACE inhibitors.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been 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.

Adalimumab

Humira (Abbott Australia)

vials/pre-filled syringes containing 40 mg solution

Approved indication: rheumatoid arthritis

Australian Medicines Handbook section 15.2.1

Modern treatment for rheumatoid arthritis aims to modify the disease process with drugs such as methotrexate.[1] In some patients treatment with disease-modifying drugs is unsuccessful and biological agents such as the inhibitors of tumour necrosis factor alpha (TNF-α) may be needed.[2]

Adalimumab is a genetically engineered antibody. It is a 'humanised' antibody as its gene sequence is not derived from animals. Adalimumab binds to TNF-α preventing it from acting on receptors on the surface of cells. This blocks the inflammatory process and results in a rapid fall in the erythrocyte sedimentation rate and concentrations of C-reactive protein.

Although adalimumab only needs to be administered once every two weeks, it has to be injected. After subcutaneous injection it takes five days to reach the peak serum concentration. These concentrations are higher than the concentration in synovial fluid. Serum concentrations are increased if the patient is also taking methotrexate.

Significantly more patients respond to adalimumab than to placebo. After 26 weeks 46% of patients will have had a 20% improvement compared to 19% of those given a placebo. A study of 36 patients who took adalimumab for two years found that there was no radiological progression of the arthritis in 15.[3]

Adalimumab has also been studied in combination with methotrexate. After 24 weeks there was a 20% improvement in 45 of the 67 patients taking methotrexate and adalimumab 40 mg. Only nine of the 62 patients who took methotrexate and a placebo had a similar response.[4]

As adalimumab has an immunosuppressant effect there is a risk of serious infection. Patients should be checked for latent tuberculosis before they start treatment. Caution is also needed if the patient has a demyelinating disease. Antibodies to adalimumab can develop during treatment and this tends to reduce the therapeutic response. Some patients experience hypersensitivity reactions.

During clinical trials 6.6% of patients discontinued treatment with adalimumab because of adverse effects. Common adverse effects include injection site reactions, dizziness and infections.

Treatment may reduce haemoglobin and increase lipid concentrations.

Although a 20% improvement was the outcome used to establish efficacy in trials[4], patients may not notice much change. Less than one patient in four will experience a 70% improvement in their arthritis while taking methotrexate and adalimumab. Currently, there is limited information whether the modest benefits seen in the trials will translate into long-term prevention of disability. There is also concern that long-term inhibition of TNF-α could increase the risk of autoimmune diseases or cancer.

There are no direct comparisons of adalimumab with the other TNF-α inhibitors. A meta-analysis suggests that no product is clearly more efficacious than the others.[5]

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Alefacept

Amevive (Biogen-Idec)

vials containing 7.5 mg and 15 mg as powder for reconstitution

Approved indication: chronic plaque psoriasis

Australian Medicines Handbook section 8.6

Some patients with severe psoriasis will require systemic treatment to control the inflammation. Sometimes this requires the use of immunosuppressants such as cyclosporin and methotrexate.

Alefacept is an immunosuppressant protein produced by genetic engineering. It binds to the CD2 receptor on T lymphocytes. This interferes with the lymphocyte activation which may contribute to the inflammation and proliferation of keratinocytes in psoriasis. Treatment with alefacept also reduces the lymphocyte count.

The recommended treatment regimen is 15 mg intramuscularly or 7.5 mg intravenously. Doses are given weekly for 12 weeks. Although there is limited information about the pharmacokinetics of alefacept, it has a half-life longer than 10 days after intravenous injection.

A trial, using a range of intravenous doses, compared alefacept with placebo in 229 patients. As judged on the 0–72 scale of the psoriasis area and severity index, there were significant improvements in the patients given alefacept. Overall, 19 (11%) of the 170 patients randomised to take alefacept, but none of the placebo group, were clear of psoriasis at the end of the course of injections. Compared to their baseline measurements, 60% of the patients given 0.075 mg/kg had a 50% reduction in their psoriasis score.[1]

Another placebo-controlled trial investigated intramuscular alefacept (10 mg or 15 mg) in 507 patients with chronic plaque psoriasis. Twelve weeks of treatment resulted in 57% of the patients given 15 mg alefacept having a reduction of at least 50% in their psoriasis scores. The peak effect of the drug occurred after the course of injections was completed.[2]

Although the improvement in the patients' psoriasis can continue after treatment, some may benefit from a second course. A two course regimen was studied in a trial of 553 patients with chronic plaque psoriasis. These patients were randomised to receive two courses of intravenous alefacept 12 weeks apart, or a course of alefacept followed by placebo, or a course of placebo injections followed by alefacept. Two weeks after completion of the second course, 55% of the 183 patients who had received two courses of alefacept had a greater than 50% reduction in their psoriasis scores. Only 25% of the 142 who had received a placebo in their second course achieved the same outcome. The median duration of the response, in patients who responded well to their first course of alefacept, was more than seven months.[3]

Although symptoms such as chills and injection site reactions are common problems with alefacept, it has the potential for more serious adverse effects. Patients need their differential lymphocyte count checked every other week because of the risk of lymphopaenia. Alefacept should be withheld if the CD4 lymphocyte count is below normal.

