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Editorial

Biosimilars are not (bio)generics

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Key word: bioequivalence.

(Aust Prescr 2009;32:146–7)

Biological drugs are well established in the treatment of many conditions, with the likelihood of increasing use in future years. These therapies include the products of biotechnology such as recombinant proteins and antibodies (collectively termed biopharmaceuticals) as well as several older drugs produced through purification techniques such as heparins and conjugated oestrogens. Biosimilars (Europe) or 'follow-on' biologics (USA) are biological products that are similar, but not identical, to an innovator product that is already marketed and whose patent has typically expired. Biosimilars cannot be considered 'generic' equivalents of innovator products as they are not necessarily clinically interchangeable and in some cases may exhibit different therapeutic effects. It is critical that physicians and pharmacists truly understand the complex factors which apply to this new and challenging area.

In this issue…

Many people travel during the Christmas holidays. Those travelling long distances by air will be interested in the review of flying and thromboembolism by Frank Firkin and Harshal Nandurkar.

International travel can contribute to the spread of infectious diseases including influenza. Several vaccines designed to control the spread of influenza are reviewed in the new drugs section.

Flying can cause earache, but ear infections are a more common problem in children. Peter Morris and Amanda Leach examine the evidence supporting the treatments used to manage otitis media.

Mouthwashes can be used to manage dental plaque, but Camile Farah, Lidija McIntosh and Michael McCullough say that these products have their limitations. They also warn that some mouthwashes have adverse effects, including a controversial association with oral cancer.

Controversy has also surrounded the use of mifepristone in Australia. Although the focus has been on abortion, David Healy informs us that the drug has several other potential uses.

Biological drugs are far more complex than conventional small molecule pharmaceutical products. Whereas conventional drugs can be completely characterised on the basis of their chemical structures, biological drugs tend to be recombinant three-dimensional proteins with structural complexity and a high molecular weight. This makes them difficult to characterise. The complexity of biological drugs also emanates from the elaborate manufacturing processes involved in their production.[1]

A major concern with biological drugs is immunogenicity.[1] As these products are often manufactured in living cells (for example hamster, rabbit or bacterial cells), they are considered foreign by the human body and induce immune responses such as neutralising antibodies. Immunogenicity can be affected by various factors including manufacturing processes and impurities. Impurities may derive from chemicals or antibiotics used during production or from microbial or viral contamination. These can compromise the purity of the final protein and may alter its structure or properties.

The imminent patent expiry of many biological drugs will open the door for greater numbers of biosimilars to enter the market. Marketing approval of biosimilars is a much more complicated issue than approval of generic equivalents of conventional drugs. The clinical performance of biological drugs is highly dependent on the method of production and purification. Immunogenicity can be altered with different formulations or different manufacturing processes (that is, differences in host cells, purification and processing, formulation and packaging). Verifying similarity or comparability of a biosimilar with an innovator product therefore requires much more than demonstrating bioequivalence, which is sufficient for conventional generic drugs. The need for vigilance related to the immunogenicity of biological agents was highlighted by the development of antibody-associated pure red cell aplasia in patients treated with recombinant erythropoietin (epoetin) following a relatively simple manufacturing change.[2]

Analytical tests can characterise molecular mass, protein content, glycosylation pattern, *in vitro* activity, physicochemical integrity, stability, impurities and additives of a biosimilar product. However, these analyses will not guarantee equivalent efficacy and safety to the innovator drug in the relevant patient population.

The therapeutic equivalence of biosimilars and innovator drugs can be assessed in a switching study where patients are switched between the two products. This determines whether the biosimilar induces an immunological response (using assays to detect neutralising antibodies), and whether efficacy and safety are affected when products are switched.[1] The results of such a trial determine if the sponsor of a biosimilar can claim for interchangeable use with the innovator product. These studies are costly and time-consuming. As the complexity of the protein product increases, such as with long-chain or heavily glycosylated proteins and monoclonal antibodies, more clinical data are required to fully characterise the clinical properties of the biosimilar.

The European Union has taken a global lead in establishing guidelines for the approval of biosimilars. As of January 2008, four biosimilars have been approved in Europe – two human growth hormone analogues and two erythropoiesis-stimulating agents. The Therapeutic Goods Administration has adopted the European Medicines Agency (EMEA) guidelines[3] on the non-clinical and clinical requirements for a biopharmaceutical. The guidelines call for far more rigorous testing than would be needed for a chemical generic product. These requirements include pharmaco-toxicological assessment, and pharmacokinetic, pharmacodynamic, efficacy and clinical safety studies.[4]

Due to the unpredictability of the onset and incidence of immunogenicity, postmarketing surveillance is a priority with biosimilars. The European guidelines require the manufacturer to submit a comprehensive pharmacovigilance plan with a focus on monitoring immunogenicity after the product has been marketed. This plan must be established at the time of marketing approval.[4] Also, stringent quality control guidelines recommend that both innovator and biosimilar manufacturers ensure consistency in their production by performing rigorous purity and activity profiling between batches.[5] Providing clinicians with the product summary, the evaluation of the clinical data used for approval, and advice about substitution will be critical for patient care.

Biopharmaceuticals are relatively expensive compared to chemical drugs because of their complex manufacture and clinical development and the costs of handling, distribution and delivery systems. The main reason for using a biosimilar is that it is cheaper than the original product.[6] However, the potential cost-savings associated with biosimilars will be less than the savings from ordinary generics. This is due to the higher manufacturing costs, more extensive testing requirements – generally efficacy and safety have to be demonstrated separately for each of the claimed indications[7] – and the need for a postmarketing pharmacovigilance plan.

Incorporating biopharmaceuticals as therapeutic options into patient management is the new reality. Awareness of the quality, safety and efficacy issues and the differences between biosimilars and innovator products is essential for patient safety. Any decisions to substitute one biopharmaceutical with another should be made with the knowledge and prior consent of the physician. In particular, pharmacovigilance is a shared responsibility between the pharmaceutical industry, physicians, pharmacists, nurses and patients.

References

1. Gottlieb S. Biosimilars: policy, clinical, and regulatory considerations. Am J Health Syst Pharm 2008;65 (14 Suppl 6):S2-8.
2. Louët S. Lessons from Eprex for biogeneric firms. Nat Biotechnol 2003;21:956-7.
3. Therapeutic Goods Administration. Clinical guidelines: European Union guidelines adopted in Australia. www.tga.gov.au/docs/html/euguide/euad_clin.htm#clinicalsimilar [cited 2009 Nov 12]
4. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. London: EMEA; 2006. www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf [cited 2009 Nov 12]
5. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. London: EMEA; 2006. www.emea.europa.eu/pdfs/human/biosimilar/4934805en.pdf [cited 2009 Nov 12]
6. Roger SD, Goldsmith D. Biosimilars: it's not as simple as cost alone. J Clin Pharm Ther 2008;33:459-64.
7. Kingham RF, Lietzan E. Current regulatory and legal considerations for follow-on biologics Clin Pharmacol Ther 2008;84:633-5.

Professor McKinnon serves on the Sanofi Aventis Biosimilar Advisory Committee. Dr Lu is supported by an Australian National Health and Medical Research Council public health training fellowship.

Australian Prescriber and the environment

Australian Prescriber is now printed on paper which is more than 50% recycled (30% pre-consumer 25% post-consumer). Thanks to an arrangement with the printing company Blue Star Print ACT, the journal now uses paper made with pulp certified by the Forest Stewardship Council and produced using processes meeting the standard of ISO14001 environmental certification. The plastic used to wrap *Australian Prescriber* is biodegradable.

Flying and thromboembolism

***Frank Firkin**, Associate Professor and Senior Haematologist, St Vincent's Hospital; and **Harshal Nandurkar**, Associate Professor, Department of Medicine, University of Melbourne, and Head of Haematology, St Vincent's Hospital, Melbourne*

Summary

The risk of deep vein thrombosis and pulmonary embolism increases during, and for several weeks after, flights of four or more hours. Venous stasis due to prolonged immobility and obstruction to venous return from the legs is believed to accentuate any inherent predisposition of the traveller to venous thromboembolism. The incidence increases with flight duration, oestrogen ingestion, a prior episode of venous thromboembolism and coexisting medical or surgical conditions associated with increased risk. Clinically evident episodes occur at an incidence of about one per 4500 long-haul flights. The incidence increases in patients with other risk factors for thromboembolism, so prophylaxis with low molecular weight heparin can be considered. In people at low risk the adverse effects of prophylaxis outweigh the potential benefits.

Key words: economy class syndrome, heparin.

(Aust Prescr 2009;32:148–50)

Introduction

Deep vein thrombosis and pulmonary embolism related to air travel are a cause of concern. The risk of venous thromboembolism is influenced by the conditions prevailing during flight, and the passenger's inherent predisposition to develop venous thrombosis.

Factors implicated in increasing the risk of venous thromboembolism include the duration of the flight and the prothrombotic situation created by venous stasis in the lower limbs. This stasis has been attributed to prolonged immobilisation, obstruction of venous return by compression of lower limb veins and as part of a general reduction in blood flow due to in-flight dehydration. In view of the cramped conditions the problem has been called 'economy class syndrome', but this is probably a misnomer.

Features of the individual traveller associated with an increase in risk of venous thromboembolism include certain physical attributes, female gender, oral contraceptive use, inherited or acquired states that predispose to venous thromboembolism, and a previous history of venous thromboembolism.

Coexisting medical conditions which also increase the risk of venous thromboembolism include active cancer and congestive cardiac failure. These features help to determine a traveller's risk of developing venous thromboembolism.

What is the risk of venous thromboembolism in healthy travellers?

Surveys have sought to identify flight conditions and passenger characteristics that confer increased risk to healthy or 'low-risk' travellers. One relatively large study that obtained statistically significant values for certain risk factors has been helpful.[1] The increase in the risk of developing clinically significant venous thromboembolism is very low in flights of less than about four hours or 4000 km. After four hours the risk increases progressively with increasing flight duration. The average increase in incidence of venous thromboembolism relative to not undertaking a flight is about one event per 4500 passenger flights in excess of four hours. Thromboembolism is therefore a relatively uncommon event in healthy travellers on long-haul flights.[1]

Most clinically significant events occur at the end of a long-haul flight or soon afterwards, with the incidence falling to baseline levels after about 2–4 weeks. People who have to take several long-haul flights increase their risk of thromboembolism.[1]

Risk factors in healthy travellers

Several factors increase the relative risk of venous thromboembolism on long-haul flights (Table 1). The risk appears moderately higher in females, in keeping with the overall slightly greater on-ground risk in women. Taking a combined oral

Table 1

Factors that confer risk of venous thromboembolism on long-haul flights

Moderate risk	Relatively high risk
Oral contraceptive use	Previous venous thromboembolism
Excess body mass index	Recent surgery
Inherited thrombotic states	Congestive cardiac failure
Varicose veins	Active cancer
Short stature	Combination of moderate risk factors
	Very long-haul flights (more than 10 000 km)
	Prolonged immobility

contraceptive pill increases this risk by a similar degree to that in women who are not undertaking long-distance air travel. The risk does not increase as much in older healthy people as would be expected from the trend normally associated with increasing age.[1]

Thromboembolism is more likely to occur in association with prolonged immobility, above normal body mass index, and short stature.[1–3] These physical characteristics have the potential to reduce venous return from the legs although venous stasis is yet to be confirmed under flight conditions. In another survey, obesity and window seating were associated with increased venous thromboembolism risk, in keeping with the likelihood of reduced mobility in those seats.[3]

There is evidence that healthy individuals seated for prolonged periods in aeroplane seats on the ground develop leg oedema in about four hours. There is a decrease in popliteal venous return of about 40%, with an even greater reduction if the feet do not reach the floor. It is reasonable to extrapolate that such adverse physiological consequences are equally relevant to long journeys in vehicles. While the relationship has not been scrutinised as much as in air travel, there is an association between long-distance ground travel and venous thromboembolism.

Oral contraceptives

Oral contraceptive use has been incriminated as a risk factor for venous thromboembolism during long-haul flights. This gives rise to questions about the type of oral contraceptive and whether stopping or changing to an alternative form of contraception will lower the risk of venous thromboembolism.

The increased risk of venous thromboembolism is mainly associated with the combination of oestrogen and progestogen. Later 'generation' formulations have not been associated with a lower risk. After stopping a combined oral contraceptive pill the risk of venous thromboembolism gradually returns to baseline, although this takes the equivalent of 2–3 menstrual cycles. Progestogen-only preparations have less risk of venous thromboembolism, but there is still a 2–3 month delay before the increased risk subsides if the woman switches to them from a combined pill.

