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Editorial

The emperor's new clothes – can chemotherapy survive?

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Keywords: antineoplastics, cancer.

(Aust Prescr 2006;29:2–3)

'An Australian study suggests that the benefits of chemotherapy have been oversold … Why has it been oversold? Are you suggesting that medical oncologists in Australia are just sort of marketing shysters or what?' These were some of the questions posed by Dr Norman Swan when he presented the Health Report on ABC Radio National on 18 April 2005.[1] Dr Swan was quizzing Associate Professor Graeme Morgan, the lead author of a controversial article entitled 'The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies'.[2]This article reported that chemotherapy has improved survival by less than 3% in adults with cancer.

These provocative figures were derived from a literature search of all randomised clinical trials reporting a five-year survival benefit attributable solely to cytotoxic chemotherapy in 22 major adult malignancies. The common malignancies of bowel, lung, breast and prostate were included. The total number of newly diagnosed cancer patients for each malignancy in 1998 was determined from cancer registry data in Australia and the USA. The absolute number to benefit was the product of the total number of patients with that malignancy, the proportion or sub-group(s) with that malignancy showing a benefit, and the percentage increase in five-year survival due solely to cytotoxic chemotherapy. The overall contribution was the sum total of the absolute numbers of patients showing a five-year survival benefit expressed as a percentage of the total number for the 22 malignancies.

Overall cancer survival, following all kinds of treatment, is approximately 63%. Based on the calculations in the study the contribution of chemotherapy to adult survival from cancer was estimated to be 2.3% in Australia and 2.1% in the USA. The authors, two of whom are radiation oncologists, but one of whom is a practicing professor of medical oncology, concluded that 'chemotherapy only makes a minor contribution to cancer survival' and 'to justify the continued funding and availability of drugs used in cytotoxic chemotherapy, a rigorous evaluation of the cost-effectiveness and impact on quality of life is urgently required'.

The paper attracted much attention. In the medical oncology community, there was much outrage and indignation at this 'misleading and unhelpful' paper. Associate Professor Michael Boyer, head of medical oncology at Royal Prince Alfred Hospital, Sydney, commented, 'The fact is that from a patient's perspective they are not really interested in how much chemotherapy contributes to the cure of all patients, what they are interested in is how much it will contribute to their particular disease and their stage of their disease … I don't think this paper helps from a patient's perspective. Similarly from a public funding, or public policy point of view, lumping everything together is not a terribly helpful way …'.[1]

Associate Professor Boyer raised concern about the study methodology and the fact that 'if you start … saying how much does chemotherapy add in the people that you might actually use it [in], the numbers start creeping up … to 5% or 6% …'.[1] It is true that the paper used definitions of convenience and excluded certain cancers with high cure rates from chemotherapy, such as leukaemias, childhood cancers and other curable rare cancers. In addition, the study did not account for the contribution of chemotherapy in increasing the efficacy of other modalities, for example in 'downstaging' before surgery or when used concurrently with radiation. The data set, from

In this issue…

Chemotherapy is an accepted treatment for cancer, but how many patients are aware of its very limited effect on survival? Eva Segelov questions whether our current approach to therapy is sustainable. Perhaps there will be a greater role for angiogenesis inhibitors in oncology, but as Stephen Clarke, Rohini Sharma and Paul Mainwaring point out, much more research is needed.

The breaches of the Medicines Australia advertising code make interesting reading. None of the drugs found in breach made it into the top ten most commonly prescribed drugs by population.

Drug utilisation can be improved by stopping medicines that are no longer needed. Rob Smith advises on how to withdraw antiepileptic drugs from children who are seizure-free.

1998, does not reflect recent advances with more modern chemotherapy drugs, although again their impact on survival is modest.

The article did not aim to address quality of life or other benefits from chemotherapy, or any parameters relating to palliation, which after all is the aim of the great majority of chemotherapy. It also does not discuss the curative benefit of other drugs in the medical oncology armamentarium, such as hormone therapy or 'targeted' drugs, such as bevacizumab or trastuzumab. One should not throw the baby out with the bath water, so to infer that medical oncology has no role in the management of cancer patients would be mischievous. Similarly, the article discusses issues to be considered in the formation of public policy, rather than making any statements on the management of individual patients.

Individual patients are concerned about their own chance of survival. Many patients will accept chemotherapy despite the small absolute benefit in survival.[3] A useful tool for adjuvant therapy for breast and bowel cancer, which uses a mathematical model for working out the benefit of chemotherapy, is Adjuvant! (www.AdjuvantOnline.com). Although such a model may show the small benefit, the patients and their families are often seeking a cure if at all possible. Their concerns are individual and immediate. They want to know the 'worth' of chemotherapy, but it is unlikely that the cost of the treatment is ever raised as a factor in an individual patient decision. Cost only becomes a significant issue if the treatment is not subsidised and the patient has to pay.

We are still left with the finding that the overall contribution of cytotoxic chemotherapy to survival in the 22 cancers reviewed in the study is less than 3%. Is this apparent heresy merely sour grapes from our radiation colleagues (who have previously shown a 16% survival benefit for radiation therapy[4]), or could it actually represent something close to the truth? At 2% or 6%, surely the message is the same. Modern Western society, with its obsession with cure at all costs and the focus on the outcome for an individual, has a track record of subverting community welfare on issues relating to 'big picture' sustainability.

Failure to come to terms with rationalisation of high cost medicine and the inability to convince multinational pharmaceutical corporations to provide drugs at a sustainable price will mean that our treatments are likely to have less, not more impact in the future, as only a portion of society will be able to afford them. Let us rise to the challenge rather than shrink from the spotlight. We have to hope that in the decades to come the contribution of chemotherapy to survival and well-being is significantly increased. However, we must realise that until we as prescribers, and the community as consumers, recognise our limitations and rationalise our resource utilisation, we may never achieve this goal.

References

1. The health report: chemotherapy [radio program transcript]. http://www.abc.net.au/rn/talks/8.30/helthrpt/stories/s1348333.htm [cited 2006 Jan 13]
2. Morgan G, Ward R, Barton M. The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies. Clin Oncol 2004;16:549-60.
3. Lindley CM, Vasa SP, Sawyer WT, Winer EP. Eliciting preferences for adjuvant therapy in patients with early stage breast cancer: tradeoffs between treatment, cure, and survival. Proceedings of the 31st annual meeting of ASCO; 1995. Abstr 149.
4. Barton MB, Gebski V, Manderson C, Langlands AO. Radiation therapy: are we getting value for money? Clin Oncol (R Coll Radiol) 1995;7:287-92.

Conflict of interest: none declared

Letters

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

Assessment of thyroid function in pregnancy

Editor, – Some further points on testing thyroid function need to be added to the useful information in Associate Professor Tran's review, 'Biochemical tests in pregnancy' (Aust Prescr 2005;28:98–101). First, a small but significant decrease in the concentration of serum free T4, most marked in the third trimester, has been clearly documented.[1,2] In addition, albumin-dependent methods of free T4 estimation show marked negative bias, relative to the non-pregnant reference interval; in the late third trimester, such methods may give subnormal free T4 estimates in up to 50% of samples.[3] These methods are unsuitable for assessing thyroid status during pregnancy[4], unless results are evaluated in relation to reference intervals that reflect method-specific bias at various stages of pregnancy. Clinical chemists need to be aware of this issue when choosing an appropriate free T4 method for obstetric practice and by indicating appropriate reference intervals.

Professor Tran's counsel that 'Graves' disease needs to be rigorously controlled' in pregnancy goes beyond interpretation of test results. This advice must be tempered by the fact that any degree of maternal hypothyroidism in

the first trimester can have an adverse effect on fetal brain development[5,6], and that overtreatment in the third trimester can be associated with fetal goitre.[6] As thyrotoxicosis of immune origin often becomes less severe during pregnancy, it is often advisable to decrease the dose of antithyroid drug to minimise the chance of these adverse effects.[6] As pointed out by Professor Tran, the exact cause of newly-diagnosed thyrotoxicosis can be difficult to establish in early pregnancy. When the disorder is mild, as judged by clinical rather than laboratory criteria, it may be best followed without treatment for several months until there is a clear indication for active treatment.[6]

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References

1. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997;18:404-33.
2. McElduff A. Measurement of free thyroxine (T4) levels in pregnancy. Aust N Z J Obstet Gynaecol 1999;39:158-61.
3. Roti E, Gardini E, Minelli R, Bianconi L, Flisi M. Thyroid function evaluation by different commercially available free thyroid hormone measurement kits in term pregnant women and their newborns. J Endocrinol Invest 1991;14:1-9.
4. National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Free thyroxine (FT4) and free triiodothyronine (FT3) estimate tests, in pregnancy. Section 3B 3c(i). http://www.nacb.org/lmpg/thyroid_LMPG_Word.stm [cited 2006 Jan 13]
5. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549-55.
6. Mandel SJ, Cooper DS. The use of antithyroid drugs in pregnancy and lactation. J Clin Endocrinol Metab 2001;86:2354-9.

Associate Professor H.A. Tran, author of the article, comments:

Professor Stockigt's comments are appreciated. As usual, they are incisive and informative. The small but significant decrease in serum free tetra-iodothyronine (fT4) can, in part, be explained by the peak of thyroid binding globulin concentrations in the third trimester, although these remain within the reference range in most cases.[1]

Selecting a special method for the obstetric population serviced by the relevant laboratory would always be a challenging task given the large scope of services imposed upon large laboratories by the current practice of pathology. The nuances of such a task are probably best reserved within the realm of clinical biochemists' practice.

As emphasised, the management of thyrotoxicosis in pregnancy is not a simple task. It should not be simply a matter of medication adjustment according to biochemical results, which are never error proof. The literature is littered with, sometimes fatal, adverse reactions[2] where laboratory results as given, are acted upon, when instead a considered and competent clinical assessment is warranted. As inferred by Professor Stockigt, it is best to first do no harm; a caveat that is not applicable to pregnancy alone.

References

1. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997;18:404-33.
2. Gutierrez-Macias A, Lizzaralde-Palacios E, Martinez-Odriozola P, Miguel-De la Villa F. Fatal allopurinol hypersensitivity syndrome after treatment of asymptomatic hyperuricaemia. Br Med J 2005;331:623-4.

Antibiotics for unapproved indications

Editor, – I would like to revisit the use of various antibiotics for 'orphan' indications. One example is rifampicin for deep infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). There are few oral antibiotics available for the treatment of MRSA infections, but the combination of rifampicin and fusidic acid is commonly used and is recommended in Therapeutic Guidelines: Antibiotics.

In 1994, *Australian Prescriber* published a response to a query (Aust Prescr 1994;17:95) asking why rifampicin was not subsidised for osteomyelitis. The response said that no application had been submitted for the use of rifampicin for this indication.

Would it be possible for the Therapeutic Goods Administration to approve an 'orphan' indication for well-known drugs where they are recommended by recognised guidelines? Perhaps for such indications, a simplified application to the Australian Drug Evaluation Committee could be made by clinicians or their representative bodies.

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Dr Leonie Hunt, Director, Drug Safety & Evaluation Branch, Therapeutic Goods Administration, comments:

The Therapeutic Goods Administration (TGA) is able to approve indications for extensions of use of medicines, including antibiotics, after it has received an application from a sponsoring company, supported by data to establish quality, safety and efficacy for the intended use.

For an extension of indication, quality will usually have been established and the focus is on safety and efficacy. In order to

facilitate the lodgement of applications for the treatment of rare conditions, which may otherwise not be cost-effective, the TGA has introduced an Orphan Drug Scheme, whereby all evaluation fees are waived provided the sponsor obtains designation for the product for the indication. The usual criteria for determining a disease is rare are the orphan criteria that it is not likely to affect more than 2000 people.

The TGA has also adopted a number of modifications to data packages to facilitate applications for older, off-patent or orphan products. These include literature based submissions, whereby companies can submit published papers as the basis for an approval of a product or an extension of use of a product. Unfortunately, the TGA has no power to approve products for new indications in the absence of an application, but it is always happy to discuss with sponsors the modified data requirements for products where there is a demonstrated clinical need.

Top 10 drugs

These tables show the top 10 subsidised drugs in 2004–05. The tables do not include private prescriptions.