The immunosuppressive effects of alefacept increase the risk of infections, particularly if the course is repeated. Some patients developed malignancies, such as lymphoma, during the clinical trials.

Psoriasis is a chronic disease, but the safety and efficacy of more than two courses of alefacept is unknown. While alefacept has a greater effect than placebo, up to 35% of patients will improve while taking a placebo.[2] As alefacept is likely to be expensive, it would be useful to know which patients will respond. Approximately nine patients need treatment to achieve clearance of one person's psoriasis.[1] Phototherapy and drugs such as topical corticosteroids were prohibited during the

trials, so it would be interesting to know how these treatments compare with alefacept.

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Atomoxetine hydrochloride

Strattera (Eli Lilly)

10 mg, 18 mg, 25 mg, 40 mg and 60 mg capsules

Approved indication: attention deficit hyperactivity disorder

Australian Medicines Handbook section 18.5

Controversy surrounds the diagnosis of attention deficit hyperactivity disorder and its treatment with stimulant drugs (see Aust Prescr 1995;18:60-4). Prescribers now have the option of treating patients with atomoxetine, a non-stimulant drug.

Atomoxetine inhibits the reuptake of noradrenaline by presynaptic neurons, but it is uncertain if this explains the therapeutic effects. The drug is well absorbed, but its bioavailability varies with each patient's oxidative metabolism. The bioavailability is higher in patients with reduced metabolism and their plasma concentrations of atomoxetine are also higher because metabolic clearance is reduced. As the metabolism of atomoxetine involves cytochrome P450 2D6 there is a potential for interactions with other drugs metabolised by this enzyme system. The half-life of atomoxetine is 5.2 hours, but this increases to 21.6 in poor metabolisers. Most of the metabolites are excreted in the urine.

A placebo-controlled dose-response study titrated twice-daily doses of atomoxetine at weekly intervals in 297 children. It found that, after eight weeks, a total daily dose of 1.2 mg/kg improved the children's symptoms on a variety of rating scales. This dose reduced the score on the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD RS) by 13.6, from a baseline score of 39.2, while placebo achieved a reduction of 5.8 from a baseline score of 38.3.[1]

Another trial compared once-daily doses with placebo for six weeks in 171 children. Atomoxetine reduced the mean score on the ADHD RS by 12.8 from a baseline of 37.6, while placebo reduced the score by 5.0 from a baseline of 36.7. This suggests single daily doses have similar efficacy to divided doses.[2]

Atomoxetine has been compared with methylphenidate in a 10-week, randomised, open-label trial. In the 178 children who took atomoxetine, the ADHD RS score decreased from 39.4 to 20.0, while it decreased from 37.6 to 19.8 in the 40 children who took methylphenidate.[3]

Atomoxetine is approved for use in children over six years old and adolescents, but it can also be used in adults. A small double-blind, crossover study found that a daily dose of 80 mg atomoxetine reduced the ADHD RS from 30.0 to 21.5 while a placebo had no effect.[4] Two larger randomised placebo-controlled trials showed that 10 weeks treatment with atomoxetine produced greater reductions in the investigators' ratings of the patients' condition. In the trial involving 280 adults, it reduced the total symptom score from 33.6 to 17.6 while placebo reduced it from 33.2 to 23.9. In the other trial (256 adults) atomoxetine reduced the mean score from 34.9 to 17.6 while placebo reduced it from 34.2 to 22.6.[5]

Most of the trials were relatively short, so the long-term efficacy and safety is uncertain. Common complaints from children were abdominal pain and vomiting, while adults reported constipation, nausea, dry mouth and reduced appetite. Atomoxetine increases the pulse rate and blood pressure, but some patients will develop postural hypotension. In adults there may be urinary hesitancy or retention and atomoxetine can impair sexual function. As atomoxetine may affect growth, height and weight should be monitored during the treatment of children.

Atomoxetine has the advantage of not being a controlled drug and it does not appear to cause dependence. However, a therapeutic advantage over stimulants has not been shown.

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Fenofibrate

Lipidil (Laboratoires Fournier SA)

67 mg capsules

160 mg film-coated tablets

Approved indication: dyslipidaemia

Australian Medicines Handbook section 6.6

Although HMG CoA reductase inhibitors are the drugs of choice for patients with hypercholesterolaemia, fibrates are sometimes considered if the high density lipoprotein (HDL)-cholesterol is low. Fibrates such as fenofibrate are more likely to be used for hypertriglyceridaemia as their main action is to decrease serum triglycerides.