Prophylaxis in low-risk travellers

While regular walks around the cabin during long-haul flights could be expected to avert the risk conferred by prolonged lower limb venous stasis, restrictions imposed by blockages in the aisle and by immobility during sleep make this impractical. It remains to be proved that performing the airlines' currently recommended leg exercises while seated will be beneficial during long-haul flights.[3] However, a study under controlled conditions on the ground found that vigorous ankle flexion with feet against resistance causes prompt recovery of lower limb venous return after prolonged immobility.

Studies on small numbers of travellers have claimed to show a reduction in deep vein thrombosis from the use of lower leg compressive stockings. This benefit remains to be proven in the prevention of clinically significant venous thromboembolism in low-risk travellers.[3]

Antiplatelet drugs such as aspirin, or anticoagulants such as low molecular weight heparin or warfarin, have not been proven to be of benefit in reducing the incidence of venous thromboembolism in low-risk travellers. These drugs can induce bleeding so they are not recommended in this population. The known risk of adverse effects outweighs the chance of possible benefit.

Factors conferring moderate to high risk

Table 1 shows the factors associated with a moderate to high risk of venous thromboembolism during or soon after long-haul flights. While pulmonary embolism is associated with high-risk factors such as previous venous thromboembolism, active cancer and heart failure, many cases occur in patients who only have moderate risk factors.[2] These factors closely resemble those that confer an increased risk of venous thromboembolism under different circumstances, such as surgery or prolonged immobility in bed-bound patients. It is therefore reasonable to consider that the pathogenesis of flight-related venous thromboembolism is similar to venous thromboembolism in other situations. If the person is at high risk of thromboembolism on the ground, they will be at a greater risk during a long-haul flight. Under these circumstances the benefit of anticoagulant prophylaxis may outweigh the risk of adverse effects.

Assessing high-risk travellers

An example of an individual at high risk of venous thromboembolism would be someone with a previous history of venous thromboembolism, particularly if associated with laboratory evidence of inherited states, such as Factor V Leiden, or acquired states that predispose to venous thromboembolism (thrombophilia). While screening tests for thrombophilia have an important role in evaluating thrombotic events, they have limited value in predicting significantly increased risk during flight in healthy people. Their predictive value does however increase with a family history of venous thromboembolism or use of oral contraceptives.

Predictive value of tests

Screening tests for thrombophilia can reveal abnormalities that increase the risk of venous thromboembolism, however many other factors have a major impact on the degree of risk. The personal and family history of venous thromboembolism is particularly important information. Detection of an inherited abnormality in a healthy person with no personal or family

history of venous thromboembolism does not indicate a greater than average risk of venous thromboembolism in relation to an event such as a plane flight. Thrombophilia screening is therefore unhelpful in an intending traveller. Conversely, an unequivocal family history of venous thromboembolism indicates increased risk. Thrombophilia screening is then appropriate to evaluate whether heritable contributors to the increased risk can be identified and whether they have been transmitted to the intending traveller.

Prophylaxis in high-risk travellers

Travellers at high risk of venous thromboembolism are candidates for anticoagulant prophylaxis during the period of increased risk imposed by lengthy air travel. Those at particular risk include, for example, passengers with a history of venous thromboembolism, active cancer or recent surgery, especially orthopaedic surgery to the lower limbs. There is no evidence that aspirin protects against venous thromboembolism. Either subcutaneous low molecular weight heparin or oral warfarin reduces the risk of venous thromboembolism. Low molecular weight heparin injected immediately before flight, in the recommended dose for prophylaxis in high-risk settings, is considerably more convenient than anticoagulation with warfarin.

References

1. Kuipers S, Cannegieter SC, Middeldorp S, Robyn L, Büller HR, Rosendaal FR. The absolute risk of venous thrombosis after air travel: a cohort study of 8,755 employees of international organisations. PLoS Med 2007;4:1508-14.
2. Lapostolle F, Surget V, Borron SW, Desmaizieres M, Sordelet D, Lapandry C, et al. Severe pulmonary embolism associated with air travel. N Engl J Med 2001;345:779-83.
3. Schreijer AJM, Cannegieter SC, Doggen CJM, Rosendaal FR. The effect of flight-related behaviour on the risk of venous thrombosis after air travel. Br J Haematol 2008;144:425-9.

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Flying and thromboembolism: a patient's perspective

Hannah Baird, a 38-year-old professional manager, developed a problem after the five-hour flight from Sydney to Perth.

HB: I had a deep vein thrombosis a few years ago so I wanted to reduce the risks of recurrence by drinking lots of water and moving around the cabin as much as possible. However, after standing for about 10 minutes I was asked by the flight attendant to return to my seat.

The next day my left calf was a bit sore. There was no swelling so I thought it was just some muscle stiffness from sitting down for a long time. I went for a walk to try and loosen it up, but that made no difference.

There was a low level ache in my calf that came and went. After two days my leg was more painful and swollen and the ache more continuous. As it was more difficult to walk, I went to an accident and emergency department.

AP: *What did the hospital say?*

HB: The doctors thought it was unlikely I had a deep vein thrombosis as my calf swelling was minimal. I had an ultrasound and was told that I had 'phlebitis'. The treatment was a daily dose of enoxaparin for six weeks. I was given one demonstration of how to inject myself and then I was discharged with no follow-up. I was told to find a general practitioner and get a referral for a nuclear medicine scan.

The hospital said that I should not fly for a month, however given the impracticalities of not returning home to Sydney they agreed that flying after one week was possible. I could do little else but rest in my hotel, as it was difficult to walk.

AP: *How did you manage the treatment?*

HB: The injections stung a bit. I suffered bruising after my first injection, but I got better at injecting myself in the abdomen every morning. About two weeks into the six-week course my leg had improved.

At the end of the course I had a lot of syringes and needles. My local general practice would not take them because of the cost of disposal, nor could I find a pharmacy to take them. My local council has a needle disposal service, but it only operates between 9 am and 5 pm, Monday to Friday. That's not much good for people who work full-time.

AP: *Did you have further assessments?*

HB: I have no family history of thrombosis, I don't smoke and I was not taking oestrogens so my general practitioner referred me to a specialist for investigation. The specialists described my initial blood tests as 'strange', so just repeated them. These repeat tests did not show any clotting problems.

AP: *What advice were you given for future flights?*

HB: The specialist recommended that I wear stockings, drink water, no alcohol and inject a small dose of enoxaparin before and after flights, trains or car journeys of over two hours. Everybody tells you to wear support stockings, but

the problem is, where do you find them? Nobody seems to know. I had to ring around a lot of places before I found somewhere that could supply them.

AP: *Any other comments on your experience?*

HB: When I was in Western Australia I had to use taxis to get between my hotel, the hospital, the general practitioner, the X-ray rooms, etc. Some people may have difficulty getting to their appointments if they are unable to use public transport and cannot afford a taxi.

It would be helpful to get advice about when you can resume physical activity while you are being treated for a thrombosis. I like to go to the gym, but I was unsure when it would be safe to start exercising again. About a year later I had a pulmonary embolism, so I am now on warfarin for life.

Book review

Therapeutic Guidelines: Endocrinology. Version 4.

Melbourne: Therapeutic Guidelines Limited; 2009. 366 pages. Price $39, students $30, plus postage. Also available in electronic format as eTG complete.

***Chee Koh**, Academic General Practice Registrar, Department of General Practice, University of Sydney, Westmead Hospital*

Like previous editions, this book aims to provide 'busy health practitioners' with therapeutic information that is 'clear, practical, authoritative and succinct'.

The layout and structure of the book remains largely unchanged from the previous edition. However, the chapter 'Getting to know your drugs' has returned to the front of the book.

Merits of the book include:

- its use of simple language and clear, concise presentation of information
- comprehensive and up-to-date chapters on diabetes and its management
- timely updates on topics such as obesity and male hypogonadism.

The book has some shortcomings. There is no chapter on the use of hormones for transgender conditions – even in my training practice in a regional setting I am starting to see occasional, but increasing numbers of, transgender patients seeking quite complex advice about hormone therapy and issues surrounding its use. Also, the book's textbook-like structure detracts from it being the quick reference guide that busy doctors love to have handy.

Despite the shortcomings, this latest edition remains an invaluable guide in clinical practice, and has remained true to its core values since its inception.

Mifepristone: an overview for Australian practice

***David L Healy**, Chairman, Department of Obstetrics and Gynaecology, Monash University, Melbourne*

Summary

Mifepristone was the first antiprogestogen to be developed for clinical use. It is not only a progesterone receptor antagonist, but also acts as a glucocorticoid receptor antagonist. The fundamental importance of progesterone for human conception and throughout pregnancy has meant that mifepristone has been used in other countries for emergency contraception and medical abortion in the first and second trimester of pregnancy. It has also been used to manage fetal death *in utero* in the third trimester of pregnancy. There are other potential uses based on its mechanism of action, such as reducing the bleeding associated with uterine fibroids.

Key words: Cushing's syndrome, meningioma, pregnancy, progesterone, progestogen, RU486, therapeutic abortion.

(Aust Prescr 2009;32:152–4)

Introduction

Most health professionals will be familiar with the antioestrogens, clomiphene citrate and tamoxifen. These drugs have been used for years for conditions as diverse as infertility and breast cancer respectively. It was not until 1983 that a drug with antiprogestogenic activity was developed.[1] Mifepristone was the first drug to compete with progesterone at its receptor.

Pharmacology

The progesterone receptor is one of several proteins synthesised by the action of oestradiol on the endometrium. This receptor is a dimer of two distinct proteins and binds progesterone which is a planar steroid. By contrast, mifepristone is a non-planar molecule. This bent, rigid, molecular structure seems important for antisteroid compounds.

Mifepristone binds to the progesterone receptor five times more avidly than progesterone. It also binds with the glucocorticoid receptor three times more strongly than dexamethasone. By contrast, mifepristone binds to the androgen receptor with only one quarter of the affinity of testosterone and has essentially no binding to the mineralocorticoid receptor or oestradiol receptors.

Approximately 85% of mifepristone is absorbed after oral administration. It has a long elimination half-life.

Medical abortion

The World Health Organization (WHO) estimated in 1994 that approximately 150 000 unwanted pregnancies were aborted each day, with at least 500 women dying daily from abortion attempts, especially in low income countries.[2] This led the WHO to assess the combination of mifepristone and various prostaglandin analogues for medical abortion.

Several double-blind randomised controlled trials showed that mifepristone 200 mg, when combined with misoprostol, a prostaglandin E_1 derivative, was as effective as surgical abortion. Misoprostol is only about 1% of the cost of other prostaglandins, is stable at room temperature and is associated with much less pain than gemeprost, so it has become widely used.[3]

Mifepristone can be used as early as five weeks of pregnancy. By contrast, surgical abortion is generally delayed until seven weeks or later. About 1% of women will abort following mifepristone but before the administration of misoprostol. The adverse effects of mifepristone are minimal, but misoprostol can cause nausea, vomiting, diarrhoea and headache.

Following approval from the Therapeutic Goods Administration in March 1994, the WHO selected Monash University and Family Planning Victoria to participate in an international multicentre, double-blind randomised controlled trial of mifepristone and misoprostol for termination of early pregnancy. This trial showed that the efficacy of the mifepristone–misoprostol regimen was the same with 200 mg of mifepristone as with 600 mg of mifepristone.[4]

Regimens

The WHO and the Royal College of Obstetricians and Gynaecologists have shown that a combination of mifepristone followed by misoprostol is the most effective and safe medical method for inducing abortion in the first and second trimester of pregnancy.[4] A typical regimen for medical abortion was 600 mg oral mifepristone followed by 400 microgram of misoprostol administered vaginally 48 hours later. As first shown by the WHO Taskforce on Postovulatory Methods of Fertility Regulation[4], the dose of mifepristone used currently in Australia is 200 mg. This is consistent with the recommendations of the Royal College of Obstetricians and Gynaecologists and with practice in New Zealand. A dose of misoprostol 800 microgram is administered intravaginally 48 hours after administration of mifepristone and most women will abort within the next six hours.[5] For women having medical abortion at up to nine weeks of pregnancy, effective and complete abortion typically occurs in up to 97.5% of women given the 200 mg mifepristone/800 microgram misoprostol regimen.[5]

When mifepristone is not available, as is the situation in many low income countries, abortion can be induced with misoprostol

alone or with intramuscular methotrexate alone. However, complete abortion is less likely and repeated administration is often necessary.