Table 1

Top 10 drugs supplied by DDD/1000 pop/day *

Drug	PBS/RPBS †
1. atorvastatin	98.173
2. simvastatin	55.967
3. ramipril	33.741
4. diltiazem hydrochloride	30.097
5. omeprazole	20.628
6. irbesartan	20.169
7. salbutamol	18.844
8. frusemide	18.775
9. aspirin	18.162
10. sertraline	17.604

Table 2

Top 10 drugs by prescription counts

Drug	PBS/RPBS †
1. atorvastatin	8,074,202
2. simvastatin	6,275,577
3. paracetamol	4,772,865
4. omeprazole	4,411,857
5. irbesartan	3,370,315
6. atenolol	3,247,475
7. salbutamol	3,062,355
8. esomeprazole	2,983,645
9. irbesartan with hydrochlorothiazide	2,938,448
10. ramipril	2,903,048

Table 3

Top 10 drugs by cost to Government

Drug	Cost to Government ($A)	DDD/1000/day PBS/RPBS †	Prescriptions PBS/RPBS †
1. atorvastatin	460,930,251	98.173	8,074,202
2. simvastatin	369,659,052	55.967	6,275,577
3. omeprazole	177,075,832	20.628	4,411,857
4. fluticasone with salmeterol	165,690,424	– ‡	2,764,969
5. clopidogrel	151,235,466	7.551	1,925,546
6. olanzapine	149,497,256	2.892	710,453
7. esomeprazole	143,233,727	11.465	2,983,645
8. pravastatin	119,587,717	13.983	2,102,171
9. alendronic acid	108,587,183	8.543	2,115,898
10. pantoprazole	104,291,272	10.971	2,586,383

* 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.

† PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

‡ Combination drugs do not have a DDD allocated

Source: Drug Utilisation Sub-Committee (DUSC) Drug Utilisation Database, as at 10 Oct 2005.

Management of bite injuries

Jennifer Broom, Advanced trainee in infectious diseases, The Prince Charles Hospital, Brisbane; and Marion L. Woods, Consultant Physician, Infectious Diseases, Royal Brisbane and Women's Hospital, Brisbane

Summary

Most mammalian bites are caused by dogs, cats or humans. Cat and human bites often become infected, so antibiotic prophylaxis should be considered in addition to wound management. Early referral for surgical assessment of human bites to the hand may be required. Amoxycillin with clavulanate is suitable for prophylaxis in most cases. Prophylaxis is usually continued for 5–7 days. Depending on their immunisation status, patients may need vaccination against tetanus.

Key words: antibiotics, wounds, tetanus vaccine.

(Aust Prescr 2006;29:6–8)

Introduction

Bite injuries account for 1% of emergency department visits. Dog bites are the most common, followed by cat and human bites. Management is determined by the species of the biter, assessment of the injury and knowledge of host factors. Risk factors for bite wound infection include comorbid conditions such as diabetes, liver disease (iron-overload states) and asplenia.

Bacterial infections from bite wounds are usually polymicrobial

The bacteria associated with bite infections may come from the environment, from the victim's skin flora, or most frequently, from the 'normal' oral flora of the biter. The principles of management of bite injuries include cleaning and debriding the wound (often requiring surgical consultation), consideration of prophylactic antibiotics, treatment of infectious complications when they develop and appropriate use of tetanus vaccination.

Presentation

Patients presenting with bite injuries can be separated into two distinct groups. The first group present early, 8–12 hours after a bite, because of concern about infection of the wound or disfigurement as a consequence of the injury. These patients predominantly have a contaminated wound with no signs of infection. It is important to consider the role of prophylaxis in these patients.

The second group presents more than 12 hours after the injury. They usually have signs of a developing infection such as fever, purulent wound discharge, pain and local adenopathy.

Dog bites

Dog bites are the most common bite injury. They account for 80–90% of presentations. The annual incidence of dog bites requiring emergency department treatment is 12.9 per 10 000 persons, with children aged 5–9 (particularly boys) having an incidence of 60.7 per 10 000 persons aged 5–9 years. Face, neck and head bites are more frequent in children.[1]

Between 4 and 25% of dog bite wounds become infected. The median time to presentation with the first symptoms of infection is 24 hours.[2] Factors that may increase the risk of infection include deeper wounds, puncture injuries, crush wounds and wounds on the hand. Although studies do not clearly show that antibiotics prevent infection after a bite, it is common practice to offer antibiotic prophylaxis to patients with more severe wounds or to those with risk factors for infection.

Asplenic patients are at particular risk for infection with *Capnocytophaga canimorsus*. This infrequently diagnosed pathogen can produce meningitis, endocarditis and sepsis. Penicillin is the treatment of choice for infections with this organism.

Cat bites

Cat bites occur particularly in women and in an older patient group. A large percentage of cat bites are puncture wounds that are known to have an increased risk of infection. Although cats have less jaw power than dogs, the rate of infection with cat wounds is greater. Without antibiotic prophylaxis around 30–50% of the cat bites seen in emergency departments become infected.[2]

Human bites

Human bite wounds account for 2–3% of bite presentations. These injuries are commonly infected with human oropharyngeal flora.

Clenched fist injuries are the most severe of human bite injuries. They commonly present as a small wound over the metacarpophalangeal joint of the dominant hand as a result of the patient striking another person's teeth with a clenched fist. Human bite wounds to the hand more commonly develop bacterial infection than human bites at other sites, with clenched fist injuries conferring the highest risk, particularly because of the potential for breaching the metacarpophalangeal joint space to produce septic arthritis or osteomyelitis. Patients with hand

wounds should be referred early to hand surgeons to evaluate the need for exploration to prevent loss of function. Admission to hospital for intravenous antibiotic therapy may be required.

Antibiotic choice

Bacterial infections from bite wounds are usually polymicrobial and are often mixtures of aerobes and anaerobes.

Dog and cat bites

The oral flora of dogs and cats frequently contain *Pasteurella* species, in contrast to human oral flora. Empirical antibiotic therapy for both prophylaxis and established infection in dog and cat bites should be directed against pasteurella, streptococci, staphylococci and anaerobes. Oral amoxycillin with clavulanate is the most useful drug, but for patients with a penicillin allergy other antibiotic combinations such as clindamycin plus ciprofloxacin, or clindamycin plus trimethoprim-sulfamethoxazole, may be used. Prophylaxis is generally given for 5–7 days, although there are no clear guidelines. Treatment of an established infection is usually for 7–10 days. Longer periods of intravenous therapy are required for more severe infections, especially those involving bones or joints.

Human bites

Human bite injuries transfer a larger number of bacteria than dog or cat bites due to a greater density of normal oral flora. Other important differences between human bites and dog and cat bites are the presence of *Eikenella corrodens*, the absence of *Pasteurella multocida*, and a higher frequency of beta-lactamase-producing organisms and anaerobes.

The most commonly isolated organisms from human bites include alpha- and beta-haemolytic streptococci, *Staphylococcus aureus*, *Staphylococcus epidermidis*, corynebacteria, and *Eikenella corrodens*.[2,3] *Eikenella corrodens* should be considered because of its unusual antimicrobial sensitivities; it is sensitive to penicillin and amoxycillin with clavulanate, but resistant to 'first generation' cephalosporins, methicillin and clindamycin.

A Cochrane review of antibiotic prophylaxis after mammalian bites has concluded that the risk of infection is reduced with antibiotic prophylaxis after human bite injuries.[4] Appropriate prophylactic antimicrobial choices for human bite injuries include amoxycillin with clavulanate. Alternative regimens for patients with penicillin allergy include clindamycin plus either ciprofloxacin or trimethoprim/sulfamethoxazole or doxycycline (to treat *Eikenella corrodens*). Prophylaxis for 5–7 days is reasonable (although not clearly defined in the literature), with longer periods required for infected wounds.

Bites from other animals

Other animal bites are less common in practice but the most frequently encountered are rat bites. Although antibiotic prophylaxis is not indicated for minor injuries, a clinical syndrome of rat-bite fever should be kept in mind if patients present with malaise, fever and progressive arthralgia following a rat bite. The causative organism in the rare cases reported in Australia is *Streptobacillus moniliformis*.[5] In Asia the causative organism is *Streptobacillus minor*. The organism may be grown in blood cultures. Treatment is intravenous penicillin for 5–7 days followed by oral penicillin for seven days.

An extremely rare but fatal viral encephalitis may occur after bat bites or scratches in Australia. The causative agent is Australian bat lyssavirus which is nearly identical to rabies virus.[6] Australian bat lyssavirus infection should be considered in a patient with a history of a bat bite or exposure, who presents with meningoencephalitis. Long incubation periods can occur. The most important initial management of bat bite or scratches is immediate wound care with soap and water (20% soap is viracidal for rabies virus and presumably so for bat lyssavirus). Rabies vaccine and immunoglobulin should be administered as for post-exposure rabies prophylaxis.

Human bite injuries transfer a larger number of bacteria than dog or cat bites

Tetanus prophylaxis

Complete management of bite injuries should include consideration of tetanus immunisation. Any wound may be contaminated with tetanus spores, but wounds contaminated with dirt, saliva or certain types of wounds such as crush injuries and puncture wounds are more likely to be associated with tetanus inoculation. Patients presenting with bite wounds who have not been vaccinated in the past five years should be vaccinated. Those who are considered to have impaired immunity, and in whom the wound is considered to be tetanus-prone, should be considered for human tetanus immunoglobulin.

Conclusion

Each bite injury should be individually assessed. Management should take into account the type of animal that has inflicted the bite, any patient risk factors for infection, local and systemic signs of infection, and the patient's vaccination status. If antibiotics are indicated, check the patient's antibiotic allergies. Early surgical consultation for wound debridement is advised, particularly if there is a possibility that the bite has involved deep tissue or bone.

References

1. Weiss HB, Friedman DI, Coben JH. Incidence of dog bite injuries treated in emergency departments. JAMA 1998;279:51-3.
2. Goldstein EJ. Bite wounds and infection. Clin Infect Dis 1992;14:633-8.
3. Smith PF, Meadowcroft AM, May DB. Treating mammalian bite wounds. J Clin Pharm Ther 2000;25:85-99.

4. Medeiros I, Saconato H. Antibiotic prophylaxis for mammalian bites. The Cochrane Database of Systematic Reviews 2001, Issue 2. Art. No.: CD001738. DOI: 10.1002/14651858. CD001738.
5. Kadan D, Chih D, Brett A, Segasothy M. A case of rat-bite fever. Intern Med J 2002;32:193-4.
6. Hanna JN, Carney IK, Smith GA, Tannenberg AE, Deverill JE, Botha JA, et al. Australian bat lyssavirus infection: a second human case, with a long incubation period. Med J Aust 2000;172:597-9.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 27)

1. Human bites transfer more bacteria than bites from other animals.
2. Dog bites become infected more often than cat bites.

Book review

Drugs of abuse. 2nd edition. Simon Wills. London: Pharmaceutical Press; 2005. 376 pages*

Alex Wodak, Director, Alcohol and Drug Service, St Vincent's Hospital, Darlinghurst, NSW

The aim of this book, now in an extensively revised second edition, is to be a detailed but easily digestible guide for healthcare professionals who work with drug users. As the author notes, the use of psychoactive drugs is long-standing, ubiquitous, often associated with considerable harm and subject to considerable variation over time.

Basic concepts and common complications of psychoactive drugs are covered in two somewhat perfunctory introductory chapters. A chapter is devoted to each major drug category under the following headings: history, effects sought, administration, pharmacology, adverse effects, dependence, drug–drug interactions with therapeutic medications, potential effects on concurrent medical conditions, pregnancy and breastfeeding.

The text is up to date, including material on relatively new illicit drugs (such as gamma hydroxybutyrate) and recent developments (such as use of the internet as an information resource). Separate chapters are appropriately devoted to tobacco and alcohol. The health and economic costs to individuals and communities from legal drugs dwarf the costs associated with illicit drugs.