After absorption fenofibrate is rapidly metabolised to fenofibric acid. By acting on the perioxisome proliferator activated receptor, fenofibric acid reduces total cholesterol, low density lipoprotein (LDL)-cholesterol, triglycerides, apolipoprotein B and very low density lipoprotein (VLDL). Fenofibric acid increases HDL. These effects make fenofibrate suitable, as an adjunct to diet, for the treatment of type II, III, IV and V dyslipidaemia, and the dyslipidaemia associated with type 2 diabetes. It can also be prescribed if dietary changes have not controlled hypercholesterolaemia.

Several placebo-controlled trials have confirmed the effect of fenofibrate on lipids. Some trials have compared fenofibrate with HMG CoA reductase inhibitors. In one study of 265 patients with primary hyperlipidaemia, fenofibrate was as effective as pravastatin in reducing total cholesterol and LDL-cholesterol. Fenofibrate had a greater effect than pravastatin on HDL-cholesterol (13.2% versus 5.6% increase) and triglycerides (38.7% versus 11.8% decrease).[1] Another 12-week trial of 181 patients found that fenofibrate increased HDL-cholesterol more than atorvastatin (13.3% versus 5.3%).[2] In patients with type 2 diabetes and mixed hyperlipoproteinaemia the increase in HDL-cholesterol was similar with fenofibrate and atorvastatin (10% versus 11%), but atorvastatin caused a greater reduction in total cholesterol (24% versus 16%).[3] Although gemfibrozil is currently the first-choice fibrate for hypertriglyceridaemia, there are no published comparisons with fenofibrate.

In the clinical trials the most common complaint was abdominal pain, but laboratory tests revealed that 7.5% of patients develop liver function abnormalities. Liver function should be monitored, as cholestatic and chronic active hepatitis have occurred during treatment. As fenofibrate is metabolised in the liver and excreted in the urine, it is contraindicated in patients with hepatic or severe renal dysfunction.

Fenofibrate affects the clotting process[3] and will prolong the prothrombin time. Patients taking warfarin will need to reduce their dose of anticoagulant. Although fibrates rarely cause rhabdomyolysis themselves, concomitant treatment with an HMG CoA reductase inhibitor should usually be avoided because of the increased risk of muscle damage.

Although fenofibrate has been available overseas for several years, there is not much information about its effect on cardiovascular disease. It should probably not be the first-choice fibrate until more outcome data are available.

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Granisetron

Kytril (Mayne Pharma)

ampoules containing 3 mg/3 mL

2 mg tablets

Approved indications: nausea and vomiting

Australian Medicines Handbook section 12.3.4

Granisetron is another $5HT_3$ antagonist (dolasetron, ondansetron and tropisetron are already available). It is approved for the prevention and treatment of nausea and vomiting due to cytotoxic drugs or surgery. Although it is approved for prevention, there are limited data to support the use of granisetron in the treatment of nausea and vomiting due to radiotherapy.

Chemotherapy releases serotonin from the gut and this results in stimulation of vagal nerve terminals and the chemoreceptor trigger zone. Granisetron acts by antagonising the peripheral and central $5HT_3$ receptors (see 'Serotonin receptor agonists and antagonists' Aust Prescr 1991;14:46-51).

Granisetron is diluted then infused over five minutes, shortly before the cytotoxic therapy is given. A 3 mg dose will prevent vomiting in 50–70% of adult patients given cisplatin. If this preventive regimen does not work, the infusion may be repeated twice in 24 hours. The addition of a corticosteroid increases the effectiveness of granisetron.

To prevent postoperative nausea and vomiting in adults, 1 mg is slowly injected before the anaesthetic is given. A single dose is also effective in treating established postoperative nausea and vomiting.

The tablets can be given before chemotherapy and then continued for up to one week. This formulation has a bioavailability of 60% with peak plasma concentrations

being reached two hours after a dose. The half-life of granisetron is approximately nine hours with most of the drug being metabolised by the liver. No dosage adjustment is recommended for patients with hepatic or renal impairment.

Headache is the most frequent adverse reaction, but patients may also complain of constipation or sleepiness. Granisetron promotes liver cancer in rats, but the clinical significance is uncertain. Altered liver function has been reported in humans.

Serotonin antagonists may be no more effective than a regimen of metoclopramide and dexamethasone, but they are usually easier to give. Practitioners will now have to decide whether to prescribe dolasetron, ondansetron, tropisetron or granisetron. The drugs appear to be similar in effectiveness, so the choice of treatment may be influenced by its price.

* At the time the comment was prepared, information about this drug was available on the web site 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 web site of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int).

NEW FORMULATIONS

Galantamine

Reminyl (Janssen-Cilag)

8 mg, 16 mg and 24 mg prolonged release capsules

Mesalazine

Pentasa (Ferring)

1 g/100 mL enemas and 1 g suppositories

Salofalk (Orphan)

500 mg tablets

Olanzapine

Zyprexa IM (Eli Lilly)

10 mg powder for injection (vials)

Risperidone

Risperdal Quicklet (Janssen-Cilag)

0.5 mg, 1 mg and 2 mg wafers

Answers to self-test questions

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

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