Medical and surgical abortion compared

In most studies of women undergoing first trimester abortion, approximately 25% choose medical abortion, a further 25% prefer surgery and the remainder have no strong preference for either technique.[6,7] The requirements for a medical abortion differ in many respects from those of a surgical abortion. Some patients strongly prefer that friends or family can be present during medical abortion, and patients are not required to fast. Patients in the WHO studies commented on a more friendly approach with medical abortion, which they considered psychologically beneficial at a time when anxiety levels were increased.[8]

Randomised comparisons of medical abortion and surgical abortion at 10–13 weeks gestation have been undertaken.[9] The clinical outcomes were equivalent. The Royal College of Obstetricians and Gynaecologists recommends that abortion services must provide a choice of methods for abortion.[10] Women considering the option of medical abortion or surgical abortion should be told that they may require (further) surgery if the abortion is incomplete. All women undergoing medical or surgical abortion should attend for the recommended medical care after the procedure. Completeness of abortion is typically judged on clinical grounds at this follow-up.

Other uses

As mifepristone has antiprogestogenic activity, it has been studied in situations where its action on receptors may alter the course of the conditions.

Intrauterine fetal death

Progesterone is critical for establishing and maintaining pregnancy. The first WHO study in Australia used mifepristone to manage fetal death in late pregnancy. In these cases, the baby has died, but the placenta has not and it continues to synthesise progesterone for some weeks. This prevents labour and continues the pregnancy in very difficult emotional circumstances for the woman carrying a dead baby. For women with an unexplained fetal death *in utero*, and who have an unripe cervix, mifepristone typically induces delivery within 72 hours.

Contraception

Mifepristone has been used as an emergency contraceptive. In randomised controlled studies, it appears as effective as other regimens, such as those using levonorgestrel. In WHO studies of emergency contraception within seven days of unprotected intercourse, mifepristone was effective at doses of 600 mg, 50 mg and even 10 mg.[11] This is important in low income countries with limited pharmaceutical resources.

Uterine fibroids

Uterine fibroids, or leiomyomata, are the most common tumours in women. The fibroids and their nourishing blood vessels are rich in progesterone receptors. Several trials have shown that mifepristone can reduce the size of uterine fibroids and effectively reduce menstrual blood loss. A recent randomised double-blind clinical trial of 10 mg mifepristone or placebo found that mifepristone reduced uterine and fibroid size and reduced menstrual blood loss. It also increased haemoglobin concentration. As expected from its antiprogestogenic action, endometrial hyperplasia has been observed after three months continued use of mifepristone.[12]

Cushing's syndrome

As mifepristone is a glucocorticoid receptor antagonist, it has been studied in Cushing's syndrome. The first patient to be treated received mifepristone doses of up to 1500 mg daily for nine weeks. No adverse effects were observed. Some patients with Cushing's syndrome have been treated with mifepristone for up to 10 years.[13]

Endometrial hyperplasia has been reported in long-term treatment with mifepristone. It appears to be the result of unopposed oestradiol action on the endometrium due to progesterone receptor blockade. Regular vaginal ultrasound every four months to monitor for endometrial hyperplasia is recommended in women receiving long-term treatment with mifepristone.

Meningioma

Meningioma is a generally benign tumour of the central nervous system. Surprisingly, many of these tumours contain progesterone receptors. Unlike breast cancer, meningiomas are commonly strongly progesterone receptor positive yet only rarely oestrogen receptor positive. Mifepristone inhibits growth of meningioma cells in culture and reduces the size of human meningioma implanted into nude mice.

Patients with unresectable meningioma have been treated with oral mifepristone 200 mg daily for a median duration of therapy of 35 months (range 2–157 months). In one series there were 19 women and 9 men with persistent or recurrent unresectable meningioma.

Eight patients responded to therapy, as shown by reduced tumour size on computerised tomography or magnetic resonance imaging and improvement in visual field examination.[14] Endometrial hyperplasia did occur in three premenopausal women, but did not prove dose limiting.

Breast cancer

Progesterone receptors are found in normal breast tissue and in specimens from breast carcinoma. It was therefore hoped that mifepristone would be of value in treating breast cancer, especially in view of its long-term safety in patients with Cushing's syndrome. Unfortunately, the results of clinical trials have been disappointing in advanced breast carcinoma.[15]

Future directions

Recently, selective progesterone receptor modulators have been developed. These are the 'successors' to mifepristone. They show partial agonist and partial antagonist effects on various progesterone target tissues. For example, asoprisnil has antiproliferative effects on the endometrium and can decrease the size and growth of uterine fibroids by reducing uterine artery blood flow.[16]

Conclusion

In the 25 years since its use was first reported, mifepristone has been registered and widely used for medical abortion in many countries with regulatory standards comparable to Australia. These include the United Kingdom (since 1991), Sweden (1992), USA (2000) and New Zealand (2001). The WHO estimates that at least 1.5 million medical abortions have been undertaken in Europe, with at least 500 000 medical abortions in China and 500 000 in the USA.[17]

Introduction of mifepristone for medical abortion produced a furore which continues to this day. Mifepristone has not yet been sponsored by a pharmaceutical company for use in Australia. There has recently been a change in legislation in Australia.[18] A sponsor may emerge for mifepristone in the near future.

References

1. Healy DL, Baulieu EE, Hodgen GD. Induction of menstruation by an antiprogesterone steroid (RU486) in primates: site of action, dose-response relationships, and hormonal effects. Fertil Steril 1983;40:253-7.
2. Khanna J, Van Look PFA, Griffin PD, editors. Challenges in reproductive health research: biennial report, 1992–1993. Geneva: World Health Organization; 1994.
3. McKinley C, Thong KJ, Baird DT. Pregnancy: the effect of dose of mifepristone and gestation on the efficacy of medical abortion with mifepristone and misoprostol. Hum Reprod 1993;8:1502-5.
4. World Health Organization Task Force on post-ovulatory methods of fertility regulation. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial. BJOG 2000;107:524-30.
5. World Health Organization. Safe abortion: technical and policy guidance for health systems. Geneva: WHO; 2003.
6. Termination of pregnancy. A resource for health professionals. Melbourne: The Royal Australian and New Zealand College of Obstetricians and Gynaecologists; 2005. www.ranzcog.edu.au/womenshealth/pdfs/Termination-of-pregnancy.pdf [cited 2009 Nov 12]
7. Macnaughton M. The abortion pill (mifepristone/RU486): widening the choice for women. London: Birth Control Trust; 1990.
8. Mamers PM, Lavelle AL, Evans AJ, Bell SM, Rusden JR, Healy DL. Women's satisfaction with medical abortion with RU486. Med J Aust 1997;167:316-7.
9. Ashok PW, Kidd A, Flett GM, Fitzmaurice A, Graham W, Templeton A. A randomized comparison of medical abortion and surgical vacuum aspiration at 10-13 weeks gestation. Hum Reprod 2002;17:92-8.
10. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion. London; RCOG: 2004. www.rcog.org.uk/womens-health/clinical-guidance/care-women-requesting-induced-abortion [cited 2009 Nov 12)
11. Comparison of three single doses of mifepristone as emergency contraception: a randomised trial. Task force on postovulatory methods of fertility regulation. Lancet 1999;353:697-702.
12. Bagaria M, Suneja A, Vaid NB, Guleria K, Mishra K. Low-dose mifepristone in treatment of uterine leiomyoma: a randomised double-blind placebo-controlled clinical trial. Aust N Z J Obstet Gynaecol 2009;49:77-83.
13. Johanssen S, Allolio B. Mifepristone (RU 486) in Cushing's syndrome. Eur J Endocrinol 2007;157:561-9.
14. Grunberg SM, Weiss MH, Russell CA, Spitz IM, Ahmadi J, Sadun A, et al. Long-term administration of mifepristone (RU486): clinical tolerance during extended treatment of meningioma. Cancer Invest 2006;24:727-33.
15. Perrault D, Eisenhauer EA, Pritchard KI, Panasci L, Norris B, Vandenberg T, et al. Phase II study of the progesterone antagonist mifepristone in patients with untreated metastatic breast carcinoma: a National Cancer Institute of Canada Clinical Trials Group study. J Clin Oncol 1996;14:2709-12.
16. Wilkens J, Chwalisz K, Han C, Walker J, Cameron IT, Ingamells S, et al. Effects of the selective progesterone receptor modulator asoprisnil on uterine artery blood flow, ovarian activity, and clinical symptoms in patients with uterine leiomyomata scheduled for hysterectomy. J Clin Endocrinol Metab 2008;93:4664-71.
17. Grimes DA. Risks of mifepristone abortion in context. Contraception 2005;71:161.
18. Parliament of Australia Senate. Inquiry into Therapeutic Goods Amendment (Repeal of Ministerial responsibility for approval of RU486) Bill 2005. 2006 Feb 8. www.aph.gov.au/senate/committee/clac_ctte/completed_inquiries/2004-07/ru486/report/index.htm [cited 2009 Nov 12)

Further reading

Healy DL, Fraser HM. The antiprogesterones are coming: menses induction, abortion, and labour? Br Med J (Clin Res Ed) 1985;290:580-1.

De Costa CM. Medical abortion for Australian women: it's time. Med J Aust 2005;183:378-80.

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. College statement. Termination of pregnancy. 2009. www.ranzcog.edu.au/publications/statements/C-gyn17.pdf [cited 2009 Nov 12)

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 171)

1. Mifepristone is a glucocorticoid receptor antagonist.
2. In the first nine weeks of pregnancy, mifepristone and misoprostol induce complete abortion in only 50% of patients.

Managing otitis media: an evidence-based approach

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Summary

Otitis media is a common illness in young children. Historically it has been associated with frequent and severe complications. These days it is usually a mild condition that often resolves without treatment. This has led us to re-evaluate many interventions that were used routinely in the past. Evidence from a large number of randomised controlled trials can help in discussing treatment options with families. In Australia, Aboriginal children have more severe disease and will benefit from effective treatment of persistent (or recurrent) bacterial infection.

Key words: antibiotics, children, ear.

(Aust Prescr 2009;32:155–9)

Introduction

Otitis media is a common illness in young children (and occurs much less frequently in children over six years of age).[1,2] In developed countries, otitis media is the commonest indication for antibiotic prescribing and surgery in young children. In the United States, annual costs were estimated to be US$3–5 billion in the 1990s.[1]

Diagnosis

Otitis media is best regarded as a spectrum of disease. The most important conditions are acute otitis media without perforation, acute otitis media with perforation, otitis media with effusion and chronic suppurative otitis media (see Table 1). There is currently a lack of consistency in definitions of different forms of otitis media (especially acute otitis media).

Children with middle ear infections will usually present with features related to:

- pain and/or fever (acute otitis media)
- hearing loss (otitis media with effusion)
- ear discharge (acute otitis media with perforation or chronic suppurative otitis media).

In some children, otitis media will be detected as part of a routine examination. Making an accurate diagnosis is not easy. Generally it requires a good view of the whole tympanic membrane and the use of either pneumatic otoscopy or tympanometry (to confirm the presence of a middle ear effusion). Studies of diagnostic accuracy in acute otitis media have found ear pain to be the most useful symptom, but not very reliable on its own. Bulging, opacity and immobility of the tympanic membrane are all highly predictive of acute otitis media. Normal (pearly grey) colour of the tympanic membrane makes acute otitis media unlikely.[3]

Acute otitis media

Most children will experience at least one episode of acute otitis media.[1] The peak incidence of infection occurs between 6 and 12 months. Although the pathogenesis of this condition is multifactorial, both viruses and bacteria are implicated.[1]

The pain associated with acute otitis media resolves within 24 hours in around 60% and within three days in around 80% of patients.[2] Young children (under two years of age) are less likely to experience spontaneous resolution.[4]

Complications of acute otitis media include chronic suppurative otitis media, mastoiditis, labyrinthitis, facial palsy, meningitis, intracranial abscess, and lateral sinus thrombosis.[5] Mastoiditis was the most common life-threatening complication in the pre-antibiotic era. It is now rare in developed countries. A small proportion of children with acute otitis media will experience recurrent acute otitis media (three episodes in six months, or four episodes within 12 months).[1]

Table 1

Clinical features of otitis media

Condition	Clinical features
Acute otitis media without perforation	Bulging tympanic membrane with or without ear pain
Acute otitis media with perforation	Recent discharge through perforated tympanic membrane with or without ear pain
Recurrent acute otitis media	Recurrent clinical diagnosis of acute otitis media (at least three in six months)
Otitis media with effusion	Asymptomatic persistent middle ear effusion confirmed by pneumatic otoscopy or tympanometry
Chronic suppurative otitis media	Discharge through a perforation of the tympanic membrane for more than six weeks

Otitis media with effusion

This is the commonest form of otitis media and affects all children but is usually asymptomatic. The point prevalence in screening studies is around 20% in young children.[1] It is more common in Aboriginal communities and was detected in over 40% of young children in a recent survey in the Northern Territory.[6]

Otitis media with effusion can occur spontaneously, as part of rhinosinusitis, or following an episode of acute otitis media. The same respiratory bacterial pathogens associated with acute otitis media have been implicated in its pathogenesis.

Most children will improve spontaneously within three months and complications from this illness are uncommon.[1] A small proportion of children who have persistent otitis media with effusion have associated hearing loss. The average hearing loss associated with otitis media with effusion is around 25 decibels.[1] Despite large numbers of studies, a causal relationship between otitis media with effusion and speech and language delay has not been proven.[5,7]

Chronic suppurative otitis media

Occasionally, children with acute otitis media with perforation will go on to develop chronic suppurative otitis media. In developed countries, chronic suppurative otitis media is now very uncommon and most often occurs as a complication of tympanostomy tube insertion. However, in impoverished populations including those in developed countries, chronic suppurative otitis media occurs as a complication of acute otitis media with perforation. In rural and remote communities in northern Australia, more than 20% of young children are affected.[8]

Chronic suppurative otitis media is the most disabling form of otitis media.[5,9] Although there is a lack of well-designed longitudinal studies, this type of otitis media is most likely to persist without treatment.

The range of bacterial pathogens associated with chronic suppurative otitis media is considerably broader than that seen in acute otitis media. The associated hearing loss is usually more than that seen in otitis media with effusion. Chronic suppurative otitis media represents the most important cause of moderate conductive hearing loss (greater than 40 decibels) in many developing countries.[9]

Interventions

A range of different interventions has been recommended for middle ear infections. Fortunately, many of these have been assessed in randomised controlled trials (see Table 2). This evidence can help with decision making, particularly when discussing options with families.

Acute otitis media

Most children with acute otitis media will improve spontaneously within 14 days and complications from this illness are uncommon. There are data from randomised controlled trials on antibiotics, antihistamines, decongestants, myringotomy and analgesics (see Table 2).[2] Antihistamines, decongestants and myringotomy showed no benefit.

The options at this stage are symptomatic relief with analgesics and either watchful waiting or antibiotics. Antibiotics are most appropriate in the following children:

- aged less than two years with bilateral acute otitis media
- with acute otitis media with perforation
- at risk of complications like chronic suppurative otitis media or mastoiditis (e.g. Aboriginal children living in remote communities, children with immunodeficiency syndromes)
- those who have already had 48 hours of watchful waiting.[4]

Aboriginal children in many communities have a relatively high risk of complications and so you would expect this group to be prescribed antibiotic treatment more often. Current national guidelines recommend amoxycillin 50 mg/kg/day in 2–3 daily doses.[10]

'Wait and see' prescribing

If the child is not in a high risk group but the family prefers antibiotic treatment, the clinician should discuss 'wait and see' prescribing. Provision of a script for an antibiotic along with advice only to use it if the pain persists for 48 hours will reduce antibiotic use by two-thirds (with no negative impact on family satisfaction).[11] If antibiotics are to be used, there is evidence that a longer course of treatment (at least seven days) is more effective, but the beneficial effects are modest (persistent acute otitis media reduced from 22% to 15%). Amoxycillin is the most often prescribed antibiotic for this indication in Australia. Although some clinicians have strong preferences for other antibiotics, there is no evidence that any one of the commonly used antibiotics is more effective than the others.

Recurrent acute otitis media

Prophylactic antibiotics, adenoidectomy and tympanostomy tube insertion have been assessed in randomised controlled trials (Table 2).[2] Antibiotics given for 3–6 months are effective but the benefits are modest. A Cochrane review did not find any evidence that alternative antibiotics were more effective than amoxycillin.[12] The rates of acute otitis media also reduce spontaneously without treatment so that absolute benefits are less impressive than anticipated. Insertion of tympanostomy tubes also appears to reduce acute otitis media and the effect is similar to antibiotics. Either of these options could be considered in those children with very frequent severe infections (especially if occurring before the peak of respiratory illness in winter). However, children with tympanostomy tubes may develop a discharging ear, so this is not a good option in children at increased risk of suppurative infections (including those with

Table 2

Evidence from randomised controlled trials to assist discussion about managing otitis media*

Question	Clinical evidence	Source
Prevention		
Why didn't the conjugate pneumococcal vaccine prevent all these infections?	In 3 studies (39 749 participants), acute otitis media episodes were reduced by 6% (e.g. from 1 to 0.94 episodes per year). Insertion of tympanostomy tubes was reduced from 3.8% to 2.9%.	Systematic review[15]
Should children have influenza vaccine?	In 11 studies (11 349 participants), there were inconsistent results. There was a modest protection against acute otitis media during influenza season in some studies.	Systematic review[16], meta-analysis[17]
Treatment of initial acute otitis media		
Do you recommend antihistamines and/or decongestants?	In 12 studies (2300 participants), there was no significant difference in persistent acute otitis media at 2 weeks.	Systematic review[18]
What about antibiotics?	In 8 studies (2287 participants), persistent pain on days 2–7 was reduced from 22% to 16%.	Systematic review[19]
	Analysis of individual patient data from 6 studies (1643 participants) found that persistent pain was reduced from 55% to 30% in children under 2 years with bilateral acute otitis media, and from 53% to 19% in children with acute otitis media with perforation.	Meta-analysis of individual patient data[20]
Is myringotomy worth considering?	In 3 studies (812 participants), early treatment failure actually increased from 5% to 20%.	Meta-analysis[5]
Do analgesics like paracetamol or ibuprofen help?	In 1 study (219 participants), persistent pain on day 2 was reduced from 25% to 9%.	Randomised controlled trial[21]
Treatment of recurrent acute otitis media		
Is there a role for prophylactic antibiotics?	In 16 studies (1483 participants), acute otitis media episodes were reduced from 3 to 1.5 episodes per year.	Systematic review[12]
What about adenoidectomy?	In 6 studies (1060 participants), there was no significant reduction in rates of acute otitis media.	Meta-analysis[5], randomised controlled trials[22–24]
Do tympanostomy tubes help?	In 5 studies (424 participants), acute otitis media episodes were reduced from 2 to 1 episode per year.	Meta-analyses[5,25], randomised controlled trial[24]
Treatment of persistent otitis media with effusion		
Do antibiotics work?	In 9 studies (1534 participants), persistent otitis media with effusion at around 4 weeks was reduced from 81% to 68% (antibiotic courses for 14–30 days).	Meta-analysis[5]
Do tympanostomy tubes help?	In 11 studies (about 1300 participants), there was a modest improvement in hearing; 9 decibels at 6 months and 6 decibels at 12 months. There was no improvement in language or cognitive assessment.	Systematic review[26], meta-analysis of individual patient data[27]
What about antihistamines and decongestants?	In 7 studies (1177 participants), there was no difference in persistent otitis media with effusion at 4 weeks (75%).	Meta-analysis of individual patient data[27], systematic review[28]
Should we try one of those autoinflation devices?	In 6 studies (602 participants), there were inconsistent results. There was a modest improvement in tympanometry at 4 weeks in some studies.	Systematic review[29]
What about using antibiotics plus oral steroids?	In 5 studies (418 participants), persistent otitis media with effusion at 2 weeks was reduced from 75% to 52%.	Systematic review[30]
Treatment of chronic suppurative otitis media		
Do topical antibiotics work?	In 7 studies (1074 participants), persistent chronic suppurative otitis media at 2–16 weeks reduced from around 75% to 20–50%.	Systematic review[31,32]
Can we use ear cleaning alone?	In 2 studies (658 participants), there were inconsistent results. There was no reduction in persistent chronic suppurative otitis media at 12–16 weeks (78%) in a large African study.[33]	Systematic review[31,32]

* See online publication for references 15–33

immunodeficiency or persistent bacterial rhinosinusitis). For these children, prophylactic antibiotics or prompt antibiotic treatment of infections are probably the more appropriate choices. Consistent with this, the benefits of long-term antibiotics in reducing perforation of the tympanic membrane have been demonstrated in a randomised trial of Aboriginal infants living in a remote community.[13] In this study, infants with otitis media with effusion were randomised to twice-daily amoxycillin or placebo for up to six months. Episodes of acute otitis media continued to be treated with antibiotics, so benefits were presumably due to the fact that many episodes go unrecognised.

Otitis media with effusion

There is evidence from randomised controlled trials on treatment effects of antibiotics, insertion of tympanostomy tubes, autoinflation devices, antihistamines and decongestants, and antibiotics plus steroids (see Table 2).[14]

A course of watchful waiting may be appropriate initially. For those children who have persistent otitis media with effusion in both ears associated with hearing loss, a trial of antibiotics is reasonable. Insertion of tympanostomy tubes is most appropriate in children where the primary concern is the conductive hearing loss and communication difficulties. In randomised controlled trials of early versus late insertion of ventilation tubes, watchful waiting for 6–12 months did not adversely affect speech and language development. Children with the most severe conductive hearing loss or established speech and language problems are more likely to benefit.

Children who experience frequent suppurative infections (including those with immunodeficiency or persistent bacterial rhinosinusitis) are at greatest risk of developing chronic suppurative otitis media as a complication of tympanostomy tubes. Families should be informed that a small proportion of children will suffer recurrent persistent otitis media with effusion when the tympanostomy tubes are extruded, and may need a second operation. In these children, tympanostomy tubes plus adenoidectomy is a reasonable option.[5]

Chronic suppurative otitis media

Topical antibiotics, topical antiseptics, systemic antibiotics, and ear cleaning have been investigated in randomised clinical trials (see Table 2).[9] After a discussion with their doctor, most parents would choose topical antibiotic treatment initially. However, even though this is an effective treatment, prolonged or repeated courses of treatment are often required. If this is the case, topical quinolones will provide a slight benefit in terms of reduced risk of ototoxicity. Under the Pharmaceutical Benefits Scheme, ciprofloxacin ear drops are subsidised for Aboriginal and Torres Strait Islander people (aged one month or older).

Conclusion

Otitis media is a common illness that will usually resolve completely without specific treatment. Many interventions have been assessed in randomised controlled trials but none have had substantial absolute benefits for the populations studied. For most children, symptomatic relief and watchful waiting (including education of the parents about likely clinical course) is the most appropriate treatment option. Antibiotics have a role in children with (or at risk of) persistent bacterial infection and in children with discharge through a perforated tympanic membrane.

References

1. Rovers MM, Schilder AG, Zielhuis GA, Rosenfeld RM. Otitis media. Lancet 2004;363:465-73.
2. Bradley-Stevenson C, O'Neill P, Roberts T. Otitis media in children (acute). BMJ Clin Evid 2007;12:301.
3. Rothman R, Owens T, Simel DL. Does this child have acute otitis media? JAMA 2003;290:1633-40.
4. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet 2006;368:1429-35.
5. Rosenfeld RM, Bluestone CD. Evidence-based otitis media. 2nd ed. Hamilton: BC Decker Inc; 2003.
6. Morris PS, Leach AJ, Silberberg P, Mellon G, Wilson C, Hamilton E, et al. Otitis media in young Aboriginal children from remote communities in Northern and Central Australia: a cross-sectional survey. BMC Pediatr 2005;5:27.
7. Roberts JE, Rosenfeld RM, Zeisel SA. Otitis media and speech and language: a meta-analysis of prospective studies. Pediatrics 2004;113(3 Pt 1):e238-48.
8. Leach AJ, Morris PS. The burden and outcome of respiratory tract infection in Australian and aboriginal children. Pediatr Infect Dis J 2007;26(10 Suppl):S4-7.
9. Acuin J. Chronic suppurative otitis media. BMJ Clinical Evidence 2007;02:507.
10. Morris P, Ballinger D, Leach A, Koops H, Hayhurst B, Stubbs L, et al. Recommendations for clinical care guidelines on the management of otitis media in Aboriginal and Torres Strait Islander populations. Canberra: Office for Aboriginal and Torres Strait Islander Health, Commonwealth Department of Health and Aged Care; 2001.www.health.gov.au/internet/main/publishing.nsf/Content /64B3D2636590623FCA25722B0083428D/$File/recs.pdf [cited 2009 Nov 12]
11. Spurling GKP, Del Mar C, Dooley L, Foxlee R. Delayed antibiotics for respiratory infections. Cochrane Database Syst Rev 2007;3:CD004417.
12. Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. Cochrane Database Syst Rev 2006;4:CD004401.
13. Leach AJ, Morris PS, Mathews JD. Compared to placebo, long-term antibiotics resolve otitis media with effusion (OME) and prevent acute otitis media

with perforation (AOMwiP) in a high-risk population: a randomized controlled trial. BMC Pediatr 2008;8:23.

14. Williamson I. Otitis media with effusion in children. Clinical Evidence 2007;08:502.

For references 15–33 see
www.australianprescriber.com/magazine/32/6/155/9/

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 171)

3. Antibiotics are not appropriate for bilateral acute otitis media in children less than two years old.
4. Topical antibiotics are an effective treatment for chronic suppurative otitis media.

Top 10 drugs

These tables show the top 10 subsidised drugs in 2008–09.

Table 1

Top 10 drugs by DDD/1000 pop/day *†

Constituent drug	PBS/RPBS ‡
1. atorvastatin	77.71
2. irbesartan	36.63
3. ramipril	28.62
4. perindopril	27.46
5. simvastatin	27.31
6. paracetamol	21.77
7. candesartan	21.44
8. esomeprazole	21.34
9. aspirin	17.79
10. frusemide	17.49

Table 2

Top 10 drugs by prescription counts †

PBS drug name	PBS/RPBS ‡
1. atorvastatin	10 950 483
2. esomeprazole	5 888 347
3. simvastatin	5 164 548
4. paracetamol	3 912 494
5. perindopril	3 891 971
6. pantoprazole	3 491 231
7. atenolol	3 224 057
8. metformin hydrochloride	3 201 944
9. rosuvastatin	3 165 641
10. irbesartan	3 134 403

Table 3

Top 10 drugs by cost to Government †

PBS drug name	Cost to Government ($A)
1. atorvastatin	621 164 182
2. clopidogrel	210 600 588
3. esomeprazole	205 083 299
4. rosuvastatin	201 708 668
5. simvastatin	170 511 054
6. salmeterol and fluticasone	164 181 553
7. olanzapine	158 870 974
8. ranibizumab	154 941 222
9. rituximab	112 256 755
10. venlafaxine	111 236 036

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people, in every thousand Australians, are taking the standard dose of a drug every day. The DDDs now include not only the use of the drug alone, but also its use in combination products.[1]

† Based on date of supply. Does not include private prescriptions or prescriptions under PBS co-payment.

‡ PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

Source: Drug Utilisation Sub-Committee (DUSC) Database as at 28 September 2009. © Commonwealth of Australia.

Reference

1. Department of Health and Ageing. Australian Statistics on Medicines 2007. Canberra: Department of Health and Ageing; 2009. www.health.gov.au/internet/main/publishing.nsf/Content/pbs-pubs-asm2007 [cited 2009 Nov 12]

Medicines Australia Code of Conduct: breaches

The Medicines Australia Code of Conduct guides the promotion of prescription products by pharmaceutical companies.[1] Each year Medicines Australia publishes a report, from its Code of Conduct Committee, which details all the complaints that have been received about advertising and other promotional activities.

Many of the complaints in this year's report[2] have resulted from monitoring of 'educational events'. Pharmaceutical companies that are members of Medicines Australia provide reports of these activities. Reviewing events which exceeded certain thresholds is one of the functions of the Medicines Australia Monitoring Committee. This committee can refer cases to the Code of Conduct Committee.

The Monitoring Committee was the source of most complaints where a breach of the Code of Conduct was found. Only four of the successful complaints were made by health professionals. About a quarter of all complaints arise from pharmaceutical companies criticising their competitors.

Anyone can make a complaint, and healthcare professionals and members of the public can ask to remain anonymous. This year two complaints came from consumer organisations and there was even a complaint from a drug company representative about their own employer. A breach of the Code was found in about half of the complaints made during the year.

Sanctions can be applied to companies which are found to have breached the Code of Conduct. These may take the form of fines in addition to the withdrawal of promotional material. In some cases the company is required to write a corrective letter to the health professionals who received the material.

When reaching a decision, on whether or not promotional material has breached the Code of Conduct, the Code of Conduct Committee has to consider the details of the complaint and the response of the advertiser. This may require looking at the evidence from clinical trials and how this has been presented. This year's report included examples of selective citation of data, misleading graphical presentations and inappropriate comparisons between products. The Code of Conduct Committee also has to rule on sponsorship and media matters. This year some media releases were found to be promotion rather than news. While donating a proportion of sales to charities may be acceptable for groceries, the Code of Conduct Committee determined that offering to give 25 cents per prescription to a research institute was a breach of the Code.

For educational events the Code of Conduct Committee may have to decide if hospitality has been excessive. A degustation menu for specialists resulted in a $20 000 fine for one company, while providing a $120 bottle of wine cost another company $15 000. Six companies were fined at least $100 000 for their promotional activities. These included a meeting for specialists on Hayman Island, a media release promoting a drug to the public, and producing misleading promotional materials. The largest fine of $175 000 was for several breaches of the code including leaving an internal company document in a general practitioner's surgery. While these fines are large by Australian standards a company in the USA has recently agreed to pay US$2.3 billion for misleading promotion.[3]

Table 1 shows the cases where at least one breach of the Code of Conduct was found. Detailed information about the complaints can be found in the annual report of the Code of Conduct Committee.[2] A new version of the Code of Conduct is scheduled to be implemented on 1 January 2010.[4]

References

1. Medicines Australia. Code of Conduct. 15th ed. 2006. Amended 2007. www.medicinesaustralia.com.au [cited 2009 Nov 12]
2. Medicines Australia. Code of Conduct Annual Report 2008–2009. Canberra: Medicines Australia; 2009. www.medicinesaustralia.com.au [cited 2009 Nov 12]
3. US Department of Justice. Justice Department announces largest health care fraud settlement in its history: Pfizer to pay $2.3 billion for fraudulent marketing [media release]. 2009 Sep 2. www.justice.gov/opa/pr/2009/September/09-civ-900.html [cited 2009 Nov 12]
4. Medicines Australia. Code of Conduct review. www.medicinesaustralia.com.au/pages/page223.asp [cited 2009 Nov 12]

Table 1

Breaches of the Code of Conduct July 2008 – June 2009

Company	Brand (generic) name	Material or activity	Sanction imposed by Code of Conduct Committee
Actelion	–	Educational event	$20 000 fine
AstraZeneca	Crestor (rosuvastatin)	Promotional material	$100 000 fine withdraw material and cease use corrective letter
	Nexium (esomeprazole)	Promotional material	$85 000 fine withdraw materials corrective advertisement
Bayer	Levitra (vardenafil)	Promotional material	$40 000 fine withdraw materials corrective advertisement
Eli Lilly	Cialis (tadalafil)	Media releases	$60 000 fine
Eli Lilly & Boehringer Ingelheim	Cymbalta (duloxetine)	Media release	$100 000 fine withdraw and cease use
Gilead	Truvada (tenofovir with emtricitabine)	Promotional material	$75 000 fine withdraw material corrective letter
GlaxoSmithKline	Seretide (salmeterol with fluticasone)	Promotional material	$175 000 fine withdraw material corrective letter
	Avamys (fluticasone)	Promotional material	$100 000 fine withdraw material corrective letter
Ipsen	Somatuline Autogel (lanreotide)	Promotional material	withdraw material corrective letter
Janssen-Cilag	–	Educational event	$50 000 fine
	–	Educational event	$20 000 fine
	–	Educational event	$15 000 fine
	–	Educational event	$10 000 fine
Merck Serono	–	Educational event	$20 000 fine
Novartis	Exelon (rivastigmine)	Media release	$15 000 fine
	–	Educational event	$5 000 fine
	–	Educational event	$20 000 fine
	Famvir (famciclovir)	Promotional material	$5 000 fine
Nycomed	Somac (pantoprazole)	Promotional material	$90 000 fine withdraw material corrective letter and advert
	–	Educational event	$5 000 fine
Organon	–	Educational event	$100 000 fine
Orphan	Salofalk (mesalazine)	Promotional material	$10 000 fine withdraw material and cease use corrective letter
Pfizer	–	Educational event	$5 000 fine
Sanofi Aventis	Plavix (clopidogrel)	Promotional material	$25 000 fine withdraw material
	–	Educational event	$60 000 fine
	Plavix (clopidogrel)	Sponsorship	$25 000 fine cease promotion of sponsorship
Servier	Coversyl (perindopril)	Promotional activities	$100 000 fine withdraw materials
Sigma	Various	Starter packs	$15 000 fine
Solvay	Lipidil (fenofibrate)	Promotional material	$75 000 fine withdraw material corrective letter/advert

Mouthwashes

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Summary

A mouthwash may be recommended as an antimicrobial, a topical anti-inflammatory agent, a topical analgesic, or for caries prevention. Many different mouthwashes are commercially available and patients and health professionals struggle to select the most appropriate product for a particular need. The selection needs to take into consideration factors such as the patient's oral condition, their disease risk and the efficacy and safety of the mouthwash. Mouthwashes are an adjunct to, not a substitute for, regular brushing and flossing.

Key words: dentistry, oral disease.

(Aust Prescr 2009;32:162–4)

Introduction

Plaque is the primary aetiologic agent in the development of dental caries, gingivitis and periodontal disease.[1] Mechanical removal of plaque through frequent and efficacious brushing and flossing is the principal means of preventing periodontal diseases and diminishing the risk of caries.[2] However, some individuals lack the dexterity, skill or motivation for mechanical plaque removal. Mouth-rinsing is easier to perform and may aid in controlling supragingival plaque and gingivitis[3], but it should always be used in conjunction with mechanical hygiene. Mouthwashes should only be used for short periods of time and should never be the sole means of oral hygiene.

A mouthwash may be recommended to treat infection, reduce inflammation, relieve pain, reduce halitosis or to deliver fluoride locally for caries prevention.[4] There is a multitude of mouthwashes available for these purposes. A consensus panel has recommended that an antiseptic mouthwash should be used as a daily adjunct to mechanical cleaning for prevention of oral disease.[5] However, this panel did not explore the long-term adverse effects of daily mouthwash use and it did not recommend a particular product or offer health practitioners guidelines for selecting an appropriate product. Recommending particular mouthwashes should take into consideration the patient's ability to perform good oral hygiene practices (tooth brushing and dental flossing), the condition of their teeth, gingivae and oral mucosa, their risk of oral disease (for example, presence of xerostomia), and the proven efficacy of the mouthwash and its potential adverse effects.

Chlorhexidine

Chlorhexidine gluconate is a cationic bis-guanide with broad spectrum antimicrobial activity. It is currently the most effective mouthwash for reducing plaque and gingivitis.[6] Use of chlorhexidine is not associated with development of resistant organisms. As chlorhexidine may interact with fluoride and sodium lauryl sulfate (a detergent found in toothpastes), it should be used after rinsing with water or 0.5–2 hours after using toothpaste.

Current recommendations are for twice-daily chlorhexidine to be used only as a short-term adjunct, or as an aid in disinfection of surgical sites, to improve wound healing, or as a short-term treatment of halitosis. It is not recommended for long-term use due to its numerous adverse effects. These include tooth and restoration staining, soft tissue staining, increased calculus deposition, unpleasant taste, taste alteration, burning sensation, desquamation and mucosal irritation. Chlorhexidine may also potentiate oral discomfort in patients with chemotherapy-induced mucositis, xerostomia or ulcerative oral mucosal conditions.

Benzydamine hydrochloride

Benzydamine hydrochloride is added to some chlorhexidine-containing mouthwashes for its analgesic, anti-inflammatory, antimicrobial and anaesthetic properties. Although the exact mechanism of action of benzydamine is unknown, it is thought to affect the production of prostaglandin and thromboxane, reduce pro-inflammatory cytokine production by macrophages and stabilise cell membranes.[7]

Studies have shown that benzydamine can significantly reduce the severity, duration and incidence of radiation-induced mucositis and is well tolerated by patients. It is therefore recommended for radiation-induced oral mucositis and ulcerative mucosal conditions such as recurrent aphthous ulcerative disease.

Essential oils

Mouthwashes containing four phenol-related essential oils (thymol, eucalyptol, menthol and methyl salicylate in up to 26% alcohol) claim to penetrate the plaque biofilm and thus kill micro-organisms that cause gingivitis. These mouthwashes display broad spectrum antimicrobial activity, prevent bacterial aggregation, slow bacterial multiplication, retard plaque maturation and decrease plaque mass and pathogenicity.[8] Their mechanism of action is thought to involve bacterial

cell destruction, bacterial enzyme inhibition and extraction of endotoxin from Gram-negative bacteria. They also have anti-inflammatory and prostaglandin synthetase inhibitory activity and act as antioxidants by scavenging free oxygen radicals. Clinical studies have concluded that essential oils are effective in reducing plaque, gingivitis and halitosis due to their bactericidal and plaque-permeating abilities.[9]

Mouthwashes containing essential oils have been recommended as an adjunct to mechanical oral hygiene, particularly in patients who have impaired oral hygiene and those who suffer from gingival inflammation despite regular brushing and flossing. These mouthwashes can help support gingival health around dental implants. They are not recommended for patients suffering from xerostomia, dental erosion due to a low oral pH, or oral mucosal disease due to possible ethanol-induced mucosal irritation and dryness. These mouthwashes are unsuitable for children due to the risk of accidental ingestion of high doses of ethanol.