The author still refers to drug 'misuse' and 'abuse' although many regard these terms as unscientific and pejorative. Apart from this terminology, judgemental attitudes are (mercifully) avoided. But terminology 'sends a message' and a large part of the problem of healthcare management of people using illicit drugs includes keeping negative attitudes under control. People who 'misuse' and 'abuse' illicit drugs should be just as entitled to excellent health care as people who 'misuse' and 'abuse' cigarettes, red meat or high-fat ice cream.

The strengths of this readable book include its clarity, brevity and practicality. Arcane and academic details are avoided. The information on drug–drug interactions with therapeutic medications is particularly useful. Perhaps the introductory chapters could have been expanded as clinicians are generally more troubled navigating their way through the vexing framework questions than the more straightforward pharmacological aspects of psychoactive drugs. This is especially true in parts of the world where authorities wage a 'war on drugs', claiming to create a utopian 'drug-free world'.

This book will be a useful reference for busy clinicians managing patients using psychoactive drugs, especially general practitioners and pharmacists, but also some specialist practitioners.

* Available from Pharmaceutical Society of Australia, phone (02) 6283 4783. Price $154, $123 PSA members.

Angiogenesis inhibitors in cancer – mechanisms of action

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Summary

Tumours need to develop a new blood supply to grow and metastasise. This process is called angiogenesis. Drugs that inhibit angiogenesis are therefore being evaluated in combination with chemotherapy for the treatment of various cancers. Vascular endothelial growth factor and its receptors are intimately involved in angiogenesis so they are targets for new drugs. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor and is approved for use in metastatic colon cancer. Thalidomide also inhibits angiogenesis and may be used in the treatment of multiple myeloma.

Key words: bevacizumab, thalidomide, vascular endothelial growth factor.

(Aust Prescr 2006;29:9–12)

Introduction

Small tumours are able to grow because they can obtain nutrients and oxygen by diffusion. For tumours to enlarge further they need to develop new collateral blood vessels to provide the essential nutrients for invasion, growth and subsequent metastasis. The formation of new vessels is termed neovascularisation. This is driven by the process of angiogenesis, the sprouting of new vessels from existing vasculature.

Angiogenesis has been an appealing target for anticancer drugs for 30 years, but it is only recently that this promise has borne some fruit. There are now over 30 angiogenesis inhibitors currently in clinical trials for the treatment of malignancy (Table 1). These drugs appear to have a cytostatic rather than cytotoxic effect, leading to tumour dormancy. The available data suggest that anti-angiogenic drugs work best in conjunction with chemotherapy. Their development also involves the identification and management of a new range of toxicities.

Angiogenesis

The development of blood vessels is a complex equilibrium regulated by anti- and pro-angiogenic factors. The balance may be tilted in favour of angiogenesis by hypoxia or inflammation. This has a physiological advantage, for example in wound healing, but may be part of the pathological process in chronic inflammatory disease or cancer.

With tumour-associated angiogenesis, the cancer releases various pro-angiogenic factors (including angiogenin, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and transforming growth factor-β (TGF-β)). These stimulate endothelial cell proliferation, migration and invasion resulting in new vascular structures sprouting from the patient's blood vessels. Cell adhesion molecules, such as integrins, are critical to the attachment and migration of endothelial cells to the extracellular matrix. The receptor for platelet derived growth factor is also important in angiogenesis as it is central to the recruitment of pericytes, the cells that surround and support capillaries.

When a tumour stimulates the growth of new vessels, it is said to have undergone an 'angiogenic switch'. The principal stimulus for this angiogenic switch appears to be oxygen deprivation, although other stimuli such as inflammation, oncogenic mutations and mechanical stress may also play a role.

The angiogenic switch leads to tumour expression of pro-angiogenic factors and increased tumour vascularisation. It is associated with more advanced tumour stages and worse prognosis in several human malignancies, including malignant melanoma and gastrointestinal, breast, prostate and lung cancers.

Vascular endothelial growth factor

Of the angiogenic factors secreted, VEGF is perhaps the most specific for endothelial cells. When VEGF binds to its receptor it triggers signalling pathways that result in endothelial cell migration, differentiation and proliferation, increased vascular permeability and release of endothelial cell precursors from the bone marrow. VEGF also prevents endothelial cell apoptosis. Higher concentrations have been associated with malignant effusions.

The VEGF-related family of genes involved in angiogenesis and lymphangiogenesis produce a number of glycoproteins, called VEGFs A–E and placental growth factors (PlGF) 1 and 2. These glycoproteins have several biologically active isoforms.

Table 1
Angiogenesis inhibitors and their targets

Drug	Target	Clinical development
Monoclonal antibody		
Bevacizumab	VEGF-A	Approved in Australia
IMC-1121B	VEGFR-2	Phase I
2C3	VEGF-A	Preclinical
Receptor tyrosine kinase inhibitors		
PTK-787	VEGFR-1, -2	Phase III
AEE788	VEGFR-2, EGFR	Preclinical
ZD6474	VEGFR-1, -2, -3, EGFR	Phase II
ZD2171	VEGFR-1, -2	Phase I
SU11248 (sunitinib)	VEGFR-1, -2, PDGFR	Phase II/III
G013736	VEGFR-1, -2	Phase II
EP-7055	VEGFR-1, -2, -3	Phase I
P-547,632	VEGFR-1, -2	Phase I/II
GW786034	VEGFR-1, -2, -3	Phase I
BAY 43-9006	VEGFR-1, -2, PDGFR	Phase III
AMG706	VEGFR-1, -2, -3	Phase I
Soluble receptor chimeric protein		
VEGF-Trap	VEGF-A, PlGF	Phase I
Inhibitors of endothelial cell proliferation		
ABT-510	Endothelial CD36	Phase I/II
Angiostatin	Various	Phase I
Thalidomide	Reduction of TNF-α	Approved in Australia
Inhibitors of integrin's pro-angiogenic activity		
Medi-522	Integrin αV	Phase I/II
EMD12194 (Cilengitide)	Integrin αV	Phase I/II
Matrix metalloproteinase inhibitors		
Marimastat	MMP-1, -2, -3, -7, -9	Phase III
Prinomastat	MMP-2, -9	Phase III
BMS 275291	MMP-1, -2, -8, -9, -13, -14	Phase III
Neovastat	MMP-2, -9, -12, VEGF	Phase III
Other		
CDP-791	VEGFR-2	Phase I
Vascular targeting drugs		
Combretastatin	Endothelin tubulin	Phase I/II
AVE8062A	Endothelin tubulin	Phase I
ZD6126	Endothelin tubulin	Phase I
AS1404	Induction of TNF-α	Phase I

Key
VEGF Vascular endothelial growth factor
VEGFR Vascular endothelial growth factor receptor
EGFR Epidermal growth factor receptor
PDGFR Platelet derived growth factor receptor
PlGF Placental growth factor
TNF Tumour necrosis factor
MMP Matrix metalloproteinases

The VEGFs are produced either by direct secretion from the tumour, or by cleavage of isoforms sequestered in the extracellular matrix by enzymes such as plasmin or the matrix metalloproteinases.

VEGFs bind to at least three receptors (VEGFR-1, VEGFR-2, VEGFR-3). The isoforms can bind with other receptors (neuropilin receptors) which may also have a role in angiogenesis. The structure of each VEGF receptor includes a kinase. For example, ms-like tyrosine kinase (Flt-1) is part of VEGFR-1. These enzymes are involved in intracellular signalling when VEGFs bind to their receptors (Fig. 1).

VEGF promotes the release of other angiogenic factors and proteolytic enzymes. The release of proteolytic enzymes results in degradation of the vascular basement membrane. New vessels are formed as endothelial cells are organised into functional tubular structures. Individual vessels then connect to form networks that allow blood to circulate. The new blood vessels formed are derived from the host and not the tumour, however they are more tortuous and leaky than normal vessels.

Angiogenesis inhibition in the treatment of cancer

To stop angiogenesis requires treatment with anti-angiogenic factors, or drugs which reduce the production of pro-angiogenic factors, prevent them binding to their receptors or block their actions. The drugs being studied can be broadly defined as those that are exclusively anti-angiogenic, such as bevacizumab, and those that have additional functions, such as thalidomide and the cyclo-oxygenase (COX)-2 inhibitors.

Endogenous anti-angiogenic factors

Endostatin is the carboxy-terminal fragment of collagen XVII. It is thought to induce apoptosis in endothelial cells and inhibition of their migration to sites of neovascularisation, probably by interfering with endothelial cell adhesion. In preclinical models, endostatin has inhibited the growth of a wide variety of human primary and metastatic tumours. Clinical trials suggest that endostatin is well tolerated, but only minor evidence of antitumour activity has been observed.

Another endogenous inhibitor of angiogenesis is angiostatin. Like endostatin, it directly induces apoptosis of endothelial cells by disrupting the normal adhesion contacts between the endothelial cells. Angiostatin also acts by inhibiting VEGF and basic fibroblast growth factor (bFGF).

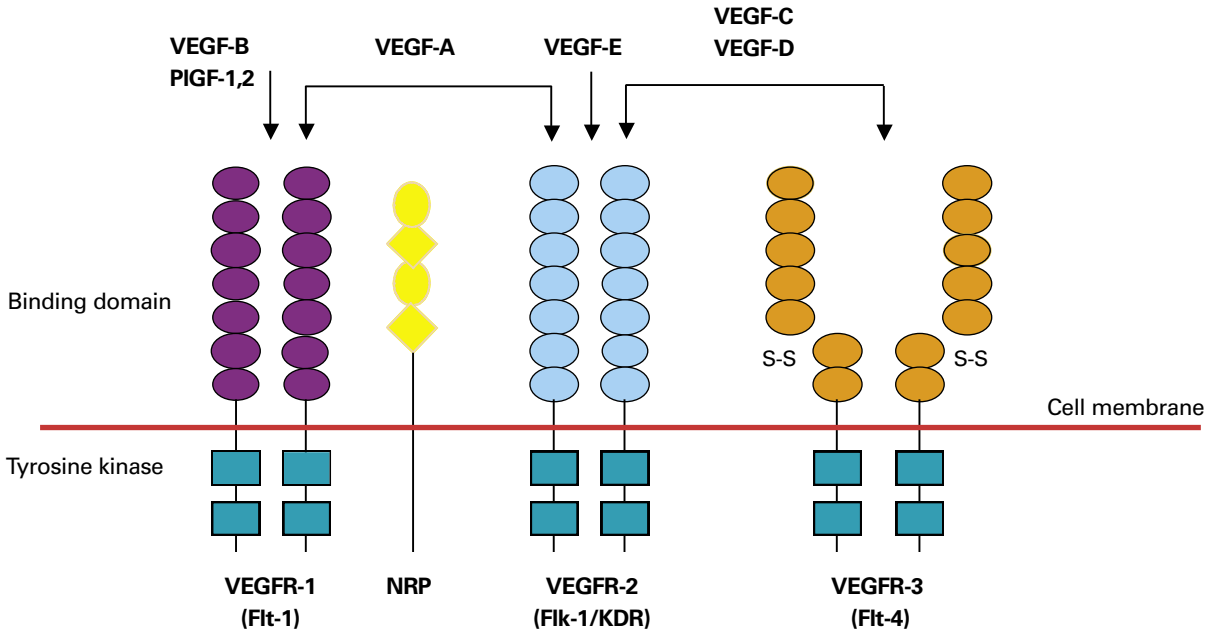
Interferon-alfa has an anti-angiogenic effect by inhibiting endothelial cell migration. It has been successfully used to treat haemagiomas, refractory giant cell tumours and angioblastomas.

Thalidomide

There has been renewed interest in this potent teratogen since it has been shown to be both an immunomodulatory and

Fig. 1

Vascular endothelial growth factor receptors [2]



The vascular endothelial growth factor receptors (VEGFR) consist of a binding domain and a tyrosine kinase domain. Each receptor is associated with a different form of tyrosine kinase (Flt-1, Flk-1/KDR, Flt-4). The neuropilin receptors (NRP) act as co-receptors for vascular endothelial growth factor (VEGF). Some of the VEGF molecules bind with more than one receptor. Placental growth factor (PlGF) binds with VEGFR-1.

anti-angiogenic drug. Thalidomide is thought to inhibit angiogenesis by reducing levels of bFGF, VEGF, COX-2 and tumour necrosis factor (TNF-α). It may also reduce tumour-induced overproduction of circulating precursors of endothelial cells.

In patients with multiple myeloma there is an increased rate of angiogenesis within the bone marrow. Thalidomide has been used in the treatment of resistant multiple myeloma as it has anti-angiogenic effects and can directly inhibit the growth and survival of myeloma cells.

VEGF inhibitors

Inhibition of the VEGF pathway has become the focus of angiogenesis research as approximately 60% of malignant tumours express high concentrations of VEGF. Strategies to inhibit the VEGF pathway include antibodies directed against VEGF or VEGFR, soluble VEGFR/VEGFR hybrids, soluble analogues of the VEGFR (VEGF-Trap) and tyrosine kinase inhibitors. One of the earliest strategies to inhibit VEGF activity involved the use of antibodies directed against VEGFRs. For example, preclinical data with anti-VEGFR-2 antibodies demonstrated decreased VEGF-induced signalling, decreased angiogenesis and decreased primary and metastatic growth in a variety of tumour systems.

VEGF-Trap is a decoy receptor. It consists of parts of VEGFR-1, VEGFR-2 and immunoglobulin G (IgG). The molecule is soluble and binds to VEGF-A before it can reach its normal receptors. VEGF-Trap binds VEGF-A 100- to 1000-fold more tightly than monoclonal antibodies. It inactivates all circulating and tissue VEGF-A isoforms and PlGF.

Several small molecule inhibitors of tyrosine kinase activity have been developed. These have activity not only against VEGFR-2, but also on other VEGFRs, fibroblast growth factor receptor, the epidermal growth factor receptors (EGFR*) and platelet derived growth factor receptors (PDGFR-α, PDGFR-β). For example, sunitinib (SU11248) has activity against VEGFR-2 and PDGFR (see Table 1).

Bevacizumab

Bevacizumab is derived from a monoclonal antibody to murine VEGF. Genetic engineering produces a 93% human and 7% murine protein sequence. The molecule has the same biochemical and pharmacologic properties as the natural antibody, but with reduced immunogenicity and a longer biological half-life. By binding to VEGF-A bevacizumab prevents it from binding with its receptors.

Preclinical studies reported impressive responses and prevention of tumour growth in almost all tumour xenografts. Bevacizumab has been studied in a number of clinical trials and is approved for use in metastatic colon cancer.

* EGFR is also known as human epidermal growth factor receptor (HER) and these abbreviations are interchangeable.

Other strategies

There are a variety of other drugs that have at least some anti-angiogenic properties. It has been known for some time that low-dose chemotherapy with cytotoxic drugs, such as the taxoids, produces some anti-angiogenic effects. In addition, inhibition of other molecular targets also has the potential to interfere with angiogenesis. These targets include EGFR, COX-2, TGF-α and the proteosome. Other drugs that have been shown to have anti-angiogenic effects in preclinical models are zoledronic acid and rosiglitazone.

COX-2 is an important mediator of angiogenesis and tumour growth. COX-2 expression occurs in a wide range of preneoplastic and malignant conditions. The enzyme has been localised to neoplastic cells, endothelial cells, immune cells, and stromal fibroblasts within tumours. It mediates its pro-angiogenic effects primarily by three products of arachidonic acid metabolism – thromboxane A_2, prostaglandin E_2 and prostaglandin I_2. These products promote angiogenesis by a number of mechanisms including stimulation of VEGF, promotion of vascular sprouting and tube formation, increased survival of endothelial cells and activation of EGFR-mediated angiogenesis. Studies have shown that selective inhibition of COX-2 activity will suppress angiogenesis *in vitro* and *in vivo* and therefore COX-2 inhibitors could be a useful adjunct to therapy.

Expression of human epidermal growth factor receptor 2 (HER-2) within tumour cells is closely associated with angiogenesis and VEGF expression. This is thought to be mediated by transregulation of HER-2 by proteins called heregulins. These heregulins regulate the expression and secretion of VEGF in breast cancer cells. Trastuzumab is a monoclonal antibody that blocks HER-2.[1] This reduces tumour cell growth and VEGF expression by the inhibition of heregulin-mediated angiogenesis both *in vitro* and *in vivo*. Trastuzumab is currently available for patients with metastatic breast cancer if the tumour overexpresses HER-2.

It is not known how much of the anticancer effects of drugs aimed at molecular structures are due to their angiogenic effects. Angiogenesis is a complex process and successful inhibition of angiogenesis may involve the combination of multiple drugs with differing modes of action.

Another strategy related to angiogenesis is the destruction of new vessels. This has led to the development of vascular targeting drugs (Table 1).

Adverse effects

The full spectrum and aetiology of toxicities produced by the angiogenesis inhibitors has yet to be defined. The induction of venous and arterial thromboses, bleeding, hypertension and proteinuria by drugs, such as bevacizumab, is probably directly related to their effects on endothelial cells. The gut perforation occasionally associated with bevacizumab may be related to induction of ischaemia. The teratogenic effects of thalidomide may have been due to its action on peripheral blood vessel development in the fetus. However, it is unlikely that the common adverse effects of thalidomide such as somnolence, rash and neuropathy are related to its effect on angiogenesis.

Conclusion

The use of angiogenesis inhibitors is an exciting new area of cancer research. Their optimal use has yet to be defined.

References

1. Ward R. Antineoplastic antibodies – clinical applications. Aust Prescr 2003;26:141-3.
2. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis [review]. J Clin Oncol 2005;23:1011-27.

Note: This article has intentionally not been fully referenced. The following articles are recommended for further reading on the topic.

Further reading

Folkman J. Tumor angiogenesis: therapeutic implications [review]. N Engl J Med 1971;285:1182-6.

Folkman J. Endogenous angiogenesis inhibitors [review]. APMIS 2004;112:496-507.

Ferrara N. Vascular endothelial growth factor: basic science and clinical progress [review]. Endocr Rev 2004;25:581-611.

Sparano JA, Gray R, Giantonio B, O'Dwyer P, Comis RL. Evaluating antiangiogenesis agents in the clinic: the Eastern Cooperative Oncology Group portfolio of clinical trials. Clin Cancer Res 2004;10:1206-11.

Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.

Bilenker JH, Haller DG. Future directions with angiogenesis inhibitors in colorectal cancer [review]. Clin Colorectal Cancer 2004;4 Suppl 2:S86-93.

Stephen Clarke is the Principal investigator for Asia Pacific for two Roche-sponsored studies involving bevacizumab. He has been a member of a Roche colorectal advisory board and an invited speaker at Roche-sponsored clinical meetings.

Self-test questions

The following statements are either true or false (answers on page 27)

3. Increased expression of angiogenic factors is associated with an improved prognosis for patients with cancer.
4. Bevacizumab may cause thrombosis and haemorrhage.

Angiogenesis inhibitors in cancer – clinical applications

Paul Mainwaring, Director, Medical Oncology, Mater Adult Hospital, Brisbane

Summary

New blood vessel formation, or angiogenesis, is crucial for sustaining tumours. Strategies are being developed to treat or prevent cancer, as a result of improved understanding of angiogenesis. Antivascular treatment may be divided into anti-angiogenic and vascular targeting therapy. It may improve survival in advanced colorectal and lung cancer. Clinical trials are using angiogenesis inhibitors in a variety of tumour types. The efficacy and safety of these drugs are still uncertain.

Key words: bevacizumab, colorectal cancer, lung cancer.

(Aust Prescr 2006;29:13–15)

Introduction

The shortcomings of 'modern' systemic therapy for cancer are well understood. Even destroying 99.9% of cancer cells is not enough to prevent relapse of a primary tumour. The most successful strategy so far has been with targeted therapy using small molecules such as tamoxifen for hormone-receptor positive breast cancer or rituximab for non-Hodgkin's lymphomas.

Angiogenesis and neovascularisation

The growth and proliferation of new blood vessels has a physiological role in wound healing and embryogenesis. It also has a pathological role in proliferative retinopathy, age-related macular degeneration and malignancy. When tumour cells are supplied by diffusion their growth is arrested at a size of 1–2 mm^3. The tumour therefore induces a proliferative vascular response from host vessels. These new vessels supply the tumour with the nutrients it needs to grow.

An increased microvessel density count has poor prognostic value in almost all tumour types. Similarly, overexpression of vascular endothelial growth factor (VEGF) suggests the patient's prognosis is poor, but more accurate surrogate markers of response, resistance and prognosis are needed.

Antivascular therapy

Antivascular therapy for cancer can be divided into two classes of drugs:

- anti-angiogenic drugs which aim to inhibit new vessel formation
- vascular targeting compounds which aim to selectively destroy the blood vessels supplying the tumour leading to secondary tumour cell death.

In numerous preclinical studies over the last decade both anti-angiogenic drugs and vascular targeting drugs have shown evidence of antitumoural activity.

Phase I clinical studies, designed to define maximum tolerated or optimal biological doses, revealed a number of relatively well-tolerated compounds. However, antivascular treatment lacked sufficient efficacy as monotherapy. Clinical trials are therefore exploring the combination of antivascular therapy in combination with other treatment modalities such as chemo- and radiotherapy.

Monoclonal antibodies

Antibodies have a variety of actions. Genetic engineering enables the production of monoclonal antibodies with antitumour activity.

Bevacizumab

Phase I clinical trials showed that bevacizumab as a single drug was relatively non-toxic and that adding it to standard chemotherapy regimens did not significantly exacerbate their toxicities. Phase II studies investigated bevacizumab in hormone-refractory metastatic prostate cancer, relapsed metastatic breast cancer and in renal cell cancer that had progressed following therapy with interleukin-2. Bevacizumab was also studied in combination with standard first-line chemotherapy in metastatic colorectal cancer and stage IIIb/IV non-small cell lung cancer. The most encouraging efficacy results were seen when bevacizumab was combined with chemotherapy in advanced colorectal cancer[1] and in non-small cell lung cancer, and when it was used as a single drug in renal cell cancer. Bevacizumab costs approximately $4000 per month so its cost-effectiveness is uncertain.

Colorectal cancer

In metastatic colorectal cancer the benefit of adding bevacizumab to the North American combination regimen of irinotecan, 5-fluorouracil and folinic acid was statistically significant across all patient sub-groups, including age, sex, performance status, number of metastatic sites and tumour load (Table 1). There were clinically relevant improvements in

response rate, progression-free survival, median duration of response and overall survival. This trial was important because it confirmed the feasibility of combining anti-VEGF antibodies with chemotherapy.[1]

Non-small cell lung cancer

In 2005 the data monitoring committee overseeing a trial in 878 patients with advanced non-squamous non-small cell lung cancer recommended that the results of a recent interim analysis be made public, because the study had met its primary end point of improving overall survival. The researchers found that patients who received bevacizumab in combination with standard chemotherapy (paclitaxel and carboplatin) had a median overall survival of 12.5 months compared to 10.2 months in patients treated with the standard combination chemotherapy alone. This difference is statistically significant.[2]

Patients with squamous cell carcinoma of the lung were not included in the study because previous clinical experience suggested that patients with this particular type of cancer had a higher risk of serious bleeding from the lung after bevacizumab therapy. Those with a history of frank haemoptysis were also not enrolled.

The most significant adverse event observed in this trial was life-threatening or fatal bleeding, primarily from the lungs. This occurred infrequently, but was more common in the patient group that received bevacizumab in combination with chemotherapy than in the patient group that received only chemotherapy. Five patients died of haemoptysis among the 434 who received bevacizumab.

Renal cancer

In patients with advanced clear cell renal cell carcinoma, the combination of bevacizumab and interferon-alfa is currently being compared to interferon-alfa alone.

Adverse effects

Bevacizumab seems more effective when combined with chemotherapy than when given as a single drug. However, the combined effects of chemotherapy and the vascular effects of an angiogenesis inhibitor could promote thromboembolic disease and myocardial infarction. Adverse reactions include a low incidence of severe hypertension, arterial and venous thromboses, proteinuria and bleeding. Another uncommon toxicity has been bowel perforation, but the aetiology has yet to be determined.

VEGF-Trap

VEGF-Trap is a potent angiogenesis inhibitor. In a phase I trial a total of 30 patients with a broad range of tumours have been treated across six dose levels. Hypertension and proteinuria are the major toxicities.

