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EDITORIAL

The secrecy of drug regulatory information

M.J. Eadie, Emeritus Professor, Department of Medicine, University of Queensland, and former chairman, Australian Drug Evaluation Committee

Index words: drug evaluation, cost-effectiveness.

(Aust Prescr 2002;25:78–9)

Recent Australian legislation has reinforced the community's desire to preserve the privacy of personal information, as far as this is compatible with the public good. Yet the community has a desire for more 'open' government and demands increased public access to information held by government. However, some of this information may have been supplied to the government in confidence. Can a satisfactory balance be found between these sometimes competing desires?

Government decisions on the marketing and subsidy of drugs depend on the assessment of data provided by the pharmaceutical industry. These data are largely 'commercial-in-confidence'. Clinical trials and other data are evaluated within the Therapeutic Goods Administration (TGA), or externally, before a new drug can be approved in Australia. The evaluations, and the TGA's recommendation based on them, are assessed by the Australian Drug Evaluation Committee (ADEC) which then recommends to the Minister for Health which drug should be approved. Unlike the situation which applies for regulatory bodies in certain overseas countries*, virtually none of the information held by the TGA is currently made available publicly. Much of it will also never appear in the medical literature. The cost-effectiveness data considered by the Pharmaceutical Benefits Advisory Committee (PBAC), when recommending that a drug be listed on the Pharmaceutical Benefits Scheme (PBS), are also secret.[1]

Would there be advantages for the community if the drug regulatory information held by government was more widely available? The evaluations, the TGA's recommendation, and the ADEC and PBAC assessments would provide an extensive and balanced source of information about a new drug. Their availability should ultimately result in better therapeutic practice, and the Australian drug regulatory process would be more transparent. Scientifically valid information concerning trials with unfavourable outcomes would be available. These negative studies currently rarely reach the public domain. Toxicological data about drugs which have been rejected for marketing would provide a valuable additional resource for predicting, on the basis of analogy, potential problems with similar drugs. Additionally, there is an ethical consideration. Should information be allowed to remain secret, when its wider availability could prevent the unnecessary repetition of studies that are likely to have negative or otherwise unfavourable outcomes? Resources would be saved and animals and human participants would be spared pointless and perhaps hazardous procedures.

Would there be disadvantages for those who currently expect that the information will remain secret? Some disadvantages for the pharmaceutical industry are obvious. The knowledge would put competitors in a stronger position, and at an earlier stage. Some item of knowledge, missed or ignored by the original owners of the information, might spark an idea which is ultimately of great commercial advantage to someone else. The original investigators who produced the pharmaceutical industry's data may find that the information was in the public domain before they had published it in the scientific literature. This might deter the better investigators from working in drug development. Evaluators of drug regulatory data, if identified, could be exposed to various external pressures. The staff of the TGA and members of ADEC and PBAC might also face increased public criticism of their recommendations.

* New drug information is available from the web sites of the US Food and Drug Administration (www.fda.gov) and the European Medicines Evaluation Agency (www.emea.eu.int).

In this issue...

There has been recent debate about increasing the transparency of the Pharmaceutical Benefits Advisory Committee. *Australian Prescriber* has previously discussed the need to know what lies behind the decision to subsidise a drug, but Mervyn Eadie reminds us that the evidence to support the marketing of a drug in Australia is also kept secret. Much of the evidence about the new drugs on page 94 is not in the public domain.

Some old drugs, such as warfarin, may have had difficulty in meeting modern drug regulatory standards. Warfarin has serious adverse effects and Lye Lin Ho and Timothy Brighton warn us about the risks of prescribing it with an antiplatelet drug.

Cats feature in two articles. Pet hair is a common cause of perennial respiratory symptoms and Richard O'Brien tells us which test to use if a clinical suspicion of allergy needs to be confirmed. Cats are the definitive host for *Toxoplasma gondii* and Peter McCluskey suggests what treatment to use when the parasite invades the eye.

Can some reconciliation be achieved between the potential public benefit available from the release of currently confidential drug regulatory information, and the understandable commercial and possibly individual wish for continued secrecy of this information? The names of the ADEC members are already public knowledge and the identity of evaluators could be concealed when their evaluations were released. It would be no bad thing if investigators, and the pharmaceutical industry, expedited the publication of original data in the scientific literature.

From the commercial-in-confidence standpoint, the timing of the public availability of governmental-held information would be critical. The pharmaceutical industry might have relatively little problem with information becoming publicly available 20 to 30 years after it was lodged with government, yet its immediate public availability appears to be unacceptable to the industry in Australia. Some mutually agreed intermediate position might be achieved. Perhaps pharmacological and clinical data could be released after PBS listing (a drug in Australia is unlikely to be widely used without such listing), or a certain time after ADEC has recommended its approval. The release of formulation data could be deferred until expiry of the drug's patent, or later, so that generic manufacturers were not advantaged. In all such matters, Australia would need to act in co-ordination with other nations.

Surely there is a case that the potential community benefit, and also ethical considerations, require that better use should be made of the treasure trove of drug information that government and industry in Australia currently keep secret?

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Professor Eadie was chairman of ADEC from 1985 to 1993.

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.

Search engines

Editor, – I read with interest *Australian Prescriber* Vol 25 No 1, 2002. In particular the letters section caught my attention. The comment on the search for information on immunisation stated that information retrieval was limited by the indexing of the databases and by databases being overburdened by too much content.

In fact the problem may simply rest with the manner in which the web page was set up. Keywords and key phrases are important factors in being found by a search engine. A search engine (e.g. Google, Lycos, Excite) is like a librarian that selects certain web pages in response to a search request according to the search engine's own criteria. Search engines rank web pages according to keywords or phrases:

- in the title
- in headings
- in the body text
- in the metatags provided for every web page as the source code or document code. You can access this code by going into 'View' on the menu bar of the browser (e.g. Netscape, Windows Explorer). This code gives instructions to browsers and search engines. It is written in HTML (Hypertext Markup Language).
- in the hyperlinks (links the reader can click on to go to other pages)
- in the URL and other tags.

How you place your keywords is integral to how easily your web site is found.

It is possible that the Webmaster of the Department of Health and Ageing did not consider 'vaccination' and 'guidelines' to be significant keywords and did not place them in a prominent position in the necessary sections. Perhaps the computing expert simply needs to have further consultation with the content expert about essential keywords or phrases in order to remove any barriers to accessing the very important database about immunisation.

Leora Ross
Pharmacist
Sydney

Does pethidine still have a place in therapy?

Editor, – We read with interest the article 'Does pethidine still have a place in therapy?' (Aust Prescr 2002;25:12-3). The author concluded that pethidine 'can be used to treat acute pain for a short time' and suggests that it results in smaller increases in common bile duct pressures as well as less urinary retention and constipation when compared with morphine.

Our Drug Committee has debated whether or not there was a place for pethidine in acute pain management. We were not convinced that there was any good evidence to suggest that repeated doses (required if analgesia is to be maintained) resulted in clinically significant reductions in bile duct pressures compared with morphine. There was also no good evidence comparing effects on urinary retention and constipation. However, it is known that signs consistent with norpethidine toxicity can be seen within 24 hours of starting treatment with pethidine if higher doses are required.

A review of the use of opioids in pain management also expressed concerns about pethidine's continuing use.[1] It states 'Since use of pethidine is not associated with any

specific advantage, it is a poor choice if multiple doses are needed' and that '… there is no good evidence to suggest that pethidine has any advantage at equianalgesic doses over other opioids for biliary or renal colic'.

For these reasons, as well as the problems that can be seen when pethidine is used for chronic pain (as mentioned in the article), our Drug Committee has recommended that hydromorphone become the second-line choice of opioid after morphine for routine acute pain management when parenteral opioids are required. Where intravenous opioids are used, fentanyl may also be a useful alternative, especially in view of its lack of active metabolites.

P. Macintyre
Director, Acute Pain Service
F. Bochner
Chairman, Drug Committee
S. Wiltshire
Project Pharmacist, Drug Committee
Royal Adelaide Hospital
Adelaide

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1. McQuay H. Pain: Opioids in pain management. Lancet 1999;353: 2229-32.

Dr A. Molloy, author of the article, comments:

I concur with the concerns of the Royal Adelaide Hospital Drug Committee regarding the use of pethidine and the fact that norpethidine toxicity can occur after repeated doses within 24 hours if high doses are required. Now that hydromorphone is available, it is certainly reasonable to consider this as a second-line choice if parenteral opioids are required in the acute pain setting. Pethidine, however, should not be taken off the formulary as it still remains a useful drug for short-term treatment of acute pain.

APMA Code of Conduct

Editor, – I read with interest the article about breaches of the APMA Code of Conduct (Aust Prescr 2002;25:41). It is good that breaches are noted in a public forum. However, I believe for completeness, there needs to be more detail about the actual advertisement and what the contentious point was rather than just reporting that the advertisement is never to be used again or the company has been fined.

I can envisage a situation where a doctor who has seen a misleading advert has its message entered into his or her consciousness where it may go on to influence prescribing habits. This is, after all, the purpose of medical advertising. The same doctor then learns that the promotional material is not to be used again, but which promotional material and what aspects of it? If you cannot recall the original advertisement how can the potentially defective prescribing practice based on that misinformation be corrected?

Mark Raines
Medical Intern and Pharmacist
Darwin

Editor's note: More details of each breach can be found in the Australian Pharmaceutical Manufacturers Association's Code of Conduct Annual Report. (The APMA is now named Medicines Australia.)

Support for *Australian Prescriber*

Editor, – At a recent meeting of the Hervey Bay Chapter of the Southern Queensland Rural Division of General Practice it was unanimously agreed to send a letter of support for *Australian Prescriber*.

Australian Prescriber appears to be the only publication that gives a balanced view of drugs and their use.

In general practice we all rely heavily on its independent views as a lot of our information comes directly from drug company representatives, which is by its nature extremely biased and incomplete.

Long may you continue to publish.

S. Rudd
Hervey Bay Chapter Co-ordinator
Southern Queensland Rural Division of General Practice
Hervey Bay, Qld.

Your questions to the PBAC

Australian Prescriber readers are invited to write in with their questions about decisions of the Pharmaceutical Benefits Advisory Committee. The segment 'Your questions to the PBAC' will publish selected questions from readers, and answers from the Committee itself. Questions may address issues such as regulatory decisions, pharmaceutical benefits listings, withdrawal of a drug from the market and Authority prescriptions.

This exclusive arrangement helps *Australian Prescriber* readers understand how the contents of the Schedule of Pharmaceutical Benefits are determined. The 'yellow book' is published quarterly by the Department of Health and Ageing, and is also available on the internet*. It provides important information for doctors, dentists and pharmacists, including a summary of changes to listed items, which medicines are included or excluded from benefit, whether restrictions apply to medicines and how much patients should pay including price premiums for particular brands where applicable.