Cetylpyridinium chloride, sodium benzoate and triclosan

Cetylpyridinium chloride is a quaternary ammonium compound with antiseptic and antimicrobial properties.[10] It is cationic and thus binds to bacterial surfaces causing disruption of the cell membrane, leakage of intracellular components and disruption of metabolism. Mouthwashes containing cetylpyridinium chloride inhibit and reduce plaque build-up. Those containing sodium benzoate as the active ingredient are thought to act by dispersing fatty, proteinaceous and carbohydrate substances. This weakens plaque attachment and aggregation making it easier to remove during tooth brushing. Triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether) is used to increase the ability of mouthwashes to bind to the oral mucosa and thus be available for longer periods of time.

Clinical studies have shown that mouthwashes with these ingredients significantly lower plaque weight and reduce gingival inflammation. However, other studies have yielded contradictory results showing that some of these products are no better than a placebo or water rinse in reducing plaque and gingivitis scores.[11]

A mouthwash has recently been released that is composed of a two-phase oil–water formula with the oil phase consisting of olive oil and other essential oils, and the aqueous phase containing cetylpyridinium chloride. This product is alcohol-free and has been shown to have a significant effect on halitosis when compared to alcohol-containing essential oil mouthwashes.[12]

Oxygenating agents

Hydrogen peroxide has been used to relieve minor gingivitis because of its oxygenating cleansing action. It is also used to relieve soreness caused by dentures, orthodontic appliances and following dental procedures. Hydrogen peroxide is a bleaching agent with strong oxidising properties and some products also contain ethanol as an antimicrobial, preservative and solvent. Other products are powders composed of sodium perborate monohydrate which undergoes hydrolysis when mixed with warm water to produce hydrogen peroxide and borate. All these products act by liberating oxygen to loosen debris, remove light stains and kill obligate anaerobes. They are also broad spectrum antimicrobials and have been shown to reduce gingivitis and staining.[13]

Oxygenating mouthwashes have been recommended for the treatment of acute ulcerative disease, to reduce gingival inflammation before fixed prosthodontic treatment, and for patients with a physical or intellectual impairment that limits good oral hygiene. They can also be used for stain removal and as a soaking solution for dentures.

Povidone-iodine containing mouthwashes

Povidone-iodine, an iodophore in which iodine is linked to povidone, displays an affinity for the cell membrane thereby delivering free iodine directly to the bacterial cell surface. It has a broad spectrum of activity against bacteria, fungi, protozoa and viruses. The mouthwash has been shown to be effective in reducing plaque and gingivitis and may be a useful adjunct to routine oral hygiene. It also reduces the incidence, severity and duration of radiation mucositis. Absorption of excess iodine has been postulated to result in metabolic complications, however this is not of concern in patients without pre-existing thyroid disease[14] and if the patient spits out the solution.

Antibacterial peroxidase mouthwashes

Mouthwashes that are directed against the bacterial peroxidase system contain four enzymes (lysozyme, lactoferrin, glucose oxidase and lactoperoxidase). They have been formulated to help restore the saliva's natural antimicrobial activity for the relief of xerostomia, gingivitis, minor gum irritations and halitosis. These mouthwashes do not contain alcohol or detergent, but they do have a low pH (5.15) which may pose a risk of dental erosion during long-term use.[15]

Fluoride-containing mouthwashes

Fluoride assists in the prevention of dental caries by promoting remineralisation with fluorapatite and fluoro-hydroxyapatite, thereby increasing enamel resistance to acid attack. Fluoride is available in different concentrations as either acidulated phosphate fluoride or sodium fluoride. Fluoride mouthwashes reduce dental caries[16] and they are recommended for patients at high risk of dental caries including those with xerostomia after irradiation and chemotherapy, those who have difficulty with oral hygiene procedures and those undergoing fixed orthodontic treatment. Fluoride mouthwashes are not indicated in children younger than six years of age as the risk of ingestion is high.

Sodium bicarbonate

A mouthwash can be prepared by dissolving one teaspoon of sodium bicarbonate in a glass of water.[17] It is recommended in patients suffering from xerostomia or erosion due to its ability to increase salivary pH and suppress the growth of aciduric micro-organisms such as *Streptococcus mutans*. Sodium bicarbonate can improve taste and it neutralises acids and thus prevents erosion. It is bland and will not irritate the oral mucosa in patients with xerostomia or oral ulcerative disease.

Alcohol in mouthwashes

Ethanol in mouthwashes is used as a solvent, preservative and antiseptic. It causes protein denaturation and lipid dissolution, so it has antimicrobial activity against most bacteria, fungi and viruses. Studies have shown that high concentrations of alcohol (above 20%) in mouthwashes may have detrimental oral effects such as epithelial detachment, keratosis, mucosal ulceration, gingivitis, petechiae and pain.

There is increasing evidence that there may be a direct relationship between the alcohol content of mouthwashes and the development of oral cancer. The risk of acquiring cancer (oral cavity, pharynx, larynx) is increased by over nine times in smokers, over five times in those who also drink alcohol, and by almost five times in those who neither smoke nor drink alcohol. A recent review of the literature suggested that it would be inadvisable to recommend the long-term use of alcohol-containing mouthwashes.[18]

Conclusion

Patients and oral health practitioners are faced with a multitude of mouthwash products containing many different active and inactive ingredients. Making informed decisions as to the suitability of a particular product for a particular patient can be a complex task. Although many popular mouthwashes may help to control dental plaque and gingivitis, they should only be used for a short time and only as an adjunct to other oral hygiene measures such as brushing and flossing. Long-term use of ethanol-containing mouthwashes should be discouraged given recent evidence of a possible link with oral cancer. Fluoride mouthwashes should be encouraged in patients with a high risk of caries.

References

1. Adams D, Addy M. Mouthrinses. Adv Dent Res 1994;8:291-301.
2. Daly CG. Prescribing good oral hygiene for adults. Aust Prescr 2009;32:72-5.
3. Dona BL, Grundemann LJ, Steinfort J,Timmerman MF, van der Weijden GA. The inhibitory effect of combining chlorhexidine and hydrogen peroxide on 3-day plaque accumulation. J Clin Periodontol 1998;25:879-83.
4. Therapeutic Guidelines: Oral and dental. Version 1. Melbourne: Therapeutic Guidelines Limited; 2007.
5. The role of antiseptic mouthrinses for effective oral disease prevention. Australas Dent Pract 2007;18:14.
6. Arweiler NB, Netuschil L, Reich E. Alcohol-free mouthrinse solutions to reduce supragingival plaque regrowth and vitality. A controlled clinical study. J Clin Periodontol 2001;28:168-74.
7. Epstein JB, Silverman S Jr, Paggiarino DA, Crockett S, Schubert MM, Senzer NN, et al. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. Cancer 2001;92:875-85.
8. Fine DH, Furgang D, Sinatra K, Charles C, McGuire A, Kumar LD. In vivo antimicrobial effectiveness of an essential oil-containing mouth rinse 12 h after a single use and 14 days' use. J Clin Periodontol 2005;32:335-40.
9. Sharma N, Charles CH, Lynch MC, Qaqish J, McGuire JA, Galustians JG, et al. Adjunctive benefit of an essential oil-containing mouthrinse in reducing plaque and gingivitis in patients who brush and floss regularly: a six-month study. J Am Dent Assoc 2004;135:496-504.
10. Witt J, Ramji N, Gibb R, Dunavent J, Flood J, Barnes J. Antibacterial and antiplaque effects of a novel, alcohol-free oral rinse with cetylpyridinium chloride. J Contemp Dent Pract 2005;6:1-9.
11. Nelson RF, Rodasti PC, Tichnor A, Lio YL. Comparative study of four over-the-counter mouthrinses claiming antiplaque and/or antigingivitis benefits. Clin Prev Dent 1991;13:30-3.
12. Loesche WJ. The effects of antimicrobial mouthrinses on oral malodor and their status relative to US Food and Drug Administration regulations. Quintessence Int 1999;30:311-8.
13. Hasturk H, Nunn M, Warbington M, Van Dyke TE. Efficacy of a fluoridated hydrogen peroxide-based mouthrinse for the treatment of gingivitis: a randomized clinical trial. J Periodontol 2004;75:57-65.
14. Adamietz IA, Rahn R, Böttcher HD, Schafer V, Reimer K, Fleischer W. Prophylaxis with povidone-iodine against induction of oral mucositis by radiochemotherapy. Support Care Cancer 1998;6:373-7.
15. Tenovuo J. Clinical applications of antimicrobial host proteins lactoperoxidase, lysozyme and lactoferrin in xerostomia: efficacy and safety. Oral Dis 2002;8:23-9.
16. Marinho VCC, Higgins JPT, Logan S, Sheiham A. Fluoride mouthrinses for preventing dental caries in children and adolescents. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD002284. DOI: 10.1002/14651858. CD002284.
17. Walsh LJ. Preventive dentistry for the general dental practitioner. Aust Dent J 2000;45:76-82.
18. McCullough MJ, Farah CS. The role of alcohol in oral carcinogenesis with particular reference to alcohol-containing mouthwashes. Aust Dent J 2008;53:302-5.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 171)

5. Chlorhexidine mouthwashes remove stains on teeth.
6. Mouthwashes containing flouride should not be used by children under six years of age.

New drugs

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

Anidulafungin

Eraxis (Pfizer)

vials containing 100 mg powder for reconstitution

Approved indication: invasive candidiasis

Australian Medicines Handbook section 5.2.2

Invasive fungal infections are relatively common in hospitalised patients, particularly those who are immunosuppressed or taking antibiotics. Many of these infections are caused by *Candida* species, especially *Candida albicans* and *Candida glabrata*. Conditions such as candidal oesophagitis are often managed with an azole antifungal. If the fungi are resistant, an echinocandin antifungal such as caspofungin may be used.

Anidulafungin is another echinocandin. These drugs act by inhibiting a fungal enzyme, glucan synthase, which is essential for the integrity of the fungal cell wall. Anidulafungin has activity against *Aspergillus* as well as against *Candida*.

As anidulafungin is not well absorbed orally, it has to be diluted and given as a daily intravenous infusion, starting with a loading dose. The drug is not metabolised, but slowly degrades. Very little is excreted in the urine so dose reductions are not needed for patients with renal or hepatic impairment.

A phase II trial randomised 123 patients with invasive candidiasis to receive an infusion of 50 mg, 75 mg or 100 mg for up to 42 days. Although 33 patients died during the study, the results suggested that higher doses of anidulafungin produced a better response.[1] At a dose of 100 mg daily, it eradicated *Candida* from 89% of the evaluable patients.[2] This dose was then evaluated in a phase III trial.

In the trial, 131 patients were given intravenous anidulafungin and 125 were given intravenous fluconazole. Most of the patients had candidaemia and many had previously taken fluconazole. Patients who responded to at least 10 days of intravenous therapy could then start oral fluconazole. After a median of 14–15 days treatment there was a favourable response in 76% of the anidulafungin group and 60% of the fluconazole group. The mortality was 23% with anidulafungin and 31% with fluconazole.[3]

Anidulafungin has been studied for other indications. A double-blind trial has compared intravenous anidulafungin with oral fluconazole in 601 patients with oesophageal candidiasis. After a median duration of therapy of 14 days the symptoms resolved in almost all patients, with a response confirmed by endoscopy in 87% of the anidulafungin group and 88% of the fluconazole group.[4]

Adverse reactions to the infusion such as flushing and rash may be minimised by infusing the drug slowly. The frequency of adverse events is similar to that seen with intravenous fluconazole.[3] Like fluconazole, anidulafungin has been associated with altered hepatic function. In the phase II trial the most frequent adverse events were hypotension, vomiting, nausea and fever.[1]

Although anidulafungin has efficacy in candidiasis there is insufficient evidence to show that it is superior to fluconazole. While the drugs appeared similar in the treatment of oesophageal candidiasis, more patients in the anidulafungin group had relapsed when followed up two weeks after treatment.[4] As few of the patients in the trials had neutropenia, the efficacy of anidulafungin for treating invasive candidiasis in this group is unknown. While an azole antifungal may remain a first choice, drug interactions or the microbiological results may prompt consideration of an echinocandin. However, there are insufficient data to determine if anidulafungin has any advantages over caspofungin.

T T T manufacturer provided clinical evaluation

References *†

1. Krause DS, Reinhardt J, Vazquez JA, Reboli A, Goldstein BP, Wible M, et al. Phase 2, randomized, dose-ranging study evaluating the safety and efficacy of anidulafungin in invasive candidiasis and candidemia. Antimicrob Agents Chemother 2004;48:2021-4.
2. Pfaller MA, Diekema DJ, Boyken L, Messer SA, Tendolkar S, Hollis RJ, et al. Effectiveness of anidulafungin in eradicating *Candida* species in invasive candidiasis. Antimicrob Agents Chemother 2005;49:4795-7.
3. Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al; Anidulafungin Study Group. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007;356:2472-82.
4. Krause DS, Simjee AE, van Rensburg C, Viljoen J, Walsh TJ, Goldstein BP, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. Clin Infect Dis 2004;39:770-5.

Influenza H1N1 vaccine

Panvax H1N1 vaccine (CSL)

single dose vials containing 15 microgram of haemagglutinin in 0.5 mL and multidose vials containing 5 mL or 10 mL vaccine

Approved indication: prevention of 2009 H1N1 influenza

Australian Medicines Handbook section 20.1

Following the rapid spread of a new influenza A H1N1 virus, also called swine flu, the World Health Organization (WHO) declared an influenza pandemic on 11 June 2009.[1] This prompted the development of a 2009 H1N1 vaccine.

Using the same methods employed to make the seasonal influenza vaccine[2], a monovalent split-virus inactivated vaccine that does not have adjuvant has been developed. The virus, which was grown in embryonated chicken eggs, was prepared from the reassortant vaccine virus NYMC X-179A derived from the influenza A/California/7/2009 H1N1 virus (recommended by the WHO).

The safety and immunogenicity of two doses of the vaccine – 15 microgram of haemagglutinin antigen in 0.25 mL and 30 microgram in 0.5 mL – have been tested in 240 healthy adults (aged 18–64 years) in South Australia.[3] Half of the participants were aged 50 or over. Pregnant women were not included in the trial. Two injections of the vaccine were given three weeks apart, in the deltoid muscle of the upper arm. An interim analysis of patient sera found that most people in the trial had produced a robust antibody response three weeks after receiving the first dose (15 or 30 microgram). Neutralising antibody titres of 1:40 or more in a haemagglutination-inhibition assay were observed in 96.7% of people in the lower dose group and 93.3% in the higher dose group. (The haemagglutination-inhibition assay quantifies the highest dilution of patient sera that is able to block haemagglutination of red blood cells by H1N1 virus.) On average, 74.2% (66.1–82.3%) of participants had either seroconverted or had a significant increase in antibody titre. However, people aged 50 or over had a lower-fold increase in antibody response from baseline compared to younger participants.[3]

The fact that most people had high antibody titres after one vaccination was an unexpected result – it was anticipated that two doses of the vaccine would be needed as most people would not have had previous exposure to the H1N1 virus. However, at baseline it turned out that over a third of participants (76 of 240) already had antibody titres of 1:40 or more in the haemagglutination-inhibition assay, regardless of their age. This proportion was even higher in people who had received the 2009 seasonal influenza vaccine – 44% of them (48 of 108) had antibody titres of 1:40 or more at baseline.

The most commonly reported adverse events in the trial were tenderness (30.8% of vaccinees), pain (20.8%) and induration (10%) at the injection site. Other common events included headache (25.8%), malaise (11.7%) and myalgia (15.8%). Three people reported influenza-like illness – one of these tested positive for 2009 H1N1 influenza eight days after vaccination while the other two people tested negative. There were no withdrawals from the trial.[3]

The vaccine is indicated for adults, adolescents and children over 10 years of age and should be given by intramuscular or deep subcutaneous injection. However, it should not be given to people who have had a life-threatening reaction to influenza vaccination, or who have had Guillain-Barré syndrome within six weeks of a previous influenza vaccination. Likewise, it is contraindicated in people who have anaphylactic hypersensitivity to eggs, chicken protein or other constituents of the vaccine. Immune responses to the vaccine may be lower in immunocompromised patients. Immunisation should be postponed in people who have a febrile illness or acute infection.

Based on the interim analysis, it appears that a single 15 microgram dose of the vaccine is immunogenic in healthy adults. However, around a third of people in the trial already had H1N1-specific antibodies before they were vaccinated.[3] The actual effectiveness of the vaccine to protect against influenza A H1N1 virus will not be known until after a mass immunisation program has taken place. Vulnerable groups of patients such as pregnant women, children, the elderly and people with impaired immunity were not included in the trial so it is not known how the vaccine will perform in these individuals.

T T manufacturer provided additional useful information

References

1. World Health Organization. Director-General statement following the meeting of the Emergency Committee. 2009 Jun 11. www.who.int/csr/disease/swineflu/4th_meeting_ihr/en/index.html [cited 2009 Nov 12]
2. Talbot HK, Keitel W, Cate TR, Treanor J, Campbell J, Brady RC, et al. Immunogenicity, safety and consistency of new trivalent inactivated influenza vaccine. Vaccine 2008;26:4057-61.
3. Greenberg ME, Lai MH, Hartel GF, Wichems CH, Gittleson C, Bennet J, et al. Response after one dose of a monovalent influenza A (H1N1) 2009 vaccine – preliminary report. N Engl J Med 2009;361:1-10.

Influenza H5N1 vaccines

Pandemrix (GlaxoSmithKline), Panvax (CSL) and Emerflu (Sanofi Pasteur)

multi-dose vials containing suspension for injection

Approved indication: prevention of pandemic H5N1 influenza

Australian Medicines Handbook section 20.1

The avian influenza A virus subtype H5N1 predominantly infects wild birds and poultry. Although rare, humans can contract the infection through close contact with infected birds, and there have been isolated reports of human-to-human transmission. The overall case fatality rate in humans is around 60%. It is

feared that the virus could evolve to spread more easily from person to person and cause a pandemic.

These vaccines have been approved by the Therapeutic Goods Administration but are only intended to be used once a H5N1 influenza pandemic has been declared. They are all 'mock-up' vaccines based on the prototype H5N1 Vietnam/1194/2004 NIBRG-14 strain. The pandemic strain will only be included in these vaccines once a pandemic occurs.

These are split-virus inactivated vaccines composed of purified antigen fractions from a recombinant virus (which is propagated in fertilised hen eggs) containing the haemagglutinin gene of the prototype strain. The GlaxoSmithKline vaccine contains 3.75 microgram of haemagglutinin per dose with an oil–water emulsion adjuvant (AS03), and the CSL vaccine contains 30 microgram of haemagglutinin per dose with aluminium phosphate as an adjuvant. The Sanofi Pasteur vaccine contains 30 microgram of haemagglutinin per dose mixed with an adjuvant – aluminium hydroxide. The vaccines should be given intramuscularly in two doses, three weeks apart.

In a trial of the GlaxoSmithKline vaccine, 86% (42 of 49) of immunised adults had seroconverted or had a significant increase in neutralising antibodies to the vaccine strain 21 days after the second vaccine dose. Similarly, 82% (41 of 49) had antibody titres of at least 1:40 in a haemagglutination-inhibition assay – this assay quantifies the highest dilution of patient sera that is able to block haemagglutination of red blood cells by H5N1 virus. In addition, up to 77% of the vaccinees produced neutralising antibodies to another prototype vaccine strain based on influenza A strain H5N1 Indonesia/5/2005, clade 2. Injection-site reactions such as pain, induration and swelling were the most commonly reported adverse events (90%, 28% and 20% of people), most of which were of mild to moderate intensity. Headache, fatigue and muscle aches were also common complaints.[1]

The CSL vaccine has been assessed in a phase II trial of 400 adults who were given a 30 or 45 microgram haemagglutinin dose. After the second dose, almost 60% of the vaccinees had antibody titres of at least 1:32 in a haemagglutination-inhibition assay.[2] There have also been trials of this vaccine in children (6 months to nine years) and the elderly (65 years and older). After the second dose, 98.3% of children and 47.5% of the older adults had seroconverted or had a significant increase in antibody titres to the H5N1 virus. The most common adverse events in adults (reported by 10% of people or more) included headache, nausea, myalgia, fatigue and injection-site reactions. In a phase I trial of this vaccine, a woman had a miscarriage after the second vaccine dose 11 weeks into her pregnancy. This was thought to be possibly related to the vaccine.[2] In children, the most common events were headache, decreased appetite, rhinorrhoea, sneezing, diarrhoea, vomiting, myalgia, irritability, fever and injection-site reactions.

The Sanofi Pasteur vaccine was assessed in 51 adults who were given the 30 microgram dose vaccine with adjuvant. After the second dose, 67% of vaccinees had antibody titres of at least 1:32 in a haemagglutination-inhibition assay. A similar proportion had seroconverted or had a significant increase in antibody titres. Three-quarters of the vaccinees had an injection-site reaction – these included pain, erythema and induration. Headache (61% of people), myalgia (37%) and malaise (20%) were also common after vaccination.[3]

It is not known if antibodies produced to these H5N1 vaccines would protect humans from infection. However in a preclinical study of the GlaxoSmithKline vaccine, immunisation protected 22 of 23 ferrets against lethal challenge with a heterologous Indonesian prototype vaccine strain.[4]

Based on the trials, it seems that two doses are needed to produce a robust antibody response to these H5N1 vaccines in healthy adults. Most people in the trials did not have antibodies to the vaccine strain before they were immunised.[1–3] Direct comparison of the immunogenicity data between trials is not really possible as immunoassays, such as the haemagglutination-inhibition assay, may vary between laboratories.

It is important to remember that the safety and efficacy of these prototype vaccines will only be determined during a pandemic once the vaccines have been made. In the event of a pandemic, it will take at least 3–6 months before vaccines such as these are ready for use.[5]

X manufacturer did not respond to request for data (GlaxoSmithKline)

X manufacturer declined to supply data (CSL)

T T T manufacturer provided clinical evaluation (Sanofi Pasteur)

References †

1. Leroux-Roels I, Borkowski A, Vanwolleghem T, Dramé M, Clement F, Hons E, et al. Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial. Lancet 2007;370:580-9.
2. Nolan TM, Richmond PC, Skeljo MV, Pearce G, Hartel G, Formica NT, et al. Phase I and II randomised trials of the safety and immunogenicity of a prototype adjuvanted inactivated split-virus influenza A (H5N1) vaccine in healthy adults. Vaccine 2008;26:4160-7.
3. Bresson JL, Perronne C, Launay O, Gerdil C, Saville M, Wood J, et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: phase I randomised trial. Lancet 2006;367:1657-64.
4. Baras B, Stittelaar KJ, Simon JH, Thoolen RJ, Mossman SP, Pistoor FH, et al. Cross-protection against lethal H5N1 challenge in ferrets with an adjuvanted pandemic influenza vaccine. PLoS ONE 2008;3:e1401.
5. Booy R, Brown LE, Grohmann GS, MacIntyre CR. Pandemic vaccines: promises and pitfalls. Med J Aust 2006;185:S62-5.

Influenza seasonal vaccine

Intanza (Sanofi Pasteur)

prefilled glass syringes containing 0.1 mL suspension

Approved indication: prevention of seasonal influenza

Australian Medicines Handbook section 20.1

This is the first intradermal influenza vaccine to be approved in Australia. It is an inactivated split virion vaccine containing haemagglutinin from three influenza strains (A/New Caledonia/20/99 (H1N1)-like strain, A/Wisconsin/67/2005 (H3N2)-like strain, B/Malaysia/2506/2004-like strain). The combination of antigens will vary each year depending on the circulating influenza strains.

Unlike the other influenza vaccines, it is administered into the dermal layer of the skin using a 1.5 mm needle. It is thought that after injection, the antigens are taken up by dendritic cells in the dermis and transported to the lymph nodes. Here they are presented to T and B lymphocytes which become activated and undergo clonal expansion.

A trial in 978 adults (aged 18–57) found that immune responses to the intradermal vaccine (9 microgram haemagglutinin per strain in 0.1 mL) were non-inferior to those of an intramuscular vaccine containing the same antigens (15 microgram haemagglutinin per strain in 0.5 mL).[1]

In another trial in 1107 older adults (aged 60 and over), mean antibody titres to the intradermal vaccine (15 or 21 microgram dose) were superior to an intramuscular comparator vaccine (15 microgram dose). However, injection-site reactions such as erythema were more common with the intradermal vaccine than with the intramuscular vaccine (78% vs 19%). Similarly, more people in the intradermal vaccine group reported induration, swelling and pruritus. Pain was similar between groups.[2]

A 9 microgram dose will be available for people aged 18–59, and a 15 microgram dose will be available for people aged 60 and over.

T manufacturer provided only the product information

References

1. Leroux-Roels I, Vets E, Freese R, Seiberling M, Weber F, Salamand C, et al. Seasonal influenza vaccine delivered by intradermal microinjection: a randomised controlled safety and immunogenicity trial in adults. Vaccine 2008;26:6614-9.
2. Holland D, Booy R, De Looze F, Eizenberg P, McDonald J, Karrasch J, et al. Intradermal influenza vaccine administered using a new microinjection system produces superior immunogenicity in elderly adults: a randomised controlled trial. J Infect Dis 2008;198:650-8.

Methoxy polyethylene glycol-epoetin beta

Mircera (Roche)

prefilled syringes containing 30, 50, 75, 100, 120, 150, 200 or 250 microgram in 0.3 mL

Approved indication: anaemia associated with chronic kidney disease

Australian Medicines Handbook section 7.5.1

Erythropoietin is a hormone produced by the kidneys which stimulates red blood cell production. Patients with chronic kidney disease may produce less erythropoietin than normal and develop anaemia (Aust Prescr 2009;32:126–8). Recombinant forms of the hormone (darbepoetin alfa, epoetin alfa, epoetin beta) have been available for several years and have been shown to benefit these patients.

Methoxy polyethylene glycol-epoetin beta is also a recombinant product. It has been chemically modified and has different activity to erythropoietin at the receptor level – it associates with the receptor more slowly, but dissociates faster. It has a much longer half-life than erythropoietin and does not need to be given as often. After subcutaneous administration, maximum serum concentrations are reached after 72 hours. The elimination half-life is 139 hours after a subcutaneous injection and 134 hours after an intravenous injection. Haemodialysis has no effect on serum concentrations of this drug.

There have been several open-label comparative trials of methoxy polyethylene glycol-epoetin beta for treating anaemia in chronic kidney disease. The main efficacy measure in these trials was correction or maintenance of haemoglobin concentrations. Two of these studies were in patients starting treatment for anaemia. The first was in 181 patients on dialysis. After 24 weeks of treatment, methoxy polyethylene glycol-epoetin beta (given intravenously once every two weeks) seemed to be as effective as epoetin (given three times a week). Following dose titration, 93% of patients receiving methoxy polyethylene glycol-epoetin beta and 91% of patients receiving epoetin alfa or epoetin beta had responded to treatment (haemoglobin increase of at least 10 g/L from baseline and haemoglobin target of at least 110 g/L without a blood transfusion).[1] In the second trial of 324 patients not on dialysis, methoxy polyethylene glycol-epoetin beta (given subcutaneously every two weeks) was non-inferior to darbepoetin alfa (given weekly). Almost all patients (98% with methoxy polyethylene glycol-epoetin beta, 96% with darbepoetin alfa) had responded to treatment by 28 weeks.[2]

In four other trials, the efficacy of methoxy polyethylene glycol-epoetin beta was assessed in patients on dialysis who were either switched to methoxy polyethylene glycol-epoetin beta or remained on epoetin therapy. When given intravenously[3,4] or subcutaneously[5,6] once every one,

two or three weeks, or once a month, methoxy polyethylene glycol-epoetin beta maintained haemoglobin levels as effectively as the original erythropoiesis-stimulating drug.

The adverse effects of methoxy polyethylene glycol-epoetin beta are similar to other erythropoiesis-stimulating drugs, and include an increase in cardiovascular and thrombotic events, and sudden death. The most commonly reported event was hypertension so methoxy polyethylene glycol-epoetin beta should not be given to patients with uncontrolled hypertension. Other common adverse events included diarrhoea, nasopharyngitis and headache. However, the frequency of these events was similar in the comparator groups.

During the trials, methoxy polyethylene glycol-epoetin beta reduced platelet count more than other erythropoiesis-stimulating drugs. Thrombocytopenia (less than 100 x 10^9 platelets/L) occurred in 9% of patients receiving methoxy polyethylene glycol-epoetin beta compared to 6.2% of patients receiving the comparator. Gastrointestinal and urinary bleeding events were also higher with the study drug than with other epoetins. The risk may be increased with co-administration of antiplatelet drugs.

This drug should be used with caution in patients with epilepsy. Care should also be taken in patients with haemoglobinopathies or a platelet count of more than 500 x 10^9/L.

Pure red cell aplasia can be caused by antibodies to erythropoietin. Patients with these neutralising antibodies should not be switched to methoxy polyethylene glycol-epoetin beta. Like other erythropoiesis-stimulating drugs, methoxy polyethylene glycol-epoetin beta increases the risk of death in patients with cancer and should not be used to treat their anaemia.

Methoxy polyethylene glycol-epoetin beta can be given subcutaneously or intravenously. Subcutaneous injections can be given in the abdomen, arm or thigh. The starting dose and the dosing frequency of this drug depend on whether the patient is already receiving erythropoietin or is starting treatment. The product information explains how to calculate the dose if a patient is switching from another erythropoietin. In treatment-naïve patients, the recommended dose is 0.6 microgram/kg every two weeks initially. Increases in haemoglobin usually occur after 7–15 days. Haemoglobin should be monitored regularly and the dose should be adjusted to maintain a target of 100–120 g/L. Rises in haemoglobin should not be above 10 g/L in a two-week period. Once the target is reached, methoxy polyethylene glycol-epoetin beta can be given once a month. Concomitant supplementary iron is recommended for all patients with serum ferritin values below 100 microgram/L, or whose transferrin saturation is less than 20%.

Methoxy polyethylene glycol-epoetin beta seems to be as effective as other epoetins for correcting and maintaining haemoglobin concentrations in patients with renal anaemia. However, evidence of direct clinical benefit such as reduced morbidity and mortality is limited.

T T T manufacturer provided clinical evaluation

References*†

1. Klinger M, Arias M, Vargemezis V, Besarab A, Sulowicz W, Gerntholtz T, et al. Efficacy of intravenous methoxy polyethylene glycol-epoetin beta administered every 2 weeks compared with epoetin administered 3 times weekly in patients treated by hemodialysis or peritoneal dialysis: a randomised trial. Am J Kidney Dis 2007;50:989-1000.
2. Macdougall IC, Walker R, Provenzano R, de Alvaro F, Locay HR, Nader PC, et al. C.E.R.A. corrects anemia in patients with chronic kidney disease not on dialysis: results of a randomized clinical trial. Clin J Am Soc Nephrol 2008;3:337-47.
3. Levin NW, Fishbane S, Canedo FV, Zeig S, Nasar GM, Moran JE, et al. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA). Lancet 2007;370:1415-21.
4. Canaud B, Mingardi G, Braun J, Aljama P, Kerr PG, Locatelli F, et al. Intravenous C.E.R.A. maintains stable haemoglobin levels in patients on dialysis previously treated with darbepoetin alfa: results from STRIATA, a randomized phase III study. Nephrol Dial Transplant 2008;23:3654-61.
5. Locatelli F, Villa G, de Francisco AL, Albertazzi A, Adrogue HJ, Dougherty FC, et al. Effect of a continuous erythropoietin receptor activator (C.E.R.A.) on stable haemoglobin in patients with CKD on dialysis: once monthly administration. Curr Med Res Opin 2007;23:969-79.
6. Sulowicz W, Locatelli F, Ryckelynck JP, Balla J, Csiky B, Harris K, et al. Once-monthly subcutaneous C.E.R.A. maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. Clin J Am Soc Nephrol 2007;2:637-46.

Vaccinia smallpox vaccine

ACAM2000 (Baxter)

lyophilised powder for reconstitution and injection

Approved indication: prevention of smallpox

Australian Medicines Handbook section 20.1

Previous vaccines have been effective in preventing smallpox, with the last case reported in Somalia in 1977. However, there are growing concerns that variola virus, which causes smallpox, may still be present in some laboratories and could be used as a biological weapon.

The disease is transmitted from human to human via saliva droplets. Most people recover from the infection caused by the *Variola minor* strain, but death can occur in up to a third of people infected with the *Variola major* strain.

This vaccine is a live attenuated vaccinia virus which cross-protects people against both strains of the variola virus. In contrast to the old vaccine – which was grown in the skin of

calves – this vaccine is produced by growing the ACAM2000 virus clone (derived from the old vaccine strain) in tissue culture. It must be given percutaneously in the upper arm using 15 jabs of a bifurcated needle, by a health professional trained in the procedure. Skin preparation should not normally be performed before the injections. However, if the vaccination site is visibly dirty, wipe it with an alcohol swab and make sure it is completely dry before giving the vaccine. This is to prevent inactivation of the virus by alcohol. After vaccination, the virus causes a localised infection at the injection site. The development of a pustule indicates that the vaccine has induced protective immunity.

The vaccine comes in multi-dose vials. Once it has been reconstituted in 0.3 mL of diluent, each vial contains approximately 100 doses.

In a phase II study, the highest dose of ACAM2000 vaccine appeared to induce equivalent immune responses to the old vaccine strain.[1] In another randomised trial of 90 people, the new vaccine was compared to the parent vaccine strain and to a similar vaccine derived from the ACAM1000 virus clone (1:1:1). All participants had developed a pustule at the injection site within a week of vaccination, but the mean erythema size was significantly larger with the old vaccine compared to the ACAM2000 and ACAM1000 vaccines (36 mm vs 18 mm and 22 mm). Viral shedding was measured by culturing swabs from the inoculation site for approximately six weeks after vaccination. In all groups, viral shedding peaked at 15 days and had stopped by six weeks when most lesions had healed.[2]

The new vaccine has also been compared to the old vaccine (3:1) in two phase III trials involving almost 3000 people – one trial enrolled people who had received a previous vaccine more than ten years earlier and the other enrolled vaccinia-naïve individuals. In people receiving the vaccine for the first time, it elicited a major cutaneous reaction in most people and was non-inferior to the comparator (96% vs 99% of individuals). However, mean antibody titres to the new vaccine were not as high as those seen with the comparator and did not meet the criteria for non-inferiority. In previously vaccinated people, antibody responses were non-inferior to the comparator.

Itching and pain at the injection site, fatigue, lymph node pain, headache, malaise and myalgia have been reported by the majority of people who have received the vaccine.[2] There is a risk of cardiac events (including fatalities) with this vaccine. In clinical trials, there were ten cases of suspected myocarditis out of 2983 people. All of these events were in vaccinia-naïve people and occurred between 9 and 20 days after vaccination. The risk of cardiac problems may be increased in people with heart conditions such as previous myocardial infarction, angina, congestive heart failure, cardiomyopathy, chest pain or shortness of breath during activity, and stroke or transient ischaemic attack. Similarly, people with at least three of the following risk factors for ischaemic coronary disease – high blood pressure, elevated cholesterol, diabetes, first degree relative with a heart condition before the age of 50 and smoking – have an increased risk of cardiac events with the vaccine.

Because live virus particles are shed from the pustule that forms after vaccination, infections can spread to other parts of the body. Accidental eye infections have been reported with the vaccine and may result in complications including keratitis, corneal scarring and blindness. People using corticosteroid eye drops are at increased risk of this. People with skin disorders, particularly eczema, have a higher risk of developing eczema vaccinatum.

The vaccine is contraindicated in individuals with severe immunodeficiency, such as people with cancer, HIV/AIDS or cellular or humoral immune deficiency, or those receiving immunosuppressive drugs, radiation therapy or alkylating agents. The vaccine is also not recommended for pregnant women because of the risk of fetal death, or in infants under one year. After vaccination, contact with individuals who have a high risk of complications should be avoided.

To prevent the spread of the vaccinia virus, patients should keep the injection-site wound covered until it heals, wash their hands after handling bandages and wash any contaminated clothing or bed sheets separately.

This vaccine may cause false-positives with syphilis testing. Positive results from the rapid plasma reagin (RPR) test should be confirmed by a more specific test such as the fluorescent treponemal antibody-absorbed (FTA) test. Similarly, the vaccine may induce false negative results with the tuberculin skin test so if this test is planned, it should be postponed for one month after smallpox vaccination. Blood and organ donation should be avoided for at least 30 days after vaccination.

This vaccine appears to be effective in inducing a cutaneous immune response similar to that seen with the older calf-derived vaccine, but antibody titres seem to be lower. There are some concerns about the cardiac safety of this vaccine.

T T T manufacturer provided clinical evaluation

References *

1. Artenstein AW, Johnson C, Marbury TC, Morrison D, Blum PS, Kemp T, et al. A novel, cell culture-derived smallpox vaccine in vaccinia-naïve adults. Vaccine 2005;23:3301-9.
2. Frey SE, Newman FK, Kennedy JS, Ennis F, Abate G, Hoft DF, et al. Comparison of the safety and immunogenicity of ACAM1000, ACAM2000 and Dryvax in healthy vaccinia-naïve adults. Vaccine 2009;27:1637-44.

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

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

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

Addendum

Subsidised medicines for Aboriginal and Torres Strait Islander people (Aust Prescr 2009;32:121)

Nasal colonisation with S. aureus

12. Mupirocin nasal ointment (2%)

Medicines Line (phone 1800 888 763)

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