Small molecule tyrosine kinase inhibitors

Inhibiting tyrosine kinase disrupts the angiogenic signalling pathways in the cells.

Sunitinib (SU11248)

In a phase I trial there were responses to sunitinib in renal cell and neuroendocrine tumours. At higher doses, tumour responses were often associated with reduced vascularisation inside the tumour and central tumour necrosis.

Sunitinib therapy induced an objective response or stable disease for more than six months in 26/48 (54%) of patients with previously progressing gastrointestinal stromal cell tumours. Six patients (13%) had confirmed partial responses.

There is an extensive clinical trials program investigating the addition of sunitinib to standard chemotherapy in most advanced solid tumours. In Australia, a phase III trial is underway comparing oral sunitinib with interferon-alfa in advanced clear cell renal cell cancer.

The toxicities associated with sunitinib include fatigue, neutropenia and thrombocytopenia.

PTK787

PTK787 inhibits the tyrosine kinases found in vascular endothelial growth factor receptors (VEGFR) 1 and 2. Early clinical trials have investigated the addition of this drug to combination chemotherapy in advanced colorectal cancer. Response rates were 10% higher than previously reported with chemotherapy alone and progression-free survival was 30% longer than previously reported. In metastatic colorectal cancer progression-free survival was slightly longer (7.7 vs 7.6 months) with PTK787 than with combination chemotherapy. It may also have some activity in advanced renal cell carcinoma.

Table 1

Response to bevacizumab in advanced colorectal cancer[1]

Regimen	Number of patients	Response rate (%)	Progression-free survival (months)	Overall survival (months)
Irinotecan/5-fluorouracil/folinic acid	411	34.8	6.2	15.6
Bevacizumab + irinotecan/ 5-fluorouracil/folinic acid	402	44.8 *	10.6 *	20.3 *

* statistically and clinically significant

ZD6474

This oral tyrosine kinase inhibitor has activity at the VEGFR-2 and the epidermal growth factor receptor (EGFR). It has been tried in 15 patients with a good performance status, who had metastatic non-small cell lung cancer which had not responded to platinum-based chemotherapy. The patients received ZD6474 in combination with docetaxel. There was no significant adverse toxicity except an acneiform rash, sometimes with desquamation or photosensitivity.

GW786034

The pharmacokinetic and pharmacodynamic properties of GW786034, another VEGFR tyrosine kinase inhibitor, have been reported in abstract form. Tumour shrinkage was observed in three patients with renal cell cancer and in one patient with Hurthel cell tumour. GW786034 is therefore being studied in Australia for renal cell carcinoma.

BAY 43-9006

BAY 43-9006 inhibits tumour cell proliferation by targeting a signalling pathway. It also exerts an anti-angiogenic effect. In a large randomised study of over 800 patients with advanced kidney cancer, median progression-free survival was 24 weeks for BAY 43-9006 versus 12 weeks for placebo (hazard ratio 0.44; $p < 0.00001$). The 12-week progression-free rate was 79% versus 50% for placebo. Final study details are yet to be published.

Thalidomide

Thalidomide has some anti-angiogenic actions. It is available in Australia for the treatment of patients with multiple myeloma which has not responded to previous chemotherapy. There have been mixed results in a range of solid tumours. Thalidomide can be combined with chemotherapy, but has an unexpectedly high rate of thromboembolic events. The other predominant adverse effects are fatigue, rash, nausea and vomiting, peripheral neuropathy and somnolence.

Vascular targeting drugs

Selective induction of tumour vascular collapse can be achieved by synthetic low molecular weight inducers of tumour necrosis factor (TNF). Strategically these drugs have the potential benefits of non-overlapping dose-limiting toxicities and selective effects in poorly-perfused hypoxic regions. They may also potentially sensitise tumours to the cytotoxic effects of chemotherapy and radiotherapy.

Unexpectedly, flavone acetic acid, which was originally synthesised as a non-steroidal anti-inflammatory drug, was found to have excellent antitumour activity in preclinical studies because of its antivascular activity resulting from TNF induction. Flavone acetic acid was chemically modified to the flavonoid 5,6-dimethylxanthenone-4-acetic acid (DMXAA), representing a promising synthetic small molecular inducer of TNF with demonstrable preclinical antitumour effects. Australian investigators are participating in trials of DMXAA in a variety of solid tumours. The dose-limiting toxicities seem to occur at significantly higher doses than those used in current studies.

The second class of leading vascular targeting drugs are small-molecule, tubulin-binding drugs. These include combretastatin A-4 and the combretastatin analogues AVE8062A and Oxi4503 as well as the phosphate prodrug of N-acetylcolchinol ZD6126. After binding and destabilisation of the tubulin cytoskeleton, these drugs induce rapid changes in endothelial cell shape. This rapid change of endothelial cell morphology leads to disruption of the endothelial cell layer and exposure of the procoagulant underlying basement membranes.

In a phase I trial, 37 patients were given combretastatin A-4. There was dose-limiting cardiopulmonary toxicity (syncope and dyspnoea or hypoxia) as well as hypotension, ataxia, dyspnoea, nausea or vomiting, headache and transient sensory neuropathy. A partial response was observed in a patient with metastatic soft tissue sarcoma. In another trial, 16 patients with solid tumours were given the drug with carboplatin. The dose-limiting toxicity of thrombocytopenia halted the dose escalation phase of the study.

Radiotherapy

Radiotherapy increases the expression of VEGF. This could be the response of the tumour to radiation stress and may contribute to tumour resistance. Blocking the radiation-mediated increase in VEGF with anti-VEGF therapy could therefore increase the destruction of tumour cells and produce additive antitumour effects. Clinical trials designed to address this issue are just beginning.

Conclusion

Antivascular therapy for cancer represents a new spectrum of molecules with a broad range of putative mechanisms of action. The activity of angiogenesis inhibitors has been demonstrated, but the indications for these drugs are unclear. The role of each drug in combination with standard therapy will take many years of clinical research.

References

1. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
2. Sandler AB, Gray R, Brahmer J, Dowlati A, Schiller JH, Perry MC, et al. Randomized phase II/III trial of paclitaxel (P) carboplatin (C) with or without bevacizumab (NSC # 704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): an Eastern Cooperative Oncology Group (ECOG) trial – E4599. Proceedings of the ASCO annual meeting; 2005 May 13-17; Orlando, USA.

Conflict of interest: none declared

Medicines Australia Code of Conduct: breaches

Medicines Australia has a code of conduct to guide the promotion of prescription drugs by pharmaceutical companies in Australia.[1] Complaints are reviewed by the Code of Conduct Committee and the results are published in its annual report. The report for 2005 is available on the Medicines Australia website.[2]

There were 51 new complaints in 2004–05. Four of these were withdrawn and three are unresolved. As the report includes two complaints held over from the previous year, it contains 46 cases completed by the Code of Conduct Committee.

As usual most of the complaints came from rival companies. It is possible that some complaints are part of a company's strategy as it jostles for market share. In some cases the Code of Conduct Committee had to decide if complainants were abusing the Code.

In 2005 there were 35 complaints in which at least one breach of the Code was found (Table 1), however one case was dismissed on appeal (it involved a $50 000 fine for offering a $500 fee for attending a round table meeting). Details of the complaints can be found in the annual report.[2]

References

1. Medicines Australia. Code of Conduct. 14th ed. Canberra: Medicines Australia; 2003.
2. 2005 Code of Conduct Annual Report. Canberra: Medicines Australia; 2005. www.medicinesaustralia.com.au

Note: Edition 15 of the Medicines Australia Code of Conduct is available from:

Medicines Australia
Level 1, 16 Napier Close
DEAKIN ACT 2600

Tel: (02) 6282 6888
Fax: (02) 6282 6299
Website: www.medicinesaustralia.com.au

Table 1

Breaches of the Medicines Australia Code of Conduct July 2004 – June 2005

Company	Complaint		Sanction imposed by Code of Conduct Committee
	Drug – brand name	Drug – generic name	
Abbott	Humira	adalimumab	Withdrawal of promotional material $5000 fine
Aspen	Permax	pergolide	Withdrawal of promotional material Company to undertake education about the Code of Conduct $2500 fine
Aspen	Tazac	nizatidine	Withdrawal of promotional material
AstraZeneca	Symbicort	budesonide/eformoterol	$100 000 fine for promoting product to advisory boards, reduced on appeal to $25 000
Baxter	meningococcal C vaccine		Withdrawal of material for general public Full-page educational advertisements to be placed in Family Circle, Women's Day, Good Health, and on company's website
Bayer and GlaxoSmithKline	Levitra	vardenafil	Withdrawal of promotional material from website for general public
Bayer and GlaxoSmithKline	Levitra	vardenafil	Withdrawal of material for general public $100 000 fine
Boehringer Ingelheim	Asasantin	aspirin and dipyridamole	Promotional material not to be used again without qualification
Bristol-Myers Squibb	Perfalgan	paracetamol	$10 000 fine for promoting product before approval for marketing
Galderma	Metvix	methyl-5-aminolevulinate	Withdrawal of promotional material

Galderma	Metvix	methyl-5-aminolevulinate	Withdrawal of promotional material
Galderma	Metvix	methyl-5-aminolevulinate	Withdrawal of promotional material
GlaxoSmithKline	Avandia	rosiglitazone	Withdrawal of promotional material Corrective letter to seminar attendees
GlaxoSmithKline	Avandia	rosiglitazone	Withdrawal of promotional material $15 000 fine
GlaxoSmithKline	Seretide	fluticasone/salmeterol	Withdrawal of promotional material
Janssen-Cilag	Pariet	rabeprazole	Withdrawal of promotional material
Janssen-Cilag	Pariet	rabeprazole	Withdrawal of promotional material Corrective letter $25 000 fine reduced to $24 000 on appeal
Merck Sharp & Dohme	Ezetrol	ezetimibe	Withdrawal of promotional material
Merck Sharp & Dohme	Fosamax	alendronate	Withdrawal of promotional material Corrective letter
Novo Nordisk	NovoMix 30	insulin	Withdrawal of promotional material $50 000 fine for discussing drug with a member of the public
Organon	Puregon Pen	follitropin beta	Withdrawal of promotional material $5000 fine
Pfizer	Celebrex	celecoxib	$150 000 fine for media release to the general public, reduced on appeal to $30 000
Pfizer	Celebrex	celecoxib	$25 000 fine
Pfizer	Somac	pantoprazole	Withdrawal of promotional material $15 000 fine
Pfizer	Zoloft	sertraline	Withdrawal of promotional material Corrective letter $20 000 fine
Roche	Xenical	orlistat	$20 000 fine for providing unbalanced information to a television station
Sanofi-Aventis	Actonel	risedronate	Withdrawal of promotional material Corrective letter $50 000 fine
Sanofi-Aventis	Epilim	valproate	Withdrawal of promotional material $50 000 fine
Sanofi-Aventis	Solian	amisulpride	Withdrawal of promotional material Corrective letter to recipients of guidelines and destruction of remaining copies $20 000 fine
Sanofi-Synthelabo	Plavix	clopidogrel	Withdrawal of promotional material Corrective advertisement
Serono	Gonal-F Pen	follitropin alfa	Withdrawal of promotional material Corrective letter $15 000 fine
Servier	Diamicron MR	gliclazide	Withdrawal of promotional material $5000 fine
Wyeth	Efexor-XR	venlafaxine	Withdrawal of promotional material $15 000 fine reduced on appeal to $14 000

Withdrawing antiepileptic drugs from seizure-free children

Robert L. Smith, Child Neurologist and Clinical Lecturer in Child Health, John Hunter Children's Hospital and University Discipline of Paediatrics and Child Health, Newcastle, New South Wales

Summary

Children with a history of epilepsy may be able to stop their treatment if they have had no seizures for at least two years. Antiepileptic drugs can be successfully withdrawn in up to 70% of cases. Each drug should be gradually tapered off over at least six weeks. This should be done sequentially if the child is taking more than one antiepileptic drug. Successful withdrawal is more likely in younger children and those with idiopathic epilepsy. Children with symptomatic epilepsies have a higher relapse rate, especially if they have associated cognitive and motor disabilities. For some parents, stopping their child's antiepileptic drugs may be more stressful than starting them.

Key words: epilepsy, electroencephalography.

(Aust Prescr 2006;29:18–21)

Introduction

Epilepsy affects 1–2% of children with peaks of onset in infancy, around the age of school entry and in adolescence. Around 70% of childhood epilepsies will eventually remit so withdrawal of antiepileptic drugs is often possible.[1] Most children are delighted at the prospect whereas parents may be apprehensive. Each child must be managed individually while considering numerous factors regarding the epilepsy, the family and the wider community.

When to stop

We normally consider withdrawing antiepileptic drugs after a child has been seizure-free for a minimum of two years. Some studies have explored stopping after one year, but this strategy is associated with a slightly higher risk of relapse. Stopping after a year can be considered if requested by parents or, for example, if a child is seizure-free but is troubled by adverse effects.

Consider the chances of successfully withdrawing treatment

Before withdrawing treatment it is important to review the diagnosis and natural history of the epilepsy by asking:

- is this epilepsy?
- do the data support the diagnosis of a particular epilepsy syndrome?
- is treatment withdrawal appropriate given the absence of seizures and the natural history of the epilepsy?

Sometimes this review may identify children who have other paroxysmal disorders such as breath holding, parasomnias, migraine, isolated acute symptomatic seizures and especially convulsive syncope.

Diagnosis predicts outcome

The type of epilepsy is one of the most important predictors of outcome.[2] A simple practical approach is to decide if the child has an idiopathic or a symptomatic epilepsy (Fig. 1).

In idiopathic epilepsies the child is neurologically normal and the brain is structurally sound. Idiopathic epilepsy may be focal (localisation related) or generalised.

Remission is most likely in:

- idiopathic localisation related (partial) epilepsies, such as benign rolandic epilepsy
- generalised epilepsies, such as childhood absence epilepsy
- onset of generalised epilepsy in early childhood rather than in adolescence.

In symptomatic epilepsies the child more often has static neurological abnormalities and a known aetiology associated with structural damage (Fig. 1). Remission is much less likely, particularly if the epilepsy began in early childhood.

Epileptic encephalopathies, including Lennox-Gastaut and West syndromes[2], encompass particularly serious associations of resistant seizures and electroencephalogram (EEG) abnormalities. Failure of control is associated with cognitive and motor decline and remission is unlikely.

Other factors

Successful withdrawal is significantly associated with[1]:

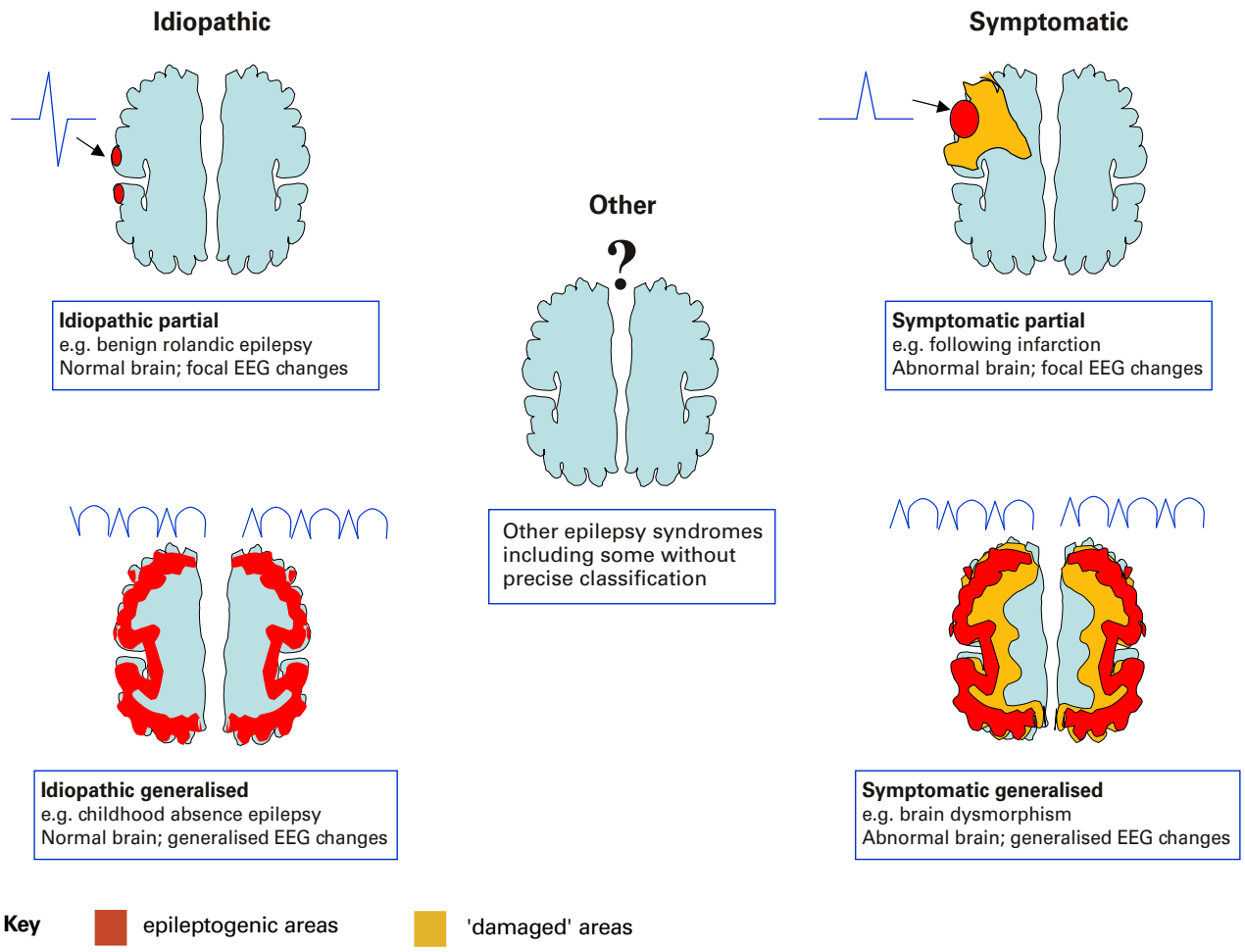
- good control with one antiepileptic drug
- children between the ages of five and nine years.

Failure of withdrawal is significantly associated with[1]:

- cognitive disability
- motor disability.

Fig. 1

The epilepsies: a simple clinical classification



In some cases antiepileptic drugs have other beneficial effects which may warrant continuing treatment despite the absence of seizures. If the drugs are continued, the reasons for ongoing treatment should be well documented and discussed with the child's parents.

Some parents may need to be persuaded to withdraw their child's treatment, even if the drugs are causing cognitive, behavioural or cosmetic adverse effects. This is particularly the case when the child's initial seizures were stressful or hard to control.

Is the child really seizure-free?

Most studies have used clinical criteria to assess when a child is seizure-free. It seems reasonable to work on the principle that the child is seizure-free if no seizures have been seen. However, a concern frequently voiced by parents is that they may be missing brief events or nocturnal seizures.

Some parents may request an EEG, however, while an epileptiform EEG prior to withdrawal is associated with a higher risk of relapse, the test is not reliable in predicting who will remain seizure-free. Similarly, a normal EEG does not guarantee remission. Children on 'spike suppressing' medication such as the benzodiazepines, sodium valproate and ethosuximide, may have a normal EEG irrespective of the state of their underlying epilepsy. We treat children and not their EEG so antiepileptic drug withdrawal is the only way of confirming remission.

Planning the withdrawal of therapy

Drug withdrawal should take place at a mutually convenient time for the child, family, school and the supervising practitioner. It may be appropriate to commence reduction:

- during school holidays as initial parental surveillance may be better
- well before the patient wants to learn to drive in order to allow a significant medication-free period
- in the summer if the child's seizures are triggered by winter illness.

It may be inappropriate to withdraw therapy:

- immediately before overseas travel

- during a period of high physical or emotional stress or excitement such as Christmas, or the start of high school
- when children are not staying at home
- when the supervising physician will be absent for the critical weaning period.

Preparing the family

The family may feel anxious about antiepileptic drug withdrawal and the venture may be unsuccessful. Always discuss and prepare them for relapse in order to reduce any subsequent disappointment.

Refresh the parents' knowledge of acute seizure management including cardiopulmonary resuscitation if requested. While not routine, the practice of having benzodiazepines available for emergency treatment in children with a history of convulsive seizures can be reassuring for some parents – especially rural families living far from medical help.

Preparing the school and other carers

Schools and preschools occasionally react to the prospect of antiepileptic drug withdrawal by cocooning a child, with resulting stigma and stress, particularly if convulsive seizures have previously occurred at school or if family anxieties are efficiently transferred. Teachers are not trained health professionals and may reasonably view the risk of relapse with trepidation. Hypervigilance with over-reporting of benign paroxysmal phenomena such as daydreaming and tantrums does happen and is potentially confusing. In difficult situations a visit from a nurse educator or one of the lay epilepsy organisations may be helpful. A new seizure management plan, if requested, should stress positive first aid management and avoid jargon and undue emphasis on frightening and unnecessary allusions to cardiorespiratory arrest or brain damage.

The plan

Give the family a written schedule of convenient dose reductions. A supply of lower dose formulations may be needed, particularly for small children.

One approach is to withdraw the antiepileptic drugs sequentially over two to three months for each drug. A study has shown no difference in relapse rate between a six-week and a nine-month taper[3], but this did not mention benzodiazepines which traditionally have been withdrawn over long periods.

In infancy, an alternative technique allows the child to 'outgrow their dose' then stop treatment when the dose per kilogram becomes negligible. This is practical because rapid somatic growth at this age produces a relative dose reduction more rapidly than in older children.

Families may be very anxious and in the short term frequent contact may be necessary. The plan should therefore include advice about how to deal with recurrent seizures and the possibility of confusing non-epileptic events with seizures.

Successful withdrawal

There is no standard definition of remission – not surprising when we try to classify anything by an absence of symptoms. The rate of remission is thought to be around 50% in children who remain seizure-free at six months with a cumulative probability of 66–96% at one year and 61–91% at two years.[1]

Post-epilepsy management

It is good to meet the family some months after successful drug withdrawal. Sometimes we need to help manage lingering anxieties and boost confidence. Children whose lives have revolved around their epilepsy may need help to refocus on health rather than sickness. Families may seek advice about the requirement for future declarations on driving licences, insurance policies or employment applications.

How long do we maintain 'epilepsy restrictions'?

The critical recommendation for any child with epilepsy is never to swim unsupervised and to shower rather than bathe. Recent campaigns encouraging all Australians not to swim alone may help to reinforce this critical issue with less stigma. Guidelines regarding driving are available from the roads authorities in each state and territory.

Conclusion

Stopping antiepileptic drugs in children is:

- generally a good idea
- usually considered after two seizure-free years
- most often successful in children with idiopathic epilepsies
- best done over a minimum of six weeks for each drug
- often a source of anxiety for parents.

Acknowledgement: Dr Ian Wilkinson made helpful comments regarding the original manuscript.

References

1. Specchio LM, Beghi E. Should antiepileptic drugs be withdrawn in seizure-free patients?. CNS Drugs 2004;18:201-12.
2. Berg AT, Lin J, Ebrahimi N, Testa FM, Levy SR, Shinnar S. Modeling remission and relapse in pediatric epilepsy: application of a Markov process. Epilepsy Res 2004;60:31-40.
3. Tennison M, Greenwood R, Lewis D, Thorn M. Discontinuing antiepileptic drugs in children with epilepsy. A comparison of a six-week and a nine-month taper period. N Engl J Med 1994;330:1407-10.

Further reading

Kilpatrick CJ. Withdrawal of antiepileptic drugs in seizure-free adults. Aust Prescr 2004;27:114-7.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 27)

5. Only 30% of children with epilepsy can stop treatment with antiepileptic drugs even if they have had no seizures for two years.
6. The withdrawal of antiepileptic drugs should only be considered in seizure-free children if the electroencephalogram is normal.

PDA review

MiniTG – the personal digital assistant version of Therapeutic Guidelines

Melbourne: Therapeutic Guidelines Limited; 2005.

Price: $125 annual subscription (single licence) for either the Pocket PC or Palm operating system personal digital assistant (PDA)

Robert A. Wilcox, Registrar, Department of Neurology, Flinders Medical Centre, Adelaide

MiniTG is a version of the popular series of Therapeutic Guidelines books designed for personal digital assistants (PDA). It therefore inherits the pedigree of solid clinical review and regular revision that has been a key feature of the series. Sensibly the team at Therapeutic Guidelines have used iSilo (http://www.isilo.com), a very robust and reliable document reading program, as a platform to run both the Palm and Pocket PC versions of miniTG. Technically miniTG will have required minimal modification of the current CD-based version of the guidelines – eTG complete. Consequently users of eTG complete will find the interface of miniTG very familiar. The only contents of eTG complete not carried over to miniTG are the direct internet links and some ready reference calculators. Indeed, one hopes that other valuable medical references might also adopt this expedient method of converting their CD-based versions to iSilo PDA documents.

The major advantage of miniTG is its portability, allowing referencing of vital clinical information at the bedside or on a house call. The basic topic divisions of the original books of Therapeutic Guidelines are retained: analgesia, antibiotic, cardiovascular, endocrinology, gastrointestinal, neurology, palliative care, psychotropic and respiratory. There is also a useful section containing information about pregnancy and breastfeeding. Each of these topics starts with a succinct 'Getting to know your drugs' section and then follows with selectable hyperlinked clinical problems or conditions. For those familiar with PDAs, the selection of topics is easy using the pointing stylus in a similar fashion to a computer mouse. Within each section there are hyperlinks to related topics or further clinical information. An especially useful feature is the list of tables, figures and boxes at the end of each major specialist area. These allow rapid review of whole topics, for example the comparison of dosage regimens and adverse effects of the commonly prescribed drugs for Parkinson's disease.

The iSilo platform itself allows format modification to adjust the size and presentation of text so topics are generally quite readable. However, the small size of most PDA screens can be limiting when viewing tables and figures in miniTG. Certainly higher resolution colour PDA screens significantly improve the miniTG display. Furthermore, some PDAs have screens that can convert from portrait to landscape display, rendering the wider tables and figures viewable without the annoyance of constantly having to scroll across the screen.

I tried the Palm PDA version of miniTG on a Palm Tungsten T3 with 64Mb internal memory, a 128Mb memory card, a landscape screen option and with the full registered version of iSilo (US$20) loaded. Running either in the internal memory or from the card, miniTG was fast and reliable and movement between topics via hyperlinks was seamless. I used miniTG for a two-week period and accessed it over 30 times. Surprisingly, I found myself using it not only at the bedside, but also while in clinic as it was faster to access than the eTG complete on our hospital computer system. On one occasion I was able to use the PDA screen at the bedside to show a patient a diagram of the Epley's manoeuvre I planned to conduct.

Overall, miniTG is a useful clinical tool for the roving clinician. The cost of purchasing the eTG complete ($250/year) and miniTG separately does seem high given the technical ease of conversion between the two formats. Given that clinic-based doctors who already use eTG complete would probably require miniTG only infrequently, a cheaper bundled price for both products would be welcome.

Minimum system requirements

- Palm or Pocket PC with 10Mb of free storage and 320x240 minimum screen resolution
- the iSilo Document Browser from http://www.isilo.com (your iSilo User ID is needed to order miniTG)
- a desktop computer (Mac or PC) to transfer files to your PDA, software for Palm or Pocket PC devices, and USB port to connect to PDA
- a valid email address to receive registration information

Anticholinergic drugs for overactive bladder

William Kuteesa, Fellow in Urogynaecology, and Kate H. Moore, Associate Professor, Pelvic Floor Unit, St George Hospital, Sydney

Summary

Anticholinergic drugs are first-line pharmacotherapy for overactive bladder syndrome. They block muscarinic receptors at the detrusor muscle, thus reducing bladder contractility. As no anticholinergic drugs are totally selective for the detrusor, adverse effects from muscarinic receptor blockade at other sites are common. New drugs with greater bladder selectivity and extended-release preparations are being developed to try to reduce these adverse effects. Most of the newer drugs have similar efficacy in reducing the symptoms of overactive bladder (when compared to placebo). Optimum benefit is obtained when the drugs are prescribed in conjunction with bladder retraining.

Keywords: incontinence, oxybutynin, tolterodine.

(Aust Prescr 2006;29:22–4)

Introduction

Overactive bladder (previously called 'unstable bladder') is a clinical symptom complex characterised by urgency (sudden and compelling desire to pass urine, which is difficult to defer), usually with frequency (more than eight voids per day) and nocturia (waking to void more than once at night). It occurs with or without urge incontinence (involuntary leakage of urine with the feeling of urgency) in the absence of infection or other irritative lesions.[1]

The urodynamic diagnosis is now termed detrusor overactivity (previously called detrusor instability) because detrusor contractions are seen during filling cystometry and these are associated with the feeling of urgency.[1] There are three categories of detrusor overactivity: neuropathic (previously detrusor hyperreflexia), obstructive (commonly associated with prostatic obstruction) and idiopathic. The term overactive bladder usually refers to the idiopathic type of detrusor overactivity.

The prevalence of overactive bladder increases with advancing age and affects about 16% of adults over 40.[2] Of these, about 30% suffer from urge incontinence, now called 'overactive bladder wet', with profound reduction in quality of life.[2,3] The remainder, now called 'overactive bladder dry', nevertheless have a debilitating condition which is likely to progress to incontinence if untreated.

Management includes bladder retraining, fluid scheduling, restricted consumption of caffeine and alcohol, and avoidance of diuretic therapy. Anticholinergic (antimuscarinic) drugs are the main pharmacotherapy, but other treatments include tricyclic antidepressants and vasopressin analogues. Patients with overactive bladder 'dry' may respond more readily to bladder training without recourse to drug therapy, although this hypothesis has not been formally tested.

Most clinicians would start treatment by teaching bladder retraining. Many public health services in Australia now offer bladder retraining therapy by specialist continence advisors.* Micturition deferment techniques are taught and a 'bladder diary' gives a guide to selecting a realistic voiding interval for the patient. Prescribing anticholinergic drugs generally allows the patient to improve more rapidly, but bladder training alone is a reasonable first-line therapy.

Rationale for anticholinergic use

Detrusor muscle contractions are essential for normal micturition, but involuntary contractions produce the symptoms of overactive bladder. Contractions depend on the activation of muscarinic receptors in the bladder by acetylcholine. The M_3 muscarinic receptor-subtype is thought to be the most important in regulating detrusor contractions.

Anticholinergic drugs block muscarinic receptor activation and inhibit the spontaneous detrusor contractions found in overactive bladder. Drug efficacy is dose-dependent, but effectiveness is often limited by unwanted antimuscarinic effects in distant organs where other acetylcholine receptor-subtypes predominate (for example salivary gland M_1/M_3, gut M_2/M_3, brain M_1 and cardiac M_2). These adverse effects are also dose-dependent. They commonly include dry mouth, dry eyes, confusion, constipation, somnolence, blurred vision and increased heart rate.

There are no currently available drugs with pure selectivity for the muscarinic receptors in the detrusor. To try to improve the benefit:harm ratio a number of anticholinergics have been developed with greater selectivity for the detrusor or the M_3 receptor, or with extended release properties.

* details available from National Continence Helpline 1800 33 00 66

Do anticholinergics work?

The ability of anticholinergic drugs to reduce detrusor contractions has been well established *in vitro* and *in vivo*, however there are questions about their clinical efficacy. Anticholinergic therapy has been extensively studied in randomised placebo-controlled trials and the Cochrane Collaboration has systematically reviewed 51 studies involving 6713 patients.[4] A striking placebo effect was observed, with 45% of those on placebo reporting cure or improvement in symptoms. (Patients in some but not all studies were given printed information about bladder training, but no formal bladder training was given.) The effect of anticholinergics was found to be a statistically significant 15% greater than placebo (equivalent to a 'number needed to treat' of seven in order to reduce leakage by one episode per 48 hours).

A problem for the review was that the studies used a wide range of outcome measures. Analysis of the two measures that were common to most randomised controlled trials revealed that anticholinergics resulted in one less micturition per 48 hours and one less incontinence episode per 48 hours.[4] From a clinical perspective, the results seem unimpressive, but there are two reasons for this. Firstly, most studies did not include concomitant bladder training, thus they failed to reflect optimal clinical practice. Secondly, the hypotheses tested by these studies may have been inappropriate. Most did not measure treatment effect upon 'urgency', the primary symptom of overactive bladder.[1] Furthermore, the modest improvements in leakage and frequency identified in the review could have had major positive impacts on quality of life, but most studies did not include quality of life measures.

Bladder training is essential treatment for overactive bladder

Which is the most effective anticholinergic?

Uncertainty still remains about which of the anticholinergic drugs is superior in efficacy, in different patient groups (male, female, elderly) and for particular symptoms. There are also few data on the socioeconomic impact of overactive bladder symptoms or therapy.[4]

Oxybutynin

Oxybutynin is the most widely used anticholinergic for overactive bladder. Early studies showed a major clinical benefit in 60% of patients (versus 3% of those on placebo) in both objective and urodynamic assessments. Dry mouth is the most bothersome and frequent adverse effect (greater than 50%) and is associated with high discontinuation rates.[5] The drug is comparatively inexpensive.

Propantheline

Propantheline is an old drug that is still widely used in Australia. It is a synthetic analogue of atropine that blocks muscarinic receptors at all sites, thus adverse effects can be severe at low serum concentrations. However, propantheline is 60% of the cost of oxybutynin.

Imipramine

Imipramine is a tricyclic antidepressant with beta$_3$ mimetic properties that relax the dome of the detrusor, but it also has significant anticholinergic effects. Drowsiness is common, especially in the first three weeks of therapy while a steady state concentration is achieved. Imipramine may therefore be useful for treating nocturia or nocturnal enuresis.

Tolterodine

Tolterodine is an anticholinergic specifically developed to treat overactive bladder. *In vitro*, tolterodine has greater specificity for bladder tissue than for salivary glands. A meta-analysis found only four appropriate randomised controlled trials comparing tolterodine with oxybutynin.[6] Both drugs are of similar efficacy, with oxybutynin being slightly superior on some outcomes such as incontinence episodes per 24 hours.[6] The exact mechanism is not understood, but tolterodine halves the incidence of dry mouth compared to oxybutynin.[6]

Trospium

Trospium is a non-selective antimuscarinic drug which is frequently used in the UK as second-line therapy. It is as effective as oxybutynin, but has a lower incidence of adverse effects (similar to tolterodine).[7] Trospium's structure limits its penetration of the blood-brain barrier and this is thought to reduce central nervous system adverse effects. This feature may be important for elderly patients.

Darifenacin

The efficacy of darifenacin, including quality of life, has been convincingly shown over placebo, but whether there is clear superiority over drugs such as tolterodine remains to be seen. Darifenacin has high M_3 receptor specificity, resulting in less impairment of cognitive or cardiac function. Some patients still develop dry mouth and constipation as M_3 receptor activity is present in the gut.

Solifenacin

Solifenacin was approved in the USA in 2004. *In vitro*, it is more selective for bladder tissue than for salivary glands. Studies suggest improvements over placebo with low rates of dry mouth (10%) and greater quality of life.[8] A well-powered comparative randomised controlled trial[8] found that tolterodine had a lower incidence of unwanted effects and lower discontinuation rates.

Extended-release products

Extended-release formulations of oxybutynin[9] and tolterodine[8] have been developed. These are thought to reduce

concentration-dependent antimuscarinic adverse events by maintaining lower and less fluctuating plasma concentrations. Once-daily administration offers greater convenience and may improve compliance. Both products seem as effective as oxybutynin, but they have a reduced frequency and severity of adverse effects.

What to prescribe

Oxybutynin should be regarded as first-line drug therapy. It fulfils criteria for cost-effectiveness, safety, efficacy, and for a significant proportion of patients, tolerability. Consideration should always be given to behavioural therapies as an adjunct, to achieve and maintain good therapeutic outcomes at the lowest drug doses.[10] Patients experiencing unmanageable adverse effects from oxybutynin may benefit from changing to second-line treatments such as tolterodine. Subsequent treatment failure may warrant specialist referral.

Only two small longitudinal studies on the duration of treatment have been carried out. Those patients who require anticholinergic therapy may typically need it for at least 3–6 months.

Minimising adverse effects

In the elderly or patients with a low bodyweight, the initial oxybutynin dose should be 2.5 mg twice daily. One can increase a morning dose or add a lunchtime dose according to the severity and timing of the urge symptoms. On the other hand, if the patient has a very dry mouth in the morning, then a lower morning dose with a larger evening dose can be used. The maximum dose is 5 mg three times daily. Tolterodine is expensive and not subsidised by the Pharmaceutical Benefits Scheme so some patients may prefer to take it in the morning and use a cheaper drug at times when dry mouth may be less bothersome.

Conclusion

Anticholinergics are clinically and statistically better than placebo for overactive bladder. Most are equally effective and all have some adverse effects. This has driven the development of drugs with greater selectivity or tolerability. Until these new alternatives undergo rigorous comparative trials, oxybutynin will remain first-line in pharmacotherapy in Australia. Outcomes are improved when anticholinergics are prescribed in conjunction with bladder training.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167-78.
2. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001;87:760-6.
3. Herbison P, Hay-Smith J, Ellis G, Moore K. Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. Br Med J 2003;326:841-4.
4. Hay-Smith J, Herbison P, Ellis G, Moore K. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. The Cochrane Database of Systematic Reviews 2002, Issue 3. Art. No.: CD003781. DOI: 10.1002/14651858.CD003781.
5. Moore KH, Hay DM, Imrie AE, Watson A, Goldstein M. Oxybutynin hydrochloride (3 mg) in the treatment of women with idiopathic detrusor instability. Br J Urol 1990;66:479-85.
6. Harvey MA, Baker K, Wells GA. Tolterodine versus oxybutynin in the treatment of urge urinary incontinence: a meta-analysis. Am J Obstet Gynecol 2001;185:56-61.
7. Junemann KP, Al-Shukri S. Efficacy and tolerability of trospium chloride and tolterodine in 234 patients with urge syndrome: a double-blind, placebo-controlled, multicentre clinical trial. Neurourol Urodyn 2000;19:488-90.
8. Chapple CR, Rechberger T, Al-Shukri S, Meffan P, Everaert K, Huang M, et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. BJU Int 2004;93:303-10.
9. Anderson RU, Mobley D, Blank B, Saltzstein D, Susset J, Brown JS, et al. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. J Urol 1999;161:1809-12.
10. Burgio KL, Locher JL, Goode PS. Combined behavioral and drug therapy for urge incontinence in older women. J Am Geriatr Soc 2000;48:370-4.

Associate Professor Moore has held consultancies with Pfizer, the manufacturer of tolterodine and darifenacin.

Self-test questions

The following statements are either true or false (answers on page 27)

7. Anticholinergic drug therapy for overactive bladder reduces the frequency of micturition by one void every two days.
8. Anticholinergic drugs with greater selectivity for M_3 muscarinic receptors have significantly greater efficacy than less selective drugs for overactive bladder.

Patient support organisation

The Continence Foundation of Australia

Website www.contfound.org.au

National Continence Helpline 1800 33 00 66

Email info@continence.org.au

Book review

Goodman & Gilman's The pharmacological basis of therapeutics. 11th ed. Brunton L, Lazo J, Parker K, editors.

New York: McGraw-Hill; 2005. 2021 pages. Price $155.95

John S. Dowden, Editor, Australian Prescriber

This textbook of therapeutics was first published in 1940, so it is not surprising that the original authors were not involved in the 11th edition. The book is now made up of chapters written by individual authors, creating a challenge for the editors. All but three of the authors work in the USA, but the textbook has an international appeal.

As in previous editions, the book is divided into sections dealing with drugs that act on each of the body's systems. There have been a few changes in this format such as the section on vitamins being absorbed into other chapters, and the chapter on the treatment of poisoning being moved into the toxicology section. New chapters include pharmacogenetics and drug metabolism.

Several sections begin with a chapter that reviews the physiology of a body system. In other sections these reviews are incorporated within the chapters. The usual pattern is to explain how a class of drugs acts and then to briefly discuss individual members of that class. The explanations of mechanisms of action are usually easy to understand especially when accompanied by diagrams. There is a bibliography at the end of each chapter for people who want to check the original research.

The problem with any textbook is that parts of it quickly go out of date. This edition was compiled recently enough to include the downfall of rofecoxib.

Unless it is already available in the USA, a new drug marketed in Australia may not be included in Goodman and Gilman. (*Australian Prescriber* is an up-to-date source of brief information on new drugs.) However, the book is a useful resource. It does not need to be on every prescriber's desk, but it is a very helpful reference for learning, or recalling, how drugs work.

New drugs

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

Lumiracoxib

Prexige (Novartis)

400 mg tablets

Approved indication: analgesia

Australian Medicines Handbook section 15.1

Lumiracoxib is a non-steroidal anti-inflammatory drug which selectively inhibits the COX-2 isoenzyme. Like celecoxib, lumiracoxib may have fewer gastrointestinal adverse effects than similar drugs which inhibit the COX-1 and COX-2 isoenzyme (see COX-2 inhibitors, Aust Prescr 2000;23:30–2).

A small study randomised 65 men to take lumiracoxib, naproxen or a placebo for eight days. While none of the volunteers who took lumiracoxib developed gastroduodenal erosions, 13 of those taking naproxen developed duodenal erosions and one man developed a gastric ulcer.[1]

A larger trial compared lumiracoxib with naproxen and ibuprofen in 18 325 people over 50 years old with osteoarthritis.[2] Although 39% of the patients did not complete the one-year trial, there was a significant difference in the incidence of gastrointestinal adverse effects. Complications occurred in 29 of the 9117 people (0.32%) in the lumiracoxib group compared with 83 of the 9127 people (0.91%) who took another non-steroidal anti-inflammatory drug.

At the time lumiracoxib was approved in Australia much of the information about its efficacy was only publicly available as conference abstracts. Several papers were presented at the 2003 congress of the European League against Rheumatism.[3]

One of the conference abstracts describes a comparison of lumiracoxib, celecoxib and placebo in 1600 patients with osteoarthritis of the knee. After 13 weeks the effect of lumiracoxib on pain and function was greater than with placebo and similar to the effect of celecoxib. There was no significant difference in the efficacy of once-daily lumiracoxib 200 mg and lumiracoxib 400 mg.[3]

An extension of another study found celecoxib and lumiracoxib had similar efficacy after nine months of treatment.[3]

In addition to osteoarthritis, lumiracoxib has also been approved for the treatment of acute pain. Few of the studies of primary dysmenorrhoea, postoperative dental pain and postoperative surgical pain have been published in full.

Lumiracoxib can cause the same problems as other non-steroidal anti-inflammatory drugs. It can affect hepatic and renal function and should be used with caution in patients with hypertension or heart failure as it can cause fluid retention. Lumiracoxib is contraindicated in patients with ischaemic heart disease, cerebrovascular disease and peripheral arterial disease.

In the comparison with naproxen and ibuprofen the incidence of cardiovascular events was higher in patients taking lumiracoxib, but the difference was not significant.[4] If the patients were taking low-dose aspirin lumiracoxib lost its significant gastrointestinal advantage over the other drugs.[2]

Most of a dose is metabolised, primarily by cytochrome P450 2C9. Although lumiracoxib therefore has several potential interactions it is not clear which will be clinically significant.

Although there is now published information about using lumiracoxib for osteoarthritis it should probably not be prescribed for other conditions until more data are available.

T manufacturer had no objection to providing data but did not actually provide it

References

1. Rordorf C, Kellett N, Mair S, Ford M, Milosavljev S, Branson J, et al. Gastroduodenal tolerability of lumiracoxib vs. placebo and naproxen: a pilot endoscopic study in healthy male subjects. Aliment Pharmacol Ther 2003;18:533-41.
2. Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 2004;364:665-74.
3. http://www.eular.org/index.cfm?framePage=/eular2003.cfm [cited 2006 Jan 13]
4. Farkouh ME, Kirshner H, Harrington RA, Ruland S, Verheugt FW, Schnitzer TJ, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet 2004;364:675-84.

Moxonidine

Physiotens (Solvay)

0.2 and 0.4 mg tablets

Approved indication: hypertension

Australian Medicines Handbook section 6.4.8

Centrally-acting antihypertensive drugs such as methyldopa and clonidine are no longer widely used to control blood pressure. Their usefulness is limited by their adverse effects. Moxonidine has been developed as a more tolerable centrally-acting drug.

The imidazoline receptors are found in the brainstem and in the kidney. Stimulation of these receptors by an agonist, such as moxonidine, reduces sympathetic activity, lowering peripheral vascular resistance, and thereby reducing blood pressure.

The tablet formulation of moxonidine is well absorbed with a bioavailability of 88%. Most of the dose is excreted unchanged in the urine. Although the half-life is only around 2.2 hours, blood pressure can be controlled by a single daily dose.

Placebo-controlled trials show that moxonidine works better than placebo and that the effect on blood pressure is similar to enalapril. Other studies have shown no statistical difference between moxonidine and hydrochlorothiazide, atenolol and nifedipine.[1]

Moxonidine has been available in the UK since 1996. Analysis of prescribing data from 409 general practitioners shows that moxonidine is not extensively used. It seems to be prescribed when several other treatments have failed to control hypertension. Out of 71 775 people with hypertension only 830 took moxonidine and 80% of these patients were taking it with at least one other antihypertensive.[2]

Although moxonidine may cause fewer adverse effects than clonidine, dry mouth and somnolence can still occur. Approximately 5% of the patients withdrew from clinical trials because of adverse events. Although the trials were short, rebound hypertension does not appear to be a major problem when moxonidine is stopped. Rebound hypertension may occur if the patient stops a beta blocker at the same time. Patients ceasing this combination should therefore withdraw the beta blocker first.

A trial of moxonidine in patients with heart failure had to be stopped because of increased mortality compared to treatment with placebo.[3] Moxonidine is therefore contraindicated in any degree of heart failure. It is also contraindicated in patients with bradycardia, heart block or renal impairment and in people more than 75 years old. Caution is required if a patient has a history of unstable angina, severe coronary artery disease or angioneurotic oedema.

X manufacturer did not respond to request for data

References

1. Messerli F. Moxonidine: a new and versatile antihypertensive. J Cardiovasc Pharmacol 2000;35(Suppl 4):S53-S56.
2. Schachter M, Mitchell G, Niziol C, Abhyankar BA. Antihypertensive efficacy of moxonidine in primary care: a 'real-life' study. Int J Clin Pract 2003;57:479-82.
3. The MOXCON Investigators. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). Eur J Heart Fail 2003;5:659-67.

Rabies vaccine

Rabipur (CSL)

vials containing lyophilised powder for reconstitution

Approved indication: rabies prophylaxis and treatment

Australian Medicines Handbook section 20.1

Rabies is caused by a lyssavirus and usually occurs after a bite by a rabid dog. A similar illness can result from infection with Australian bat lyssavirus.

Rabies vaccine is used prophylactically for people who will spend a prolonged time in areas where rabies is endemic. It is also used with immunoglobulin in the management of people who have been exposed to the virus.

This product differs from the currently available vaccine in that a different strain of virus is used and it is prepared using chick embryo cells rather than human diploid cells. Both vaccines will produce adequate amounts of antibody after the series of three injections.

Several injections are required for post-exposure prophylaxis. Protective antibody titres can be achieved within 14 days if the recommended regimen is followed.

People with a continuing risk of exposure to rabies may need a booster dose every 2–5 years to maintain their immunity. Some people developed serum sickness after boosters of diploid cell vaccines. It is uncertain if this will be a problem with the chick embryo vaccine, but it is approved for use as a booster in people previously immunised with diploid cell vaccine.

Many people will get pain at the injection site. Other reactions include headache, myalgia and rash. Rarely a vaccinee may develop anaphylaxis or a neurological disorder such as Guillain-Barré syndrome.

[T][T] manufacturer provided some data

The T-score ([T]) is explained in 'Two-way transparency', Aust Prescr 2005;28:103.

Answers to self-test questions

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

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