It may not be possible to reply to all individual questions to the PBAC. The usual editorial controls will apply so that only readers' letters and the responses selected by the Editorial Executive Committee will be published in the journal. Letters and responses may be edited before publication.

* www1.health.gov.au/pbs/index.htm

Warfarin, antiplatelet drugs and their interactions

Lye Lin Ho, Haematology Registrar, and Timothy Brighton, Staff Specialist, Department of Haematology, South East Area Laboratories Services, St George Hospital, Kogarah, New South Wales

SYNOPSIS

Patients who are being treated with warfarin may sometimes be prescribed or buy antiplatelet drugs, such as aspirin. As warfarin and antiplatelet drugs increase the risk of bleeding, their combination can put patients at risk of a major haemorrhage. This risk may be further increased by the patient's age and other illnesses. A thorough history is therefore important in assessing the risk of haemorrhage. Patients need to be informed of the risk and should be encouraged to have their international normalised ratio checked regularly.

Index words: anticoagulants, aspirin, non-steroidal anti-inflammatory drugs, thienopyridines, dipyridamole, IIb/IIIa antagonists.

(Aust Prescr 2002;25:81–5)

Introduction

Decisions about anticoagulation require an assessment of the benefits of therapy versus the hazards, namely bleeding, for each patient. Clinical trials provide strong evidence for the benefit of anticoagulants in treating thromboembolic disease. Translating this evidence from selected patient groups to the general community requires closer scrutiny of the risks of bleeding. These considerations are even more important given the widespread community usage of medications, such as antiplatelet drugs, which interact with warfarin. We need to consider the:

- mechanism of antithrombotic action (and haemorrhage) of these drugs
- potential risks of combining warfarin with antiplatelet drugs
- assessment of a patient's haemorrhagic risk
- strategies to minimise the risk of haemorrhage.

Platelets and the mechanism of thrombosis

The earliest events in thrombus formation include platelet adhesion, platelet activation, subsequent platelet aggregation and granule release. These events are inseparable from the initiation of the coagulation cascade principally by tissue factor, thrombin generation and cross-linked fibrin formation. The interactions between platelet and coagulation events during thrombus formation are numerous. Activated platelets provide the physical surface for efficient thrombin formation. In turn, the thrombin generated by activation of the coagulation cascade is a potent platelet agonist. The importance of platelets in thrombus formation is evident by the therapeutic efficacy of antiplatelet drugs in thromboembolic disease, especially arterial vascular disease.

The biochemistry of platelet adhesion, activation and aggregation is complex. Many of these events are co-ordinated by surface receptors. Platelets adhere to immobilised Von Willebrand Factor and also collagen at functional glycoprotein Ib/IX/V and collagen receptors. Adhesion results in initial platelet activation by internal signalling pathways often involving reduced intra-platelet cyclic adenosine monophosphate. Important platelet agonists *in vivo*, including thrombin, adenosine diphosphate, thromboxane A_2 and collagen, all act via specific platelet surface receptors. The final common pathway of platelet aggregation is activation of the glycoprotein IIb/IIIa receptor. An aggregate consists of platelets linked together by fibrinogen and Von Willebrand Factor bound to multiple glycoprotein IIb/IIIa receptors. Despite our limited understanding of these pathways a broad range of antiplatelet drugs has been developed (Table 1).

Antiplatelet drugs

The activation, aggregation and adhesion of platelets may all be altered by a variety of drugs. There needs to be a balance between their beneficial effects and the risk of haemorrhage.

Haemorrhagic effects of antiplatelet drugs

By a variety of mechanisms antiplatelet drugs are associated with an increased risk of haemorrhage.

Aspirin

The beneficial effect of aspirin therapy in ischaemic stroke may be associated with an excess of two symptomatic intracranial haemorrhages for every 1000 patients treated. Aspirin's antiplatelet action is probably not dose dependent beyond 75–100 mg daily so there is no additional antiplatelet effect at higher doses. However, aspirin's effect on the gastric mucosa is dose dependent. The incidence of major gastrointestinal haemorrhage is 1.5% at 300 mg/day and 2.3% at 1200 mg/day. As aspirin irreversibly blocks platelet cyclo-oxygenase its effect lasts for 5–7 days after the drug is stopped. The antithrombotic effect can be reversed by platelet transfusion in an emergency.[1,2]

Table 1

Actions of antiplatelet medications

Antiplatelet drug	*Mechanism of action*	*Antiplatelet effects*	*Additional haemorrhagic effects*
Aspirin	Irreversible blockade of platelet cyclo-oxygenase preventing the formation of thromboxane A_2	Partial inhibition of platelet activation. Does not prevent platelet adhesion.	Non-specific cyclo-oxygenase blockade leads to gastric mucosal damage and increases the risk of gastrointestinal haemorrhage
Non-steroidal anti-inflammatory drugs	Reversible blockade of platelet cyclo-oxygenase affecting platelet thromboxane A_2 activity	Partial inhibition of platelet activation. Does not prevent platelet adhesion.	Gastric mucosal damage and increased risk of gastrointestinal haemorrhage
COX-2 inhibitors	Specific inhibitors of cyclo-oxygenase-2	No direct antiplatelet effects	Cause less gastrointestinal tract mucosal damage than conventional NSAIDs. May prolong the INR.
Dipyridamole	Inhibition of adenosine uptake by the platelets. Weak inhibition of platelet cAMP * phosphodiesterase.	Weak inhibition of platelet aggregation	Often prescribed in combination with aspirin
Thienopyridines (ticlopidine and clopidogrel)	Block adenosine diphosphate mediated activation of the glycoprotein IIb/IIIa complex	Inhibition of platelet aggregation	Rarely thrombocytopenia and thrombotic thrombocytopenic purpura have been reported
IIb/IIIa receptor inhibitors (abciximab, eptifiban and tirofiban)	Direct antagonism of the platelet receptor for fibrinogen and Von Willebrand Factor. Several classes of drug available which include an antibody, synthetic peptide or synthetic non-peptide forms which require intravenous delivery.	Potent inhibition of platelet adhesion, activation and aggregation	0.3–1.0% incidence of thrombocytopenia reported. Pseudothrombocytopenia can occur with abciximab but is not an indication for cessation.

* cAMP cyclic adenosine monophosphate

Non-steroidal anti-inflammatory drugs (NSAIDs)

This heterogeneous group of drugs is associated with a significant prevalence (10–20%) of dyspepsia. The incidence of NSAID-induced gastrointestinal haemorrhage is variably quoted as 1–4% and depends on the individual drug and probably its dose. For every 1000 patients with rheumatoid arthritis who take NSAIDs for one year, 13 will suffer a serious gastrointestinal complication including bleeding. NSAID-induced upper gastrointestinal tract bleeding has a significant mortality rate of 5–10%. These drugs are widely available so large numbers of patients are exposed. The lifetime risk of major gastrointestinal haemorrhage is substantial and increases with the concomitant use of warfarin.

In contrast to aspirin most NSAIDs have short-lived antiplatelet effects. However, a platelet transfusion may still be required in an emergency such as a major haemorrhage.[3]

Trials have shown that cyclo-oxygenase-2 (COX-2) inhibitors do not directly affect platelet function.[4] Recently meloxicam, an NSAID with preferential inhibition of COX-2, has also been released. Major antiplatelet effects have not been demonstrated with its use.[5]

Dipyridamole

Significant haemorrhage is rarely attributable to dipyridamole, a relatively weak and short-lived inhibitor of platelet function. Even in combination with aspirin there is no evidence of dipyridamole increasing the risk of bleeding. The dose-related adverse effects of dyspepsia, gastro-oesophageal reflux and headache are common reasons for stopping therapy.[1]

Thienopyridines

In recent studies, treatment with a thienopyridine (ticlopidine, clopidogrel) was more effective than aspirin for the prevention of vascular disease without an increase in bleeding complications. In the CAPRIE study, there was a 1.38% incidence of major haemorrhage in the clopidogrel group which did not statistically differ from that of aspirin (1.55%).[6] However in the CURE study[7], the combination of aspirin and clopidogrel increased the rate of major bleeding (3.7%) compared to aspirin alone (2.7%). These bleeds were mostly gastrointestinal haemorrhages requiring blood transfusion or bleeding at sites of arterial puncture. There was no significant increase in fatal or intracerebral haemorrhage.[7]

The antiplatelet effect of thienopyridines is irreversible and persists for the 7–10 day lifespan of the circulating platelet. There is no antidote, and reversibility with platelet transfusion has not been well studied.[8,9]

Platelet glycoprotein IIb/IIIa receptor antagonists

In early studies, patients receiving abciximab had higher bleeding rates than placebo. In later studies, where the dose of concurrent heparin was reduced, bleeding rates were not increased. However, abciximab and tirofiban have been reported to cause pulmonary haemorrhage. Eptifibatide in combination with heparin and aspirin is associated with increased bleeding and the need for transfusion. Platelet transfusions are required if bleeding occurs particularly if the patient has drug-induced thrombocytopenia, which is sometimes profound.[9,10]

These intravenous drugs are most commonly used as an adjunct to percutaneous invasive coronary interventions as a means of reducing ischaemic complications. They are often given as an intravenous bolus (with or without a short-term infusion) in combination with various regimens of unfractionated heparin and aspirin. There is some evidence of benefit in the primary medical therapy of acute coronary syndromes.

Oral glycoprotein IIb/IIIa receptor antagonists have been associated with a significant increase in mortality and higher rates of bleeding compared to placebo or standard antiplatelet treatment.[10]

Warfarin

Warfarin inhibits the vitamin K-dependent synthesis of clotting factors II, VII, IX and X in the liver. The antithrombotic effect, and mechanism of haemorrhage, relates to low levels of these coagulation factors and a reduction in their activity in thrombus formation.

The effect of warfarin is influenced by many factors. These include the dose, patient compliance, diet and vitamin K status, various lifestyle factors such as alcohol intake, concomitant medications which affect the metabolism of warfarin, and comorbid illness especially liver and cardiac disease. The effect of warfarin on the coagulation system is assessed by a simple *in vitro* clotting assay, the international normalised ratio (INR). The dose of warfarin is adjusted according to the target INRs set for particular indications.

In practice, warfarin is a difficult drug to manage, because of its narrow therapeutic index and the need to individualise dosing. Major haemorrhage is unfortunately common. It occurs in 1–5% of patients per year and has a case fatality rate of 25–30%. Antiplatelet drugs which inhibit platelet function impose additional risks for haemorrhage by affecting primary haemostasis and further inhibition of thrombus formation. Some antiplatelet drugs may also alter warfarin metabolism and lead to an unstable INR.[11,12,1]

Drug interactions: warfarin and antiplatelet drugs

While generally the combination is avoided, antiplatelet drugs and warfarin are sometimes deliberately used in patients with embolic phenomena from prosthetic and diseased heart valves or those with refractory arterial ischaemia.

The combination of antiplatelet drugs and oral anticoagulants increases the risk of both major and minor bleeding in several ways:

- additive effects on platelet function
- interference with warfarin metabolism with a subsequent increase in the INR
- unique adverse effect profiles which increase the risk of bleeding (for example gastrointestinal tract erosions with aspirin and NSAIDs).

Warfarin and aspirin

In clinical studies of patients with prosthetic valves, the frequency of bleeding when oral anticoagulation is combined with antiplatelet therapy varies depending on the intensity of treatment and the type of antiplatelet therapy. In patients who receive high-intensity warfarin (target INR of 3.0–4.5), the addition of aspirin 100 mg daily results in higher rates of major (12.9% versus 10.3%) and total (38.7% versus 26.1%) bleeding.[1]

There is a general impression that bleeding rates are also increased with the combination of aspirin and warfarin even when the target INR is 2–3.[9]

Warfarin and dipyridamole

The addition of dipyridamole to warfarin therapy in patients with prosthetic valves does not appear to increase the risk of haemorrhage. In patients who used a combination of aspirin, dipyridamole and warfarin, the risk of bleeding depended significantly on the target INR. Patients anticoagulated to an INR of 3.0–4.5 experienced a 21% incidence of bleeding compared with 4% in the group anticoagulated to an INR of 2.0–2.9. Most of the bleeding seen with this combination was gastrointestinal in origin.[1]

Warfarin and NSAIDs

NSAID-associated gastropathy increases the risk of haemorrhage in patients taking warfarin, so combined use should be generally discouraged. Some NSAIDs also alter warfarin metabolism. COX-2 inhibitors are an option should NSAID therapy be necessary. They have a lower incidence of gastrointestinal adverse effects, but all COX-2 inhibitors may alter warfarin metabolism resulting in instability of the INR. Celecoxib and rofecoxib have both now been reported as interacting with warfarin.[13,14]

Warfarin and thienopyridines

Caution should be exercised if this particular combination is to be used because there are no safety data to support it. Oral anticoagulation has been an exclusion criterion in the trials involving thienopyridines.

Warfarin and glycoprotein IIb/IIIa receptor antagonists

There are no safety data from clinical trials as patients on warfarin have been excluded from studies of glycoprotein IIb/IIIa receptor antagonists. Patients on oral anticoagulants should have their therapy ceased or fully reversed before having coronary interventions with glycoprotein IIb/IIIa receptor antagonists. These intravenous therapies are often given in coronary care units, and their direct effect and short half-lives mean that the risk of haemorrhage occurs early, within a few hours of therapy. This class of drug therefore tends not to be as important when considering anticoagulant and antiplatelet interactions in the community.[10]

Suggested strategies to minimise the risk of bleeding

Recognise the risk

To minimise the risks of taking anticoagulant and antiplatelet drugs it is crucial to recognise the patient's risk of bleeding. Various scoring systems to stratify the risk of bleeding in

patients on warfarin have been proposed.[15] Risk factors for haemorrhage include:

- older age group
- high target INR
- cerebrovascular disease
- history of gastrointestinal bleeding or ulceration
- liver disease
- renal disease
- other comorbid disease such as heart failure, anaemia, hypertension, malignant disease and diabetes
- personal or family history of bleeding disorders.

In one study, patients classified as high risk had a 48% risk for major bleeding during 12 months of warfarin therapy. The relevance of these scoring systems to everyday practice requires prospective validation. These scoring systems highlight the importance of a simple history in identifying patients with an increased risk of bleeding, and in practice common sense should be applied.[15]

Optimise warfarin therapy

A key element for reducing bleeding in patients taking warfarin, especially if they are also taking an antiplatelet drug, is to optimise therapy.[16]

Appropriate target INR

Recent Australian Consensus Guidelines for warfarin therapy summarise the appropriate target INR and INR ranges for different clinical scenarios.[11]

Appropriate duration of therapy

When patients are prescribed warfarin the duration of therapy should be determined in advance. Periodic re-evaluation of the patient's harm:benefit ratio for warfarin should also occur. In venous thromboembolic disease in particular, there are conflicting recommendations regarding the optimum duration of warfarin treatment. In general, 4–6 months of warfarin is adequate after pulmonary embolism. For a deep vein thrombosis due to a transient event like surgery or immobilisation, 8–12 weeks of therapy is probably sufficient. In contrast, unprovoked deep vein thrombosis, recurrent venous thromboembolism or venous thromboembolism occurring in association with an underlying hypercoagulable state all warrant a longer duration of warfarin treatment. The optimum duration needs to be tailored to the individual and specialist advice may be warranted.[11]

Minimise patient risk factors for bleeding

Patient compliance with drug therapy and monitoring should be encouraged. Additional lifestyle factors should also be addressed, including the consistency of dietary intake of vitamin K, minimising alcohol use, avoidance of binge drinking, and reducing activities with considerable risk of injury.[16]

Managing the INR

Conscientious management of the INR is the key to minimising bleeding. In order to ensure the INR is as stable as possible, a blood test every 1–2 weeks may be required.

Once the target INR is set, a narrow range of tolerance is preferred. Dose adjustments need to be made on every occasion the INR is outside this range. The frequency of testing needs to be increased when dose adjustments are made. These regular checks also provide the practitioner with an opportunity to seek other relevant information regarding the patient's general health, any changes to their medications (including complementary medicines), and the presence of any symptoms of bleeding.

Antiplatelet drugs and warfarin

If antiplatelet drugs are to be concurrently used, it is prudent to keep the patient's INR at the lower end of the desired target range. These patients, by virtue of their higher risk of haemorrhage, also require frequent testing every 1–2 weeks, to enhance the control of the INR.

Using the lowest aspirin dosage possible may reduce the additive risks of haemorrhage without necessarily increasing the thromboembolic risks. Concomitant use of NSAIDs should be discouraged.

Anticipate the possibility of bleeding

Instability of the INR can be predicted. A change in a patient's health or medications should prompt their doctor to monitor the INR more frequently. Patients should be educated regarding warfarin therapy and INR management, and be vigilant for symptoms and signs of blood loss. They should be encouraged to ask for increased monitoring of their INR if their health or medications change.

Conclusion

There are risks in adding antiplatelet medications to warfarin therapy. Patient-specific risks of haemorrhage are often harder to assess than the perceived benefit of the proposed therapy. Patient selection is important to minimise the risk of bleeding. Rigorous management of the INR is required for patients taking warfarin with antiplatelet drugs.

E-mail: tbrighton@unsw.edu.au

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FURTHER READING

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 99)

1. The INR is not affected by COX-2 inhibitors.
2. Non-steroidal anti-inflammatory drugs have a more prolonged antiplatelet effect than aspirin.

Managing constipation in children

Constipation, defined as difficulty, delay or pain on defecation, is common in children and is often difficult to manage. Here, we review the assessment and treatment of affected children and the support that they, and their families, may need.

Background

Breastfed babies have a mean of about three bowel movements daily, while formula-fed babies have about two. With age, the frequency falls to about one movement daily in children over three years.[1] In one study, 96% of children aged 1–4 years had somewhere between one bowel movement every other day to three movements daily.[2] So as long as the child is pain free, parents can usually be reassured that some infrequency in defecation is likely to be normal.

Various factors may cause or increase the likelihood of constipation. Delay in passing meconium more than 48 hours after birth, or constipation in early infancy, suggests the possibility of Hirschsprung's disease, especially if there is also excessive vomiting, abdominal distension or failure to gain weight. Constipation may result from inadequate food or fluid intake, while children who drink a lot of milk may have hard stools that are difficult to pass. Chronic constipation might be associated with an intolerance to cow's milk[3], although this is more commonly associated with diarrhoea. Some medicines can induce constipation (e.g. opiate analgesics, anticholinergic drugs). Children may withhold defecation and this may make them liable to constipation. Risk factors for withholding include: 'fear' of previous treatments for constipation or coercive potty training, sometimes coinciding with the developmental stage between two and three years of age when children typically refuse to obey their parents; lack of privacy (especially in school lavatories); domestic stress; sexual abuse; or pain on defecation due to anal fissures or a perianal skin infection.

When the rectum is chronically obstructed with faeces (or incompletely emptied), it may enlarge to form a megarectum. Children with a megarectum may not sense the faecal matter in the rectum, and have diminished urgency to defecate[4,5], which may lead to faecal soiling. It is important to distinguish this involuntary soiling from encopresis, in which the child voluntarily passes normal stools in unacceptable places.

Assessment

It is important to take a detailed history of the illness from the parent and, where possible, the child, including noting of relevant dietary, family and social factors. Clinical examination should appraise the child's general health and check for poor growth and neurological problems. Palpation of the abdomen may reveal distension or faecal loading in the colon. Rectal examination can be distressing for the child and is usually unnecessary. In most instances, inspection of the perineum is sufficient to check for the presence of anal fissures, infection, skin disease, anal ectopia or anal abuse.

There is no need for a routine abdominal X-ray to diagnose constipation[6], but it may help confirm overflow incontinence in a child with faecal impaction who initially presents with diarrhoea. A potentially more helpful hospital investigation involves the child swallowing radio-opaque gut transit markers over three days and then taking an abdominal X-ray on day five.[7] This test may confirm: fast intestinal transit in children with episodes of faecal incontinence; rectal retention in children with megarectum; or pancolonic delay (colonic inertia) in older children.

Treatment

The general principles in managing childhood constipation are to: clear any faecal impaction; establish a regular and effective pattern of defecation; and to prevent recurrence.[1,8] Where possible, underlying causes should be resolved, for example, stopping constipating medicines, treating painful anal conditions and addressing possible psychosocial causes. There is a lack of evidence from randomised controlled trials to guide management choices.

Dietary intervention

Constipation can often be relieved by increasing dietary fluid and fibre. However, children may be reluctant to eat high-fibre foods such as fruit, vegetables and cereals, especially if the rest of the family eat a different diet. If the child's appetite is poor,

this needs investigation, particularly if food is avoided because of discomfort after eating. However, parents can usually be reassured that faddy eating is common and advised to avoid being too anxious at mealtimes. Rearrangement of mealtimes may help where the child withholds defecation at school; for example, eating breakfast earlier might enable the child to open his or her bowels before leaving home. The general practitioner is well placed to provide general dietary advice and reassurance, but referral to a paediatrician or child psychiatrist may be necessary where major feeding problems exist. Some infants who take large quantities of formula milk may benefit from a reduced intake. Substantial changes or restriction of dietary intake should be supervised by a paediatrician or dietitian with paediatric experience.

Laxative treatments

If dietary changes are not sufficient to produce softer and more frequent stools, starting a laxative may help. If the child is old enough, it is important to explain to them why laxatives are being given. Treatment should start with regular doses of a stool softener/osmotic laxative (e.g. lactulose) or a bulk-forming laxative (e.g. ispaghula husk, methylcellulose) to produce a soft, easily passed stool. If these drugs do not work, or if the child is withholding defecation, a stimulant laxative should be tried (e.g. senna, bisacodyl or sodium picosulfate syrup). These laxatives stimulate colonic propulsion, which quickens the filling of the rectum and intensifies rectal contractions. Defecation is therefore more frequent and so the stool is smaller and softer, which gradually reduces the child's fear of the sensation of imminent defecation. In a crossover study involving 21 children (aged under 15 years) with chronic constipation, lactulose was more likely to lead to passage of normal stools than senna and more unwanted effects (colic, diarrhoea) were noted with senna treatment.[9] However, a combination of laxatives (e.g. lactulose and senna) may be particularly effective and should be considered if individual drugs fail. If the child has a megarectum impacted with hard stools, stimulant laxatives may aggravate overflow faecal incontinence and abdominal pain; using docusate, a stimulant laxative with stool-softening properties, is a reasonable option in this situation. If this is unsuccessful glycerine suppositories or a sodium citrate enema can be considered.

To help prevent recurrence of constipation, laxative treatment should be continued for several months. As defecation becomes more regular with treatment, the effect of laxatives on frequency or urgency of defecation gradually increases. The laxative dose can then be carefully reduced, usually without symptomatic relapse. One practical strategy is to advise parents to maintain the most effective dose of laxative until defecation becomes too frequent or too urgent and then to reduce the dose slowly over a few months.

Bowel evacuation

Bowel evacuation may be necessary if: a trial of laxatives fails; the colon is impacted; or the child also experiences pain, nausea or vomiting, in addition to constipation. Ideally, such treatments (which include bowel cleansing solutions taken orally, suppositories or enemas, or manual evacuation under anaesthesia) should only be attempted by a specialist.

Bowel cleansing solutions (normally used to clear the bowel before investigations or bowel surgery) are powders made into a solution with water and then taken by mouth; few are licensed for use in young children or for the treatment of constipation. Preparations include:

- sodium picosulfate/magnesium citrate
- polyethylene glycol
- magnesium citrate
- sodium dihydrogen phosphate dihydrate.

However, children may not easily tolerate these solutions, some of which require swallowing a large volume of fluid. The solutions are sometimes given via a nasogastric tube but insertion of the tube can be stressful for the child and is hazardous if inserted incorrectly. These preparations may cause distress, nausea, vomiting, colicky pain or urgent bowel movements, may cause fluid and electrolyte imbalance, especially in small children or in the presence of renal impairment.

If oral administration is ineffective or not tolerated, it may be worth trying rectal treatment. However, administration of suppositories and enemas can be difficult, not least because the child may find the treatments unpleasant, and has to remain still while the product is retained. If rectal preparations are required, small-volume sodium citrate enemas (micro-enemas) should be used in preference to the larger-volume phosphate enemas; some older children can be taught to self-administer micro-enemas. Children may be particularly anxious about rectal treatments if they have experienced anal pain or abuse and may interpret rectal administration as punishment, especially when the enema is presented as a threat. Sedation using midazolam or temazepan may allow enemas to be used without a lasting memory of distress but repeated use of such sedation may make parents worry about possible dependence.

Manual evacuation under a general anaesthetic may be the only option if all other treatments fail, if there is faecal impaction with signs of intestinal obstruction or pressure effects on the bladder leading to urinary retention.

Biofeedback training

Around 50% of children with chronic constipation show abnormal defecation dynamics.[10] Biofeedback training aims to treat these problems, which can continue for several months despite laxative treatment. Such training teaches muscle relaxation using anorectal monitoring instruments to amplify physiological processes and to make physiological information accessible to the child's consciousness; it can only realistically be attempted in children old enough to understand the procedure. Randomised studies suggest that adding biofeedback training to conventional treatment (laxatives, counselling and toilet training), in children with chronic constipation and involuntary soiling, helps improve defecation dynamics[10,11] but without a consistent increase in clinical recovery rates.[10,11,12]

When to refer

Referral to a local paediatrician is probably advisable if:

- constipation is prolonged (over six months' duration)
- treatment in general practice has not been effective

- there is frequent soiling and distress
- there is doubt as to the cause of the symptoms
- the condition is interfering with the child's schooling and social relationships.

Paediatricians working closely with the primary care team, including the community pharmacist, and the community paediatric nursing team can build a support network for the child and family. Paediatric nurses should have good communication with school nurses and can help teachers cope with children prone to faecal soiling. Health visitors and social workers can play a key role by visiting the family at home to observe domestic circumstances, such as mealtimes, toilet arrangements and general child-rearing. If there are other behavioural difficulties such as temper tantrums, sleep disorders or hyperactivity, referral for psychological help may be most effective, and this is best initiated by the paediatrician.

Counselling and support

Few children will voluntarily discuss their constipation or incontinence with even their closest friends and many parents keep these problems to themselves. It is crucial, therefore, that the child and family are offered counselling and support throughout management. Frequent problems that need addressing include:

- parental distress
- low self-esteem of the child due to embarrassment and teasing, especially at school
- poor adherence to toileting routines and medication regimens.

So while referral to a child psychologist or psychiatrist may be unnecessary, every child should have the psychosocial aspects of their problem considered. Psychological therapy is best started gently, with reassurance and simple counselling, and then increased according to need and the availability of resources. Everyone dealing with children who have defecation difficulties must be sensitive to the child's fears and aim to increase the child's involvement and motivation in the management of the problems. A wide range of incentive charts can be used to reward adherence to toileting routines and taking medication, as well as for successful defecation. However, these measures will be fruitless if the child is too young to appreciate them or too old to be impressed by them. Also, if colonic impaction is not recognised early, the continuing lack of treatment success may deter the child from co-operating further. A booklet, *Childhood soiling – a guide for parents*, has been designed for the British charity ERIC*.

Conclusion

In healthy children, there is a wide variation in the frequency of defecation and the hardness of stools. Key indications for the treatment of constipation are pain on defecation, severe straining or overflow incontinence and soiling. With mild symptoms, simple parental reassurance or dietary advice may be all that is required and this should be offered by the primary care team. A child presenting with more severe symptoms and/or psychosocial problems may well need further treatment, which often requires the involvement of a skilled team of doctors, nurses, social workers and psychologists, working together with the child, their parents and teachers. Not all of the drugs commonly used to treat constipation are licensed for use in young children nor have they been investigated in appropriate trials. However, if dietary treatment fails, it is sensible to use laxatives, starting with stool softeners or bulk laxatives and then moving on to stimulant laxatives, using a combination of drugs where necessary. Laxatives may be needed for some months and doses should only be reduced slowly to prevent re-impaction. If laxatives fail, bowel evacuation techniques (such as oral bowel cleansing solutions, enemas or manual evacuation) may be needed but should only be used under the supervision of a paediatrician. Adding biofeedback training to the use of laxatives, counselling and toilet training does not seem to increase the chances of long-term recovery from chronic constipation and soiling.

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* Enuresis Resource and Information Centre www.enuresis.org.uk

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[R = randomised controlled trial]

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Treatment of ocular toxoplasmosis

Paul Ng, Department of Ophthalmology, Royal Prince Alfred Hospital, and Peter J. McCluskey, Department of Ophthalmology, Royal Prince Alfred Hospital, Department of Ophthalmology, St Vincent's Hospital, and Centre for Inflammation Research, School of Medical Science, University of New South Wales, Sydney

SYNOPSIS

Ocular toxoplasmosis is a potentially blinding cause of posterior uveitis. It predominantly affects children and young adults and is often recurrent. Current treatments do not effect a cure nor do they prevent recurrences. Their role lies in minimising the damaging effects of inflammation and limiting lesion size, particularly when sight is threatened.

Index words: blindness, parasite, abnormal laboratory results.

(Aust Prescr 2002;25:88–90)

Introduction

Ocular toxoplasmosis is the commonest identifiable cause of posterior uveitis. It predominantly affects children and young people (25–45 years) and is characterised by recurrences that can ultimately lead to significant visual loss. *Toxoplasma gondii* is an obligate intracellular parasite with the cat as the definitive host. It is transmitted to humans by accidental ingestion of the egg form (oocysts) in cat faecal matter which may contaminate fruit and vegetables, ingestion of the cyst form (bradyzoites) in undercooked or raw meat, and vertical transmission to the fetus during maternal primary infection by the replicating form (tachyzoites). Most clinical episodes of ocular toxoplasmosis represent reactivation of an infection that was acquired *in utero*. It is likely however, that more patients with ocular disease acquire toxoplasmosis after birth than was previously recognised.

Clinical features

Only a small proportion of infected people develop significant ocular disease. The commonest symptoms are floaters and reduced vision. The hallmark clinical signs are a vitreous cellular infiltrate associated with a creamy white retinal lesion that is typically adjacent to a pigmented chorioretinal scar (see Fig. 1). The eye may be painful and red with anterior uveitis and high intraocular pressure.

Assessment and investigations

Ocular toxoplasmosis can be confused with a large number of other causes of posterior and pan uveitis. The differential diagnosis depends largely on the clinical setting and the clinical signs. For example disease processes such as herpetic retinitis, metastatic endophthalmitis, lymphoma, metastatic carcinomas and sarcoidosis may closely mimic the signs of ocular toxoplasmosis.

The diagnosis is predominantly clinical. Using the polymerase chain reaction to test the vitreous and aqueous humours for toxoplasma DNA can be useful when the diagnosis is uncertain but is limited by low sensitivity.

Serology is of limited value, as the presence of IgG antibodies to toxoplasma is usually not helpful in determining the cause of uveitis in patients with chorioretinitis. Positive IgG antibodies to toxoplasma imply past exposure and are very common in teenagers and adults in our community. The concentrations of IgG do not alter with ocular relapses. In patients with chorioretinal lesions that are consistent with ocular toxoplasmosis, the absence of specific IgM and IgG effectively excludes the diagnosis. This knowledge is particularly important for pregnant women as primary infection during pregnancy may result in infection of the fetus. If there are IgM antibodies and no IgG antibodies, this implies that the ocular lesions are a primary infection with toxoplasma. A fourfold increase in IgG concentrations over a four-week period may also suggest primary infection.

Management

The need for therapy, type of drug treatment and duration of therapy needs to be individualised. It is determined by factors such as the location of the lesion, severity of the inflammatory response, threat to vision, status of the other eye and the immune status of the patient.

An episode of ocular infection is ultimately self-limiting in immunocompetent patients. If the infection involves the peripheral retina, has only mild associated inflammation and there is no involvement of the optic disc or macular region of the retina, then treatment is not necessary.

Therapy is usually needed for 6 to 12 weeks in immunocompetent patients and a response is determined clinically when the retinal lesions lose their fluffy white appearance, the vitreous clears and an atrophic chorioretinal scar with sharp margins develops (see Fig. 2).

Immunocompromised patients such as transplant recipients and patients with HIV infection may require long-term suppressive therapy. Pyrimethamine and/or sulfadiazine can be used to maintain control of infection.

Fig. 1

Active ocular toxoplasmosis

The lesion is indistinct due to cloudy media, there is an area of retinal opacification and associated retinal vascular sheathing, contiguous with a focus of pigmented retinal scarring. The lesion is adjacent to the optic disc and is therefore a serious potential threat to vision. Toxoplasmosis in this location usually requires therapy.

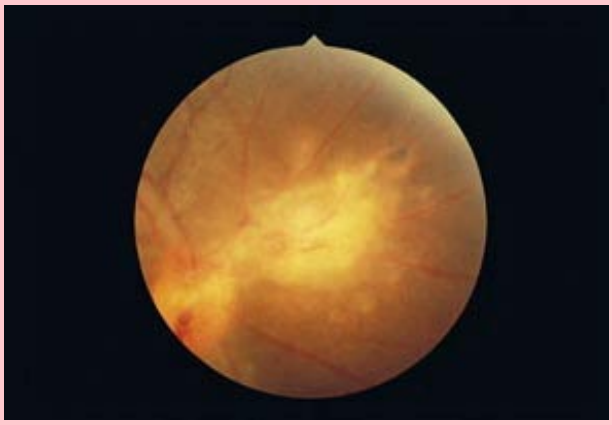
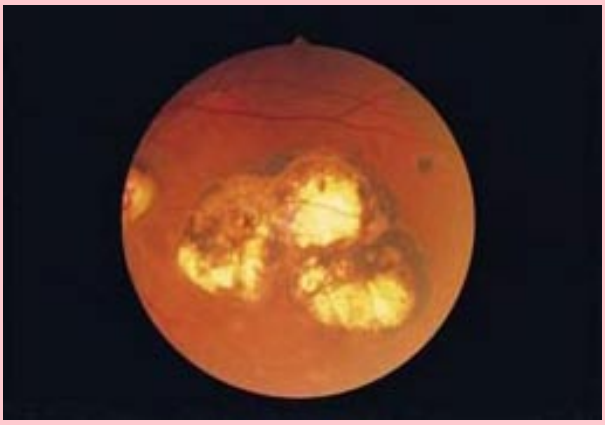


Fig. 2

Inactive ocular toxoplasmosis

There is a large retinal and choroidal scar with typical clinical features of inactive ocular toxoplasmosis. The scar involves the macula, is large in area, has heavily pigmented margins and is white centrally. It is well demarcated from the surrounding retina and the overlying media is clear.



Drug treatment

Most treatments are active against the replicating form of the parasite (tachyzoite). Some newer antimicrobials kill encysted organisms (bradyzoites) in animal models, however there are no data available for human disease.

Combination drug therapy is preferred to achieve rapid resolution, minimise inflammatory damage and to minimise resistance. The most commonly used combinations are clindamycin and corticosteroids, and pyrimethamine, sulfadiazine and corticosteroids. Combination treatment results in smaller retinal scars and is frequently used to treat patients with macular involvement. Other combinations of antimicrobials can be used, but data are limited.

Pyrimethamine

Pyrimethamine is probably the most effective single drug. It interferes with replication as it inhibits the enzyme dihydrofolate reductase in the folate production pathway. Treatment consists of a loading dose of 25 mg three times on the first day followed by a daily dose of 25 mg. The main adverse reactions are bone marrow depression (particularly leucopenia and thrombocytopenia), nausea and other gastrointestinal adverse effects.

Human cells are able to utilise exogenous folate, while toxoplasma, which lacks transmembrane transport mechanisms for folate, depends on intracellularly derived folic acid. Folinic acid 15 mg should be taken orally three times weekly to provide adequate dietary folic acid to prevent adverse effects, particularly bone marrow suppression, whenever pyrimethamine is used. A weekly full blood count is essential.

Sulfadiazine

This is a sulfur analogue and acts as a competitive antagonist for para-aminobenzoic acid (PABA), one of the precursors of folate production. Treatment consists of a loading dose of 2 g followed by 1 g four times daily. Its main adverse reactions are malaise, gastrointestinal adverse effects and hypersensitivity. Other important adverse reactions include bone marrow suppression and crystallisation in the renal tubules.

Clindamycin

Clindamycin interferes with protein synthesis. It is frequently used as a single drug or in combination with corticosteroids with excellent results. Recommended doses are 300 mg four times daily for 3–4 weeks followed by 150 mg four times daily for a further 3–4 weeks. Its serious adverse effects are diarrhoea and pseudomembranous colitis. Clindamycin has also been used as intraocular therapy by direct injection into the vitreous.

Azithromycin

This azalide antimicrobial is well absorbed. It reaches high and sustained tissue concentrations and penetrates the blood-brain and blood-ocular barriers when they are inflamed. The recommended dose is a 500 mg loading dose followed by 250 mg daily. Adverse effects are infrequent.

Atovaquone

Most experience with atovaquone has been in patients with HIV infection and toxoplasma. Poor absorption and gastrointestinal adverse effects limit its use.

Spiramycin

Spiramycin is infrequently used in Australia, but it has the lowest toxicity to the fetus and is recommended when a pregnant woman needs treatment. The recommended dose is 1 g twice daily.

Corticosteroids

Oral corticosteroids are used to limit the damaging effects of inflammation. They should always be used in conjunction with antimicrobial therapy.

Anterior uveitis and raised intraocular pressure can occur from spillover of inflammation to the anterior segment of the eye. Topical corticosteroids and ocular hypotensive medications are the treatment.

Surgery

Surgery may be needed to treat complications such as retinal detachment, cataract and epiretinal or choroidal neovascular membranes involving the macula.

Recurrences

Following primary infection, recurrences of ocular infection are common. They are managed in the same manner as primary infection. During pregnancy, relapses of ocular infection cannot transmit toxoplasmosis to the fetus.

Prevention

Ensure that fruits and vegetables are cleaned and washed. Cook all meats adequately to destroy any harboured cysts. Pregnant women should avoid cat litter pans. Adequate contraceptive precautions are needed for six months in women of childbearing age following primary toxoplasmosis infection.

Conclusion

Toxoplasmosis is the commonest identifiable cause of posterior uveitis in our community accounting for about 20% of cases. Treatment can control episodes of infection but cannot prevent recurrences.

FURTHER READING

Dodds EM. Ocular toxoplasmosis: Clinical presentations, diagnosis, and therapy. American Academy of Ophthalmology Focal Points 1999: Volume XVII Number 10.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 99)

3. Oral corticosteroids should always be used in combination with antibiotics to treat symptomatic ocular toxoplasmosis.
4. All patients who are exposed to *Toxoplasma gondii* should be treated with a combination of antibiotics.

Dental notes

Prepared by Associate Professor R.G. Woods and Associate Professor N. Savage of the Australian Dental Association

Consumer Medicine Information: dental requirements

The recommendation made in the 1991 report on the future of drug evaluation in Australia[1], that patient information be provided with all medication, is being implemented. Consumer Medicine Information (CMI) has been developed for almost all drugs in Australia. It is based on the approved product information for each drug.

CMI involves all health professionals.[2] Dentists giving or supplying drugs are required to make CMI available to patients who request it irrespective of the route of administration. In practice, most CMI will be provided by pharmacists. CMI should also be provided for medicines available from supermarkets or other non-pharmacy outlets.

A convention has been developed that dentists advise patients that CMI is available for the drugs they administer and can be provided on request. This includes CMI for local anaesthetics and other drugs given parenterally, for instance intramuscular antibiotics.

In an emergency, for instance treatment of collapse, there is unlikely to be an opportunity to offer or provide CMI before treatment. However, CMI can be made available afterwards.

A CMI supply can be obtained for manufacturers. It is also available in some electronic databases, such as E-MIMS, and to subscribers to the Australian Dental Association web site (www.ada.org.au).

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ABNORMAL LABORATORY RESULTS

Skin prick testing and *in vitro* assays for allergic sensitivity

Richard M. O'Brien, Department of Medicine, University of Melbourne, Head, Allergy Clinic, Royal Melbourne Hospital, and Head, Clinical Immunology and Allergy, Western Hospital, Footscray, Melbourne

SYNOPSIS

Specific IgE-mediated allergic reactivity can be tested for by an *in vivo* skin prick test or by an *in vitro* enzyme or fluorescence-based immunoassay, commonly called a radioallergosorbent test. Many people have circulating specific IgE but do not have clinical allergic disease. The relevance of a positive or abnormal test result therefore depends on the clinical scenario. Skin prick testing is more sensitive than radioallergosorbent tests for detection of IgE reactivity as the majority of specific IgE in the body is bound to mast cells, or other cells bearing high-affinity IgE receptors, with little in the circulation. In the majority of clinical situations, a negative skin prick test excludes an IgE-mediated allergic basis for a potentially allergic condition, such as asthma or rhinitis.

Index words: hypersensitivity, RAST, immunoglobulin.

(Aust Prescr 2002;25:91–3)

Introduction

Since the early years of the last century, before the aetiology of allergic reactivity had been established, *in vivo* techniques, including conjunctival instillation and skin testing, had been used to identify triggers of allergic reactions. The key mediator of allergic disease, IgE, was the last class of immunoglobulin to be discovered, partly because it is highly bound to mast cells, basophils and other cells and only small amounts are present in the serum. It was therefore easy to detect IgE by skin testing, but difficult to isolate or measure it in the serum. IgE was only conclusively identified and confirmed to be the elusive 'reagin' of allergy in 1967.[1,2] At about the same time, laboratory testing was expanding in all medical disciplines and it was not long before immunoassays for allergen-specific IgE were designed and commercialised. The first radioallergosorbent tests (RAST) appeared in 1974 and tests not unlike the current ones were in use by the late 1970s. Since then the relative merits of *in vivo* skin testing and *in vitro* RAST measurements have been argued by their respective proponents.

Tests for allergen-specific IgE

Skin prick testing

Skin prick testing is the conventional way to test for the presence of allergen-specific IgE and detects IgE bound to the surface of mast cells in the skin. Allergen in solution is applied to the skin, generally the volar surface of the forearm. When the skin is pricked with a lancet the allergen comes into contact with specific IgE, bound to the surface of cutaneous mast cells. The binding of the allergen leads to cell activation and the immediate release of mediators including histamine. Other mediators are released, but histamine appears to be the critical one as skin prick tests become negative after taking antihistamines. The release of mediators results in a wheal and flare type reaction and the test is generally reported as the maximal wheal diameter after 15 to 20 minutes. A wheal with a diameter 3 mm or more greater than control is generally regarded as positive. The amount of specific IgE present can be estimated by the size of the wheal. These tests are simple, quick and the most sensitive method of detecting specific IgE. Skin prick tests are particularly helpful in excluding potential allergens as a cause of symptoms as false negatives are uncommon.

Although these tests are extremely safe, with only rare reports of generalised reactions, the risk of systemic absorption remains and anaphylaxis is a remote possibility in highly sensitised individuals. Testing should therefore always be performed under the supervision of a trained and experienced clinician who has resuscitation equipment immediately available.

Patch testing

As distinct from skin prick testing which measures specific IgE, patch testing is used to detect the presence of antigen-specific T cells. The main clinical application for patch testing is in detecting antigens responsible for contact dermatitis, rather than atopic disorders such as asthma, rhinitis or eczema.

In vitro immunoassays for specific IgE

Although serum tests for specific IgE are still frequently referred to as radioallergosorbent tests, they are generally not performed by traditional radioimmunoassay. They more frequently use a commercial solid phase enzyme-linked immunoassay or ELISA with the antigen bound to some form of solid support, such as a paper disc. Following incubation of the test serum with the bound antigen, specific IgE is detected by adding labelled antibodies specific for human IgE. Results are usually presented in a semi-quantitative fashion with a score of 0 indicating no specific IgE detected; one, low level;

two, significant level; and three, four, five (and sometimes six) indicating increasingly high concentrations. As numerous allergens can potentially be tested for, most laboratories also test for reactivity to batches of somewhat related allergens, for example, food mix or inhalant mix.

Only nanograms of specific IgE are present in the serum, therefore, even in highly allergic individuals, RAST testing is not as sensitive as skin prick testing and low-level reactivity may not be detected. Tests using the mixes are even less sensitive and more difficult to quantitate than tests for individual allergens so false negative results are common. In addition to this low sensitivity there is variability between the allergen preparations used for RAST testing. Different laboratories may therefore report different results for the same serum sample. Variability is even greater between allergen mixes as standardisation is difficult. This variability between laboratories has been documented by the Quality Assurance Program of the Royal College of Pathologists of Australia.[3] A recent review of testing in US laboratories also showed considerable variation in results between laboratories testing the same serum sample.[4]

When and how to test for allergen-specific reactivity

An underlying atopic state, defined as the capacity to produce specific IgE to ubiquitous allergens, is more common than the presence of symptomatic allergic disease. Consequently, if individuals were randomly tested for allergic reactivity, many irrelevant positive results would be found. Furthermore if a patient is sensitive to one allergen, it is more likely that reactivity will be present to other allergens, even if there is no clinical sensitivity. The detection of specific IgE in the absence of a reasonable clinical suspicion of an allergy is hard to interpret. This may create problems; for example, if tests are used to investigate fairly vague symptoms, such as abdominal bloating or fatigue, and a specific food sensitivity is detected, drastic and unhelpful dietary modification may be advised. It is therefore essential that testing should only be done when there is a reasonable clinical suspicion (pre-test probability) that sensitivity to a particular allergen is present.

An underlying atopic state is more common than the presence of symptomatic allergic disease

Most of the allergens in Table 1 can be tested for by either RAST or skin prick testing.

For perennial respiratory symptoms, the most likely allergens are house dust mite, pet hair and danders and mould spores. For seasonal symptoms, grass pollens, particularly rye grass, are most frequently implicated, although tree and weed pollens, and even mould spores, can cause seasonal symptoms. Food allergens are rarely implicated in respiratory disease but can cause systemic reactions including anaphylaxis and angioedema and, on occasions, can also be relevant in eczema. In the case of serious generalised reactions, the causative food is usually obvious from the patient's history and testing is only undertaken to confirm the clinical suspicion. For severe eczema or for eczema where there is a strong suspicion that particular foods aggravate the condition, skin testing is appropriate and is generally undertaken in specialised multidisciplinary centres. Oral challenge tests are sometimes still used for confirmation of a positive skin prick test.

Table 1

Common allergens

Inhalants	House dust mite, grass pollens, pet (especially cat) hair and danders and mould spores (especially alternaria and cladosporium) are the most commonly recognised allergens.
Foods	Important particularly in children with eczema and in adults where there is a strong clinical suspicion. The most important foods are peanuts and tree nuts, egg, milk, seafood, wheat, soy and fruits. Avoidance is the mainstay of treatment. If doubt exists about the relevance of a particular finding, a double-blind oral food challenge is the most definitive test.
Insects	Honey bee (*Apis mellifera*), European wasp (*Vespula germanica*) and paper wasp (*Vespula polistes*) are the main insect stings tested for in Australia. Allergy to jumper ants (*Myrmecia pilosula*) is also very important in rural South Eastern Australia, but no test is currently available.
Medications	Antibiotics (mainly beta-lactams) and a number of anaesthetic agents.
Others	Latex and a variety of occupational allergens. Whilst tests for latex are now available there are few routine tests for most occupational allergens.

Skin prick testing remains more sensitive and more specific than *in vitro* tests for allergen-specific IgE and, in general, remains the method of first choice for detection of reactivity. It is quicker and simpler than undertaking a RAST but, on the negative side, it requires a trained clinician with access to resuscitation equipment. These requirements may result in delays before the test is carried out. If a RAST is requested it is important to specify which allergens are to be tested, as a positive result to an allergen mix does not identify the specific sensitivity and further tests are required to find the relevant (or most relevant) allergen. There are some situations where a RAST may be preferable to a skin prick test (Table 2).

Table 2

Indications for *in vitro* RAST measurement rather than skin prick testing

1. Patients with extensive skin disease with no suitable site for testing
2. Dermatographism where wheals are produced by any minor trauma
3. Current administration of antihistamines
4. Risk of anaphylaxis, especially certain foods and latex
5. Confirmation of an unexpectedly negative skin prick test
6. Lack of availability of an allergist or appropriately trained clinician

Conclusion

Either skin prick tests or RAST can accurately determine the presence of allergen-specific IgE. Skin prick testing is the preferred method as it is more sensitive, quicker and simpler. False negatives are very unusual and a negative skin prick test makes the presence of IgE mediated allergic reactivity most unlikely. Conversely specific IgE may well be present in the absence of clinical sensitivity and positive tests must always be interpreted in conjunction with the clinical findings.

E-mail: rmo@unimelb.edu.au

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 99)

5. The usefulness of skin prick tests is limited by the large proportion of false negative results.
6. Skin prick testing should only take place when resuscitation equipment is immediately available.

Web site review

Database of Individual Patient Experiences (DIPEx) web site: www.DIPEx.org

Margaret Wohlers, Information Manager, National Resource Centre for Consumer Participation in Health, Latrobe University, Melbourne, and Meredith Carter, Executive Director, Health Issues Centre, Bundoora, Victoria

DIPEx is an internet-based multimedia resource. It tries to respond to the needs of people recently diagnosed with an illness by providing both clinical information and the experiences of individual patients. 'To be diagnosed with an illness can be bewildering and frightening, especially if there is no-one around to tell you the things you really want to know'. DIPEx includes video clips, sound (testimonies of patients), and links to web sites which are reliable, but have a more specific focus, such as cancer. DIPEx itself represents an unusual collaboration between health professionals and consumer groups. It is a not-for-profit organisation funded by the UK Department of Health, Macmillan Cancer Relief, the Citrina Foundation, the Consumers Association and the Lord Ashdown Trust.

Scope

The web site is divided into modules based on particular conditions. As funding becomes available it is intended to include 'experiences of all the main illnesses'. Topic information is organised into categories of diagnosis, such as colorectal cancer, together with relevant tests, investigative procedures and links to condition-specific web sites, for example Cochrane and CancerBACUP. Links to patient experiences are a key feature of the site which also invites people to volunteer to tell their own story. The focus of these 'stories' is patient responses to particular treatments, yet the web site does not include evidence about risks of these treatments or procedures. The patient comments do include concerns and experiences of, for example, adverse effects.

Audience

Although its stated aim is to meet the needs of patients, DIPEx is also intended to play an educational role for health workers. It is likely that the site will be more successful in achieving this aim than in its more ambitious aims. In particular it is questionable to what extent it can substitute as a support group for people who are looking for timely answers to non-medical questions. However, links are provided to various support groups.

Limitations

The web site does not acknowledge that what people often need is immediate support and information about what might be available. In addition, because DIPEx aims at that 'window of opportunity' between diagnosis and treatment it is health-system focused and does not cater for the concerns of people with long-term illness.

The site uses DISCERN quality criteria for evaluating medical information on treatment choices. DIPEx claims to provide 'balanced encounters between patients and health care professionals'. However, the site content appears to be written by health professionals accompanied by links to patient testimonies. A more robust approach might be to establish an advisory group for each illness dealt with, giving both patients and practitioners equal say in the content and design of the site.

The partnership approach is badly let down in two further ways. Firstly, the background provided by health professionals is not supported by evidence or referenced. Secondly, patient testimonies consist of one person's experience rather than a range of experiences. Yet the experience of one patient invariably differs from the experience of another person. There is no evidence or discussion about factors that may influence different experiences of the same procedure or diagnosis, for example socio-economic status, current health status and life experiences.

The links to patient experiences are strangely disembodied. They do not offer the patient's story as such. Rather they are snippets of people's experiences provided in response to predefined questions. For example, 'What will it be like having this operation or taking these drugs?'

Currently, the DIPEx web site does not capture the iterative process between people in self-help groups. This means that the site itself cannot provide the kind of 'mutual support and information sharing' in the rehabilitation process that self-help groups offer. However, DIPEx is innovative in its attempts to bring together professional concerns and consumer responses. This may be particularly useful to isolated consumers who do not have access to support groups. In addition DIPEx may prompt others to seek out actual rather than virtual support groups.

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 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.

Bisoprolol fumarate

Bicor (Alphapharm)

1.25 mg, 2.5 mg, 5 mg and 10 mg tablets

Approved indication: heart failure

Australian Medicines Handbook Section 6.4.3

Some patients with heart failure will benefit from the addition of a beta blocker to their other treatments (see 'Beta blockers in heart failure' Aust Prescr 2000;23:120–3). Bisoprolol is one of the beta blockers which can be used in patients with stable, chronic, moderate to severe heart failure.

The drug is selective for beta-1 receptors. This selectivity is reduced at higher doses so the lowest effective dose should be used. Bisoprolol is lipophilic and hydrophilic. It has no intrinsic sympathomimetic activity.

First-pass metabolism reduces the bioavailability of bisoprolol to 80%. As half the dose is excreted unchanged in the urine and half is metabolised, lower doses should be used in patients with renal or hepatic impairment. The half-life of bisoprolol is normally 9–12 hours.

In the first Cardiac Insufficiency Bisoprolol Study (CIBIS) there was no significant difference in patient mortality between bisoprolol and placebo.[1] The second study (CIBIS II) enrolled more patients.[2] After an average of 1.3 years of treatment 228 (17%) of the 1320 patients given a placebo were dead compared with 156 (12%) of the 1327 patients given bisoprolol. A significant fall in sudden deaths suggests that the benefits of bisoprolol may be related to an antiarrhythmic action. Bisoprolol also resulted in significantly fewer admissions to hospital for deteriorating heart failure. The effects of bisoprolol were greatest in patients who had ischaemic heart disease and (New York Heart Association) class III heart failure.

It is important to begin with a low dose of bisoprolol and monitor patients closely as some patients' heart failure will get worse. The adverse reactions include bradycardia, hypotension and other effects typical of beta blockers.

In clinical trials, carvedilol and metoprolol have also reduced mortality when added to conventional treatment. There is no evidence to say which beta blocker is the most effective.

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Ertapenem

Invanz (Merck Sharp & Dohme)

vials containing 1 g as powder

Approved indication: specified infections

Australian Medicines Handbook Section 5.1.3

Ertapenem is one of the carbapenem antibiotics. These drugs have a broad spectrum of activity so are held in reserve for severe infections.

By inhibiting cell wall synthesis, ertapenem has a bactericidal action. *In vitro* it is active against anaerobes, Gram positive and Gram negative aerobic bacteria. Ertapenem is resistant to some beta-lactamases, but its *in vitro* activity against enterococci is limited and it is not effective against methicillin-resistant strains of staphylococci. Ertapenem is not active against *Pseudomonas aeruginosa.*

Although ertapenem can be used for infections caused by susceptible micro-organisms that are resistant to all other antibiotics, it has specific approval to be used empirically in acute pelvic infections and complicated intra-abdominal infections. It can be infused intravenously or injected intramuscularly. Infusions should take 30 minutes and should not be mixed with dextrose or other medications. Lignocaine 1% is used to reconstitute ertapenem for intramuscular injections.

Although the half-life of ertapenem is four hours, only one daily dose is needed. Most of the drug and its metabolites are excreted in the urine.

Ertapenem was compared with piperacillin/tazobactam in 665 patients with complicated intra-abdominal infections. There was a favourable clinical and microbiological response in more than 80% of the evaluable patients. Success rates exceeding 90% were seen, for both drugs, in the treatment of 412 women with acute pelvic infections. These infections included septic abortion and postpartum endomyometritis as well as post-surgical sepsis.

Serious infections can be life-threatening and cause symptoms which could be confused with adverse drug reactions. Approximately 20% of the patients given ertapenem had a drug-related adverse experience. Common adverse events include diarrhoea, headache, nausea and problems at the injection site. Seizures can occur and people with neurological disorders are particularly at risk. Abnormal laboratory results include altered liver function and neutropenia. There is a risk of anaphylaxis in patients who are hypersensitive to penicillin.

While there is now a choice of three carbapenems there currently seems little reason to switch to ertapenem apart from its once daily dose. Few clinical trials have been published and *in vitro* studies suggest its activity against some bacteria is less than that of imipenem and meropenem. This may limit its usefulness as an empirical treatment.

Editorial note

During the preparation of this new drug comment, some discrepancies emerged between the Australian product information and the prescribing information in the USA. There may be technical explanations for these differences, but the Editorial Executive Committee would like to draw readers' attention to some examples.

1. The adverse reactions section of the Australian product information does not include the American observation that there were more deaths (4.7% versus 2.6%) among the patients given ertapenem for complicated intra-abdominal infections.
2. The activity of ertapenem *in vitro* and in clinical infections varies between the documents. In the USA ertapenem has only been shown to be active against penicillin-susceptible strains of *Streptococcus pneumoniae* and beta-lactamase negative strains of *Haemophilus influenzae*. These caveats do not appear in the Australian product information.

Esomeprazole magnesium trihydrate

Nexium (AstraZeneca)

20 mg and 40 mg tablets

Approved indications: peptic ulcer, gastro-oesophageal reflux disease

Australian Medicines Handbook Section 12.1.4

Omeprazole is the most frequently prescribed proton pump inhibitor in a market worth nearly $250 million. Its patent recently expired, but the manufacturers have now marketed esomeprazole. This is the S-isomer of the omeprazole molecule.

Esomeprazole acts in the same way as omeprazole by inhibiting the proton pump in the parietal cells of the stomach (see 'Drugs that inhibit acid secretion' Aust Prescr 2000;23:57–9). In patients with gastro-oesophageal reflux disease esomeprazole 20 mg will keep the intragastric pH above pH4 for at least 16 hours in 24% of patients, compared with 14% of patients given omeprazole 20 mg.

In addition to the initial and maintenance treatment of patients with erosive oesophagitis, esomeprazole has also been approved for use in the treatment of peptic ulcers. It can be combined with amoxycillin and clarithromycin to eradicate *Helicobacter pylori* in patients with active or healed ulcers. A one week course of this combination is as effective, at healing duodenal ulcers associated with *H. pylori*, as a combination of omeprazole and antibiotics followed by a further three weeks of omeprazole. (Although a shorter course of treatment would be helpful, the trial did not study the outcome of giving omeprazole and antibiotics for just one week. As different regimens were compared it is difficult to draw conclusions about any difference between the drugs.)

The common adverse effects of esomeprazole include headache, diarrhoea, nausea and vomiting. Esomeprazole is metabolised by cytochrome P450 2C19 and 3A4 so there is a potential for interactions. Known interacting drugs include diazepam, cisapride, clarithromycin, citalopram, imipramine and phenytoin. Severe liver disease reduces the clearance of esomeprazole.

While esomeprazole has more effect on intragastric pH than omeprazole, this may not confer a significant clinical advantage. After eight weeks of treatment, a daily 20 mg dose of either drug will have healed more than 80% of patients with erosive oesophagitis. However, the manufacturers recommend using esomeprazole 40 mg for this indication. This higher dose will heal 68–78% of patients after four weeks and 87–90% after eight weeks.

Although esomeprazole has been approved for the symptomatic treatment of gastro-oesophageal reflux disease, it is not a first-line treatment for heartburn.[1]

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Fondaparinux sodium

Arixtra (Sanofi-Synthelabo)

2.5 mg/0.5 mL in pre-filled syringes

Approved indication: thromboembolic prophylaxis

Australian Medicines Handbook Section 7.1

Low molecular weight heparins, such as enoxaparin, can be used to prevent thromboembolism in surgical patients. They act by catalysing the inactivation of Factor Xa (see 'The new heparins' Aust Prescr 1996;19:104–8).

Fondaparinux is a pentasaccharide which also acts by potentiating the neutralisation of Factor Xa. This activity reaches a maximum three hours after a subcutaneous injection. There is no effect on platelet function, bleeding time or fibrinolysis.

Most of the dose stays in the circulation as it binds to antithrombin III. The half-life of fondaparinux is 17–20 hours. As the drug is mainly excreted unchanged in the urine it is contraindicated in patients with severe renal impairment. Clearance is also reduced in the elderly.

In a study of 1250 patients with a fractured femur, fondaparinux was compared with enoxaparin. The patients were treated once a day for at least five days, with most stopping their prophylaxis by the ninth day after surgery. At day 11, 8.3% of the patients given fondaparinux had evidence of a venous thromboembolism. This incidence was significantly less than in the enoxaparin group as 19% of those patients had thromboembolism.[1]

Another study involved 724 patients having elective knee surgery. The incidence of venous thromboembolism 11 days after surgery was 13% in patients treated with fondaparinux. Although the patients taking enoxaparin were given 30 mg twice daily, the incidence of thromboembolism was 28%.[2]

The comparative clinical trials used venography to show that fondaparinux had greater efficacy than enoxaparin. There were however no significant differences in the incidence of symptomatic thromboembolism or fatal pulmonary embolism.

As fondaparinux has an antithrombotic action, bleeding is its major serious adverse effect. In the clinical trials 2–3% of patients had a serious haemorrhage. Fondaparinux caused significantly more bleeding than enoxaparin after knee surgery.[2] Other adverse reactions reported in the trials of fondaparinux include anaemia, thrombocytopenia, altered liver function and injection site reactions. Particular caution is needed if fondaparinux is given to patients who have had spinal or epidural anaesthesia. There is a risk that a spinal or epidural haematoma may develop with the risk of long-term paralysis. Fondaparinux has no antidote.

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Moroctocog alfa

Refacto (Wyeth)

vials containing 250 IU, 500 IU and 1000 IU

Approved indication: haemophilia A

Australian Medicines Handbook Section 7.4

Patients with haemophilia A are at risk of having severe bleeding after minor trauma because they lack factor VIII. To prevent this bleeding, patients can be given an infusion of concentrated factor VIII. These concentrates are plasma products, so there is always a risk of transmitting infection. This led to the development of recombinant factor VIII.

Moroctocog is a genetically engineered factor VIII produced using Chinese hamster ovary cells. The production process differs from that of previously marketed recombinant products (Kogenate, Recombinate) as human albumin is not included in the final preparation.

The indications for moroctocog are similar to those of the other recombinant factor VIII products. It can be used to prevent or control surgical bleeding. Moroctocog can be given to patients who have developed neutralising antibodies, but higher doses may be required. The incidence of these antibodies following treatment is similar to that seen after treatment with the other factor VIII products.

If necessary, the activity of moroctocog can be measured. It is important to know which assay is used as one method will underestimate the activity.

Parecoxib

Dynastat (Pharmacia Australia)

vials containing 20 mg and 40 mg powder for reconstitution

Approved indication: postoperative analgesia

Australian Medicines Handbook Section 15.1.1

Parecoxib is a non-steroidal anti-inflammatory drug. It is the prodrug of valdecoxib which reduces the production of inflammatory mediators by inhibiting the enzyme cyclo-oxygenase 2.

The plasma half-life of parecoxib is only 22 minutes because of its rapid conversion to valdecoxib. Analgesia begins within 15 minutes of an intravenous or intramuscular injection and reaches a peak in two hours. Valdecoxib is extensively metabolised and most of the metabolites are excreted in the urine. This metabolism includes cytochrome P450 3A4 and 2C9, so there is a potential for interaction with drugs which inhibit or induce these enzymes. Valdecoxib can also affect other liver enzymes. It may inhibit CYP2C19 and CYP2D6 creating the potential for more interactions.[1]

The analgesic effects of parecoxib have been studied in patients having dental, gynaecological or orthopaedic surgery. Parecoxib was more effective than placebo. Depending on the surgery, the duration of analgesia after a single dose was 6–12 hours. One study compared intramuscular and intravenous doses of parecoxib with placebo and intramuscular ketorolac in 304 patients having impacted wisdom teeth extracted. All the active treatments gave more pain relief than placebo and a 40 mg dose of parecoxib was significantly better than 20 mg. Ketorolac had a significant advantage over parecoxib in the first few hours after surgery, but parecoxib gave significantly more pain relief 16 and 24 hours after treatment.[2]

Parecoxib has only been approved for use as a single perioperative injection so most of the safety data refer to single doses. It can be difficult to separate the adverse reactions from

the effects of the surgery, but some adverse events occurred more frequently with parecoxib than with placebo. These include dyspepsia, changes in blood pressure, oliguria, oedema and itching. Caution is needed if the patient has hypertension or impaired cardiac, renal or hepatic function. Parecoxib can cause gastric erosions and ulcers so patients with a history of peptic ulcer may be at risk.

Non-steroidal anti-inflammatory drugs do have a role in postoperative analgesia.[3] For patients who cannot swallow, parecoxib is probably an alternative to ketorolac, but it has not yet been widely used.

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Riluzole

Rilutek (Aventis Pharma)

50 mg tablets

Approved indication: amyotrophic lateral sclerosis

Australian Medicines Handbook Section 16.8

Amyotrophic lateral sclerosis is one of the motor neurone diseases. The degeneration of neurones progressively leads to bulbar palsy. Most patients die of respiratory failure or choking within three years of diagnosis.

The cause of the disease is unknown, but one theory is that there is an accumulation of glutamate in the affected neurones. One of the actions of riluzole is inhibiting the release of glutamate so it has been studied to see if it has neuroprotective effects.

In a placebo-controlled trial the deterioration in muscle strength was significantly slower in patients who had been treated with riluzole. After one year 57 of the 77 patients given riluzole were alive while only 45 of the 78 patients given placebo had survived.[1] This difference (74% versus 58%) was statistically significant.

A dose-ranging study established 100 mg daily as the best balance between benefit and harm.[2] Patients take 50 mg twice a day. The tablets are well absorbed, but their bioavailability is reduced by food. There is extensive hepatic metabolism, mainly involving cytochrome P450 1A2. This means there is a potential for interactions with drugs such as amitriptyline, quinolones and caffeine (CYP1A2 inhibitors), and rifampicin (CYP1A2 inducer). Most of the metabolites are excreted in the urine, so riluzole should be used with caution in patients with renal or hepatic impairment.

Patients need regular monitoring of their liver function particularly in the first few months of treatment. A fever should prompt a check of the white blood cell count as neutropenia has been reported. The most common adverse effects of riluzole are asthenia, nausea and decreased lung function. Approximately 14% of the patients in clinical trials withdrew because of adverse events.

Although riluzole offers hope to patients with amyotrophic lateral sclerosis, it is not a cure. In the dose-ranging study the unadjusted outcome did not show a significant benefit. After 18 months 134 of the 236 patients given 100 mg riluzole had survived without a tracheostomy but so had 122 of the 242 patients given a placebo.[2] In the double-blind trial, the reduction in mortality declined after the first year of therapy. Treatment appeared to be of most benefit to patients whose disease began with bulbar involvement. When the onset involved the limbs, riluzole had no significant survival advantage over placebo[1], however this finding was not confirmed in the second study.[2] Overall riluzole probably increases survival, without a tracheostomy, by two to four months.

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Sirolimus

Rapamune (Wyeth)

1 mg/mL oral solution in 60 mL glass bottles

Approved indication: renal transplantation

Australian Medicines Handbook Section 14.1.1

Patients require immunosuppression after renal transplantation to prevent rejection of the allograft. Although cyclosporin is often used as an immunosuppressant it is associated with nephrotoxicity and hypertension. Including sirolimus in the regimen may enable cyclosporin to be withdrawn 2–4 months after transplantation.

Sirolimus is a substance produced by *Streptomyces hygroscopicus*. It inhibits antibody production and the activation and proliferation of T lymphocytes. Treatment should begin as soon as possible after the transplant.

The oral solution is rapidly absorbed. As its bioavailability of 14% is affected by food, patients should consistently take the drug with or without food. Sirolimus is metabolised by CYP3A4, so it should not be taken with grapefruit juice. Other drugs which affect this enzyme may increase or decrease concentrations of sirolimus. Blood concentrations of sirolimus should be routinely monitored. As cyclosporin is one of the drugs which inhibit the metabolism of sirolimus, the dose of sirolimus required to maintain the required blood concentration will increase if cyclosporin is withdrawn from the treatment regimen. The long half-life of sirolimus (62 hours) needs to be considered when assessing the effect of a change in dose. Only 2% of the drug and its metabolites are excreted in the urine.

A study of 719 patients compared two doses of sirolimus with azathioprine, in addition to a regimen of cyclosporin and corticosteroids. After a year, the acute rejection rate in the azathioprine group was 31% compared with 22% in patients taking 2 mg sirolimus daily and 15% in those taking 5 mg sirolimus daily. The rejection episodes were less severe in the

sirolimus group, but after a year graft survival was similar in all groups.[1]

Treatment with sirolimus seemed to exacerbate cyclosporin-induced renal dysfunction and hypertension. The patients treated with sirolimus also had significantly higher creatinine concentrations. As this may be due to a drug interaction, regimens which discontinue cyclosporin could have an advantage.

In a clinical trial 430 patients were randomised to stop cyclosporin after three months or continue taking it with sirolimus and corticosteroids. Although graft survival after one year was similar (95–97%), the patients who had cyclosporin withdrawn had a significantly higher glomerular filtration rate. They also had significantly lower blood pressure. However, withdrawal of cyclosporin was associated with a higher incidence of acute rejection (20% versus 13.5%).[2]

Most patients will experience adverse events while taking a combination of drugs after renal transplantation. Very common adverse reactions include peripheral oedema, anaemia, thrombocytopenia, epistaxis and arthralgia. Immunosuppression increases the risk of infection and the development of malignancies. Patients are advised to protect themselves from sunlight to limit the risk of skin cancers. Prophylaxis against *Pneumocystis carinii* is also recommended. Sirolimus is associated with increases in cholesterol and lipids which may be severe enough to require drug treatment.

The best regimen for patients after a renal transplant is still to be determined. While sirolimus has some benefit its long-term safety and effectiveness are unknown. It also needs to be compared with other regimens, such as those using mycophenolate mofetil.

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NEW FORMULATIONS

Amino acid dipeptide 14.4%

Glamin (Baxter Health Care)

solution in 250 mL, 500 mL and 1000 mL glass bottles

Lenograstin (rch)

Granocyte (Amrad)

263 microgram (33.6 million IU) and 105 microgram (13.4 million IU) in single-use vials

Mesalasine

Salofalk (Orphan)

granules in 500 mg and 1 g sachets, and 2 g/60 mL and 4 g/60 mL enemas

Oxcarbazepine

Trileptal (Novartis)

60 mg/mL oral suspension

NEW COMBINATIONS

Dorzolamide/timolol

Cosopt (Merck Sharp & Dohme)

eyedrops containing 2.0% dorzolamide/0.5% timolol/mL

Ibuprofen/codeine phosphate

Nurofen Plus (Boots)

200 mg ibuprofen/12.8 mg codeine phosphate tablets

NEW STRENGTHS

Levonorgestrel

Postinor-2 (Schering)

750 mg tablets

Approved indication: emergency contraception

Australian Medicines Handbook Section 17.1.4

For many years health professionals have been cutting up packets of contraceptive pills to provide women with post-coital contraception. This use of the combined pill in the Yuzpe regimen has never been approved by the Therapeutic Goods Administration. An alternative to this regimen was a high dose of progestogen, but no suitable formulations were available.

This new strength of levonorgestrel has been approved for emergency contraception. One tablet should be taken within 72 hours of unprotected intercourse. This is followed by a second tablet 12 hours later. The sooner treatment begins the more effective it is.

A double-blind study compared this regimen with the Yuzpe regimen. There were 11 pregnancies in the 976 women who took levonorgestrel, and 31 in the 979 women who used the Yuzpe regimen. When the women's menstrual cycles and probability of conception were taken into account levonorgestrel prevented 86% of expected pregnancies and the Yuzpe regimen prevented 58%.[1]

Both regimens cause nausea and vomiting, however they occur significantly less frequently with levonorgestrel. If the woman vomits within two hours of taking levonorgestrel an additional tablet can be taken.

Women should not use this product as their regular form of contraception. A request for emergency contraception is an opportunity to discuss the woman's ongoing contraceptive needs. This should not be overlooked even if levonorgestrel becomes available, as it is in the UK, from pharmacies without a prescription.[2]

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Follitropin alfa

Gonal-F (Serono)

1200 IU powder for injection

Metformin hydrochloride

Diabex (Alphapharm)

1000 mg tablets

NEW PROPRIETARY BRANDS

Aciclovir

Zyclir (Arrow)

200 mg and 800 mg tablets

Cephalexin

Cefalexin-BC (Biochemie)

250 mg/5 mL powder for oral suspension

Flucloxacillin sodium

Floxsig (Sigma)

250 mg and 500 mg capsules

Midazolam

Midazolam Injection BP (Mayne Pharma)

5 mg/mL in 1 mL ampoules

Propofol

Propofol-BC (Biochemie)

200 mg/20 mL ampoules, 500 mg/50 mL and 1000 mg/100 mL vials

Pharmacokinetics Made Easy
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Telephone: (02) 6282 6755

Facsimile: (02) 6282 6855

Postal: The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
AUSTRALIA

E-mail: info@australianprescriber.com

Web site: www.australianprescriber.com

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Address correspondence to:
The Editor
Australian Prescriber
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Telephone (02) 6282 6755

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