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EDITORIAL

The changing treatment of arthritis

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Index words: anti-inflammatory drugs, osteoarthritis, rheumatoid arthritis, COX inhibitors.

(Aust Prescr 2000;23:26–7)

Arthritis falls into two very broad categories, which are not mutually exclusive. The most common is osteoarthritis, in which a primary feature is degeneration of articular cartilage, often accompanied by evidence of soft tissue inflammation ranging from subtle to overt. The other broad category contains inflammatory arthropathies, of which rheumatoid arthritis and psoriatic arthritis are the most common examples.

There is no evidence to suggest that medications have a significant influence on the natural history of osteoarthritis. Management centres on diagnosis and qualified reassurance regarding the generally slow tempo of osteoarthritis. (This contrasts with the debilitating effects and destructive potential of inflammatory arthropathies.) Patients with osteoarthritis are advised to remain physically active without abusing affected joints unnecessarily. Exercise prescriptions should be designed to enhance and maintain general fitness and not focus narrowly on the affected joint.[1] Physiotherapists can provide advice about exercises for general fitness and for maintaining the strength and range of movement in affected joints.

Medication can be used to provide relief from pain. It may be taken strategically before an activity which the patient particularly wishes to maintain but is known to cause discomfort. Paracetamol is the recommended first-line drug for pain relief in osteoarthritis. This recommendation is based on its greater safety compared to conventional non-steroidal anti-inflammatory drugs (NSAIDs).

NSAIDs are recommended for second-line analgesia on an 'as required' basis, with an accompanying warning about the increased risk for potentially catastrophic gastrointestinal adverse effects. While the relative risk for major upper gastrointestinal bleeding is similar at all ages, the absolute risk becomes far greater in the elderly. Indeed, the prevalence of osteoarthritis in the elderly is so high (affecting most people over 60 years of age) and the risk of upper gastrointestinal events from NSAIDs (which generally result in hospitalisation and sometimes death) is so substantial, that these unwanted effects are a major public health problem.

How will this situation change with the introduction of selective cyclo-oxygenase-2 (COX-2) inhibitors? We can expect a significant reduction in hospitalisation and death from NSAID-related upper gastrointestinal events. However, given the demographics of NSAID use, what new risks might emerge?

A major unresolved question is the impact that COX-2 inhibitors may have on the risk of thrombotic vascular events. This risk is unlikely to be seen in short-term efficacy trials or early post-marketing surveillance, but may only be identified in longer-term epidemiological studies. To date, there is no clinical evidence that such a risk exists. However, the selectivity of COX-2 inhibitors gives some reasons for concern.

While COX-1 is the isoenzyme of COX involved in the protective homeostasis of the stomach, where its inhibition is generally undesirable, this isoenzyme is also responsible for the production of thromboxane A_2 by platelets. Thromboxane A_2 provides the prothombotic arm of platelet vascular homeostasis and is counterbalanced by the endothelial production of prostacyclin (PGI_2) which is antithrombotic.

The balance of these mediators is such that adverse thrombotic events generally constitute a greater hazard than uncontrolled bleeding. This is why inhibition of platelet COX-1 by low dose aspirin has a generally desirable effect when given to the elderly and others at risk of thrombosis. COX-2 inhibitors do not inhibit platelets and therefore do not have the antiplatelet effect of low dose aspirin. This lack of antithrombotic protection may be compounded by the inhibition of vascular prostacyclin production by selective COX-2 inhibitors.[2] This latter effect

In this issue...

Australian prescribers will be hearing a lot about the COX-2 inhibitors in the next few months. While Peter Brooks informs us how these drugs work, Les Cleland and his colleagues remind us that anti-inflammatory drugs are not the only treatment of arthritis.

While new drugs are usually widely available, blood products can be in short supply. Mark Dean explains why more donors are needed to help prevent haemolytic disease of the newborn. With winter approaching it is timely for Peter Wormald to review the treatment of sinusitis. The cooler weather also prompts the appearance of deathcap mushrooms in parts of Australia.

Infestations can occur at any time of year and Chris Commens tells us how to manage patients with scabies.

was shown recently and supports evidence that prostacyclin synthesis is COX-2 dependent.[3]

Given available evidence and uncertainties, what provisional advice should be given regarding the selective COX-2 inhibitors in the symptomatic treatment of osteoarthritis? On the grounds of cost alone, paracetamol should remain the drug of first choice for those in whom it provides worthwhile symptomatic relief. Patients for whom NSAIDs could provide significant relief, were it not for unacceptable adverse effects or the risk of upper gastrointestinal events, stand to benefit most from COX-2 inhibitors. However, 500 low-risk patients may need to be treated with a COX-2 inhibitor instead of an NSAID to prevent one complicated ulcer.[4] It has not yet been resolved whether age itself constitutes a risk of upper gastrointestinal events which is large enough to warrant selection of a COX-2 inhibitor instead of a conventional NSAID.

However, it should be noted that low dose aspirin should be continued where it is indicated and particularly so when a selective COX-2 inhibitor is being used (see above). Since the known variability between individuals in responsiveness to particular NSAIDs seems to extend to COX-2 inhibitors, patients who are changed from an NSAID that gives relief to a COX-2 inhibitor may be disappointed. The advantage of reduced risk for a seemingly remote contingency may be associated with less complete control of symptoms.

With regard to the inflammatory arthropathies, it should be noted that management of the prototypic disorder, rheumatoid arthritis, has changed considerably.[5] In recent onset polyarthritis, there is an impetus for early intervention with multiple therapies in patients at risk for ongoing disease and a poor prognosis. While definitive therapeutic strategies are yet to be determined, combinations such as methotrexate (with a modest folate supplement), sulfasalazine and hydroxychloroquine seem to hold most promise.[6] NSAIDs, including the COX-2 inhibitors, have a marginal role in these protocols as they may reduce symptoms without improving long-term outcomes, while displacing potentially more effective longer-acting interventions. The early use of prednisolone (or other glucocorticoids) is generally unhelpful, as it confounds clinical assessment and, through its endocrine action, is associated with inevitable unwanted effects. The place of newer biological therapies such as etanercept has not yet been resolved. On the grounds of cost alone, they are likely to be restricted to patients who do not respond to conventional long-acting drugs.

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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.

Rifampicin and contraception

Editor, – The article 'Common questions about the management of meningococcal disease' (Aust Prescr 1999;22:117-8) discusses the efficacy of oral contraception following chemoprophylaxis for contacts of meningococcal disease. I have discussed this issue with the Family Planning Association and believe in-depth advice on how to manage contraception while taking rifampicin should be given to the contact.

Appropriate advice is: 'In the case of short term concurrent drug treatment, a barrier method should be used both during treatment and for seven days after discontinuation. If this would continue into the next oral contraceptive tablet-free interval, the woman should skip the tablet-free interval and start the next pack as soon as she has finished the pack in use.'[1]

This is an important issue, as advising women to stop oral contraception or use another method for four weeks after completion of chemoprophylaxis, increases the risk of non-compliance and causes further stress to the contact. It is also excessive and not necessary.

Giulietta Pontivivo
Registered Nurse
South East Sydney Public Health Unit
Sydney, NSW

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Debra Rowett and Tricia Warrick, Drug and Therapeutics Information Service (DATIS), Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia, comment:

The letter from Giulietta Pontivivo highlights the importance of providing clear advice to ensure both compliance with rifampicin and ongoing effective oral contraceptive use. It was not the intent of the article to recommend that oral contraceptives be ceased whilst on concomitant rifampicin and for four weeks after cessation of rifampicin, but rather to emphasise that, if using hormonal contraception, additional non-hormonal contraception is required over this time. This recommendation is in accordance with the Australian Medicines Handbook[1] and other standard reference texts.[2,3,4] Importantly, the British National Formulary[2] specifically highlights that 'rifampicin is such a potent enzyme-inducing drug that even if a course lasts for less than 7 days the additional contraceptive precautions should be continued for at least 4 weeks after stopping it.' Given the serious consequences of unwanted pregnancy, the recommendation of using additional non-hormonal contraception for four weeks was included in accordance with other standard reference sources. As conflicting opinion and advice is potentially confusing for both health professionals and patients, inclusion of this matter in the forthcoming revised NHMRC guidelines for the control of meningococcal disease in Australia would be welcomed.

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Assessing the statins

Editor, – We refer to the article 'Assessing the statins' by E. Hurley (Aust Prescr 1999;22:114-7). Recent updates to the pravastatin product information in relation to the drug interaction potential of the statins reflect a different perspective to that conveyed by the article.

Following a review by the Therapeutic Goods Administration a new paragraph has been inserted in the 'Drug Interactions' section. This reads:

> 'Unlike simvastatin and atorvastatin, pravastatin is not significantly metabolised *in vivo* by cytochrome P450 3A4. Therefore, plasma concentrations of pravastatin are not significantly elevated when cytochrome P450 3A4 is inhibited by agents such as diltiazem and itraconazole.
>
> In interaction studies with aspirin, gemfibrozil, nicotinic acid or probucol, no statistically significant differences in bioavailability were seen ...'

Further, we are unaware of data supporting the assertion that there is significant P450 2C9 and 2D6 isoenzyme involvement in the metabolism of pravastatin.

Simvastatin, but not pravastatin, has been associated with rhabdomyolysis in a population at high risk of drug-drug interactions (cardiac transplant patients).[1]

The article represented a degree of uniformity among the statins that is not supported by the approved product information, a situation that we feel deserves clarification for your readers.

Kim Magner
Bristol Myers-Squibb Pharmaceuticals
Noble Park, Vic.

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Ms Eve Hurley, the author of the article, comments:

In vivo data on pravastatin's hepatic metabolism and the likelihood of drug interactions through CYP P450 3A4 are useful, and superior to results of an *in vitro* study which found moderate affinity for P450 2C9, 2D6 and 3A4.[1] However, the section regarding interaction studies (which include gemfibrozil and nicotinic acid) if taken out of context, could give the impression that it is 'safe' to use these drugs in combination with pravastatin. The product information also includes information about gemfibrozil significantly increasing concentrations of a metabolite of pravastatin and the combination being 'not generally recommended'.

Rhabdomyolysis has been reported very rarely with statins, including pravastatin.[2] Statins are well tolerated and have few clinically important interactions. My review did not include information on the management of interactions, which are given in the Australian Medicines Handbook. In preference to listing approved indications, the major clinical studies (on which the indications are based) were summarised, enabling prescribers to assess the potential benefits of treatment for their patients.

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Deathcap mushrooms – warning

David G. Le Couteur, Associate Professor, Department of Clinical Pharmacology, Canberra Clinical School; Alex A. Fisher, Registrar, Department of Clinical Toxicology, Canberra Clinical School; and Robin V. McKeown, Pharmacist-in-Charge, ACT Poisons Information Service, Canberra Hospital, Canberra

Index words: *Amanita phalloides*, mushroom poisoning.

Introduction

In 1918, in Poznan, Poland, 31 children died after eating a mushroom meal prepared for them by their school. They had eaten the deadly deathcap mushrooms *(Amanita phalloides)*. Deathcaps now grow in Australia. They are thought to have been imported inadvertently from the USA attached to the roots of oak trees. Deathcaps are found mainly in the Australian Capital Territory, but are spreading and have been reported in Victoria.

Deathcaps contain a toxin, amatoxin, that inhibits protein synthesis. This toxin is not inactivated by cooking, freezing or drying. There are four clinical phases of poisoning:

- phase I – asymptomatic latent period lasting up to 24 hours
- phase II – watery diarrhoea
- phase III – symptoms temporarily resolve
- phase IV – hepatic and renal failure

Death can occur within 7–10 days after ingestion of a single cap in adults. The overall mortality is about 20%.

Treatment

The initial management of the poisoning includes vigorous gastrointestinal decontamination with activated charcoal and whole bowel irrigation. Retrospective clinical studies and animal studies support the use of high-dose penicillin (0.5–1 million units/kg/day) and silibinin (an extract of the milk thistle available only in Europe). Both penicillin and silibinin are thought to act by inhibiting the uptake of the amatoxin into hepatocytes and interfering with its enterohepatic circulation. Liver transplantation is recommended for patients who fail to respond to more conservative measures. Although liver transplantation has not yet been performed in Australia for deathcap poisoning, it has been successfully carried out in the USA since 1985.

Prevention

There are no simple and effective treatments for deathcap poisoning so increased community and clinician awareness is needed to reduce the incidence of poisonings and improve outcomes. Currently, the level of knowledge about deathcap poisonings in Australia is limited. In our series of seven accidental poisonings, the diagnosis was not made on initial presentation to hospital in five cases. Deathcap poisoning was not suspected at all in one case, despite a history of eating mushrooms and a characteristic clinical picture.[1]

In most cases of poisoning, the mushrooms have been picked in the wild and eaten by people who cannot tell the difference between deathcap mushrooms and edible mushrooms. Deathcap mushrooms are the fruit of a fungus that grows in the root systems of trees, especially oak trees. *Amanita phalloides* has a white to white-green cap with white gills and a cup (volva) at the base of the stem (see picture).

Anyone who cannot differentiate edible mushrooms from deathcaps should never pick and eat wild mushrooms. Even so, it has been pointed out that any mushroom is edible ... once!

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Amanita phalloides

Picture provided by Mr Richard Windsor

EXPERIMENTAL AND CLINICAL PHARMACOLOGY

COX-2 inhibitors

Peter M. Brooks, Executive Dean, Health Sciences, University of Queensland, Brisbane

SYNOPSIS

There are two cyclo-oxygenase enzymes: COX-1 regulates physiological function in the gut and kidney, while COX-2 is induced in inflammation and repair.

Selective COX-2 inhibitors are now available. In early clinical trials their efficacy in arthritis was equivalent to that of less selective non-steroidal anti-inflammatory drugs and they had a significantly lower incidence of gastrointestinal adverse effects. Larger and longer outcome studies are awaited to address issues such as a possible delaying effect of COX-2 inhibitors on ulcer healing and the potential for adverse cardiovascular effects.

Index words: anti-inflammatory drugs, arthritis, adverse effects.

(Aust Prescr 2000;23:30–2)

Introduction

The inhibition of prostaglandin synthesis by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) was first described over 20 years ago.[1] The NSAIDs are now one of the most commonly used medications worldwide, with annual sales in the order of US$13 billion. These drugs are frequently used for the management of musculoskeletal diseases and for other causes of acute and chronic pain. Despite their clear efficacy in the management of inflammation, NSAIDs are a significant cause of adverse events, particularly gastrointestinal ulceration[2] and altered renal function.

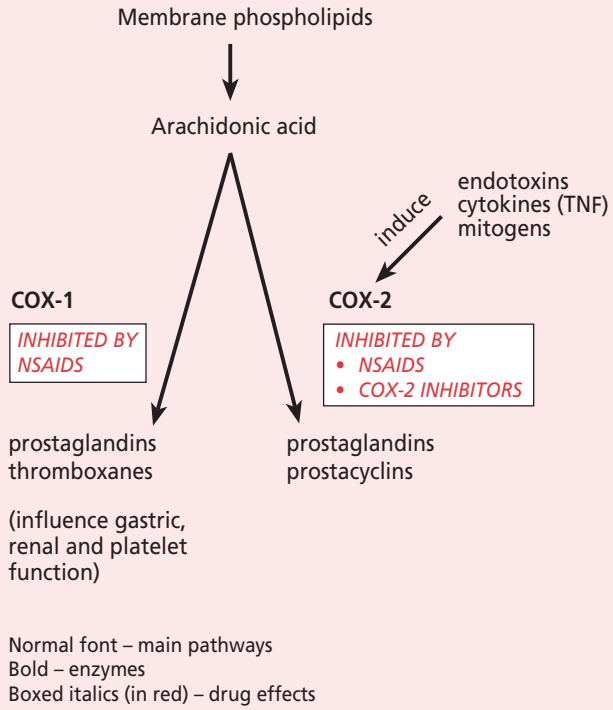
The enzyme responsible for prostaglandin synthesis is cyclo-oxygenase (COX). Following the observation that dexamethasone inhibits the increase in COX activity induced in macrophages, but has no effect on basal production of prostaglandins, it was proposed that there were two enzymes, COX-1 and COX-2.[3] The COX-1 enzyme seems to have primarily a 'housekeeping' role, subserving normal physiological function in the gut and kidney and being involved with platelet activation. The COX-2 enzyme is induced during inflammation and tissue repair and also has significant physiological roles to play in reproduction and in renal function (Fig. 1). The molecular function and protein structures of the COX isoforms were rapidly identified. This led to the development of a number of selective COX-2 inhibitors. These drugs should provide the same efficacy as the non-selective NSAIDs with fewer gastrointestinal adverse reactions.

There is a huge potential market for these drugs. In the first few months following its launch in the USA sales of one COX-2 inhibitor exceeded those of sildenafil.

Fig. 1

Cyclo-oxygenase enzymes.

COX-1 is involved in normal physiological functions including the production of protective prostaglandins in the stomach. COX-2 is induced by inflammation. Both enzymes are inhibited by non-steroidal anti-inflammatory drugs (NSAIDs). COX-2 inhibitors have little effect on COX-1 activity and so do not inhibit prostaglandin synthesis.



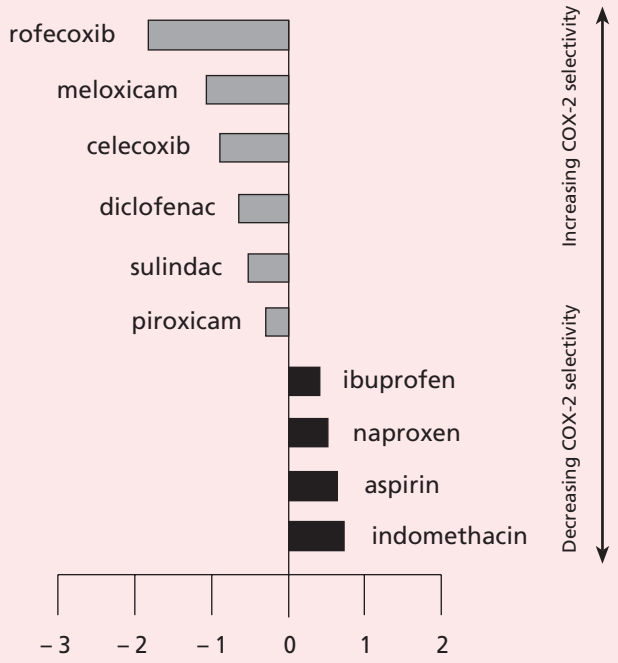
Assessment of COX-2 selectivity

There is a wide variety of assays to assess COX-1 and COX-2 selectivity.[4] This has led to confusion in the reporting of the relative effects of some of the new selective inhibitors depending on which assay system is used. The Human Whole Blood Assay is probably the best available currently to assess inhibition of COX-1 and COX-2.

This assay has recently been modified slightly as the William Harvey Human Modified Whole Blood Assay (WHMA). A

Fig. 2

Selectivity of COX-2 inhibitors and non-steroidal anti-inflammatory drugs[5] given as log inhibitory concentration (IC_{80}) ratio. The '0' line indicates equipotency.



Log [IC_{80} ratio (William Harvey Human Modified Whole Blood Assay (WHMA) COX-2/COX-1)]

wide range of COX-2/COX-1 ratios has been reported for currently available and experimental NSAIDs.[5] These data are summarised in Fig. 2 with rofecoxib being greater than 50-fold COX-2 selective, and celecoxib being 5-to-50 fold COX-2 selective. Diclofenac, sulindac and piroxicam have less than 5-fold COX-2 selectivity.

Measuring COX inhibition in gastric mucosa by using gastric biopsies may also provide important additional information. Although these investigations may define COX selectivity, they do not necessarily imply that COX-2 selective drugs will have improved safety profiles – this can only be shown by randomised controlled clinical trials.

Clinical studies

When comparing the adverse effects of COX-2 inhibitors with those of NSAIDs appropriate doses must be used. It is essential to compare doses which have similar efficacy.

Although the new COX-2 inhibitors had significantly lower incidences of gastric injury in the short term, 12-month anti-inflammatory and gastrointestinal outcome studies against standard NSAIDs are required to fully assess their efficacy and adverse effects.

Celecoxib

In single dose studies celecoxib (100 mg and 400 mg) was superior to placebo and as effective as aspirin (650 mg) in relieving the pain of dental extraction. Phase II and III studies of up to six months in doses of 100–400 mg/day for osteoarthritis and 200–800 mg/day for rheumatoid arthritis showed equivalence to naproxen 1 g daily or diclofenac 150 mg daily in terms of efficacy. In normal volunteers, endoscopic studies with celecoxib 100 mg or 200 mg twice daily for seven days revealed levels of gastric mucosal injury similar to those of placebo. Larger three-[6] or six-month studies showed the incidence of ulcers was similar to placebo and significantly reduced compared to naproxen and diclofenac.

Rofecoxib

Rofecoxib has a long half-life and is suitable for once-daily dosing in osteoarthritis and rheumatoid arthritis. A single dose of 50 mg is superior to placebo and equivalent to ibuprofen 400 mg or naproxen 550 mg for relieving acute pain after dental extraction. Gastric mucosal injury at seven days is similar to placebo, but less than ibuprofen 2.4 g daily or aspirin 2.6 g daily. A recent analysis of eight double-blind randomised controlled trials, including two one-year efficacy studies versus diclofenac 150 mg daily, in over 5000 osteoarthritis patients has reported a significantly lower 12-month cumulative incidence of perforations, ulcers and upper gastrointestinal tract bleeding with rofecoxib than with other NSAIDs (1.3% versus 1.8%).[7]

Future directions

Significant interest has now been shown in the role that inflammation (driven by COX-2) plays in conditions such as Alzheimer's disease and colonic carcinoma.[8] COX-2 is certainly induced around the inflammatory plaques seen widely throughout the central nervous system in Alzheimer's disease, and COX-2 expression is upregulated dramatically in colonic carcinoma. Epidemiological data support the argument that patients taking NSAIDs have a lower incidence and a slower rate of progression of Alzheimer's disease. NSAIDs also reduce the growth rate of colonic polyps in humans[9] and the incidence of colonic tumours in animals.

The selective COX-2 inhibitors seem to have similar effects, increasing blood pressure and reducing renal function, as the non-selective COX inhibitors. Selective COX-2 inhibitors should not be given to people with aspirin sensitivity as there are no published studies to show that this is safe for these patients. Although there is some theoretical concern relating to the potential for an increased risk of thrombosis with COX-2 inhibitors this does not seem to have been borne out by studies to date. Larger and longer-term studies are however required to answer these and other issues such as whether or not ulcer healing might be impaired by a selective COX-2 inhibitor. Since these drugs have the potential for widespread use in the community it is important that cost-effectiveness studies are carried out, although it would seem that the selective COX-2 inhibitors may be cost-effective for those patients at high risk of ulcer complications.[10]

Conclusion

The efficacy of the new drugs is not greater than that of the NSAIDs. However, if the current large outcome studies of celecoxib and rofecoxib confirm the reduced gastrointestinal toxicity then these drugs will increase the options for the treatment of arthritis.

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Professor Brooks has acted as a consultant to Searle and is on advisory boards for Merck Sharpe and Dohme.

(A summary of all clinical trials of the COX-2 inhibitors appears on the National Prescribing Service web site at www.nps.org.au under Topics)

Self-test questions

The following statements are either true or false (answers on page 47)

1. The efficacy of COX-2 inhibitors is greater than the efficacy of non-steroidal anti-inflammatory drugs.
2. It is currently unknown if an inhibitor with high selectivity for COX-2 will be safer than a less selective COX-2 inhibitor.

Your questions to the PBAC

Brand premiums

A number of years ago, benchmark pricing was introduced to the Pharmaceutical Benefits Schedule, whereby a drug company would be allowed to introduce a brand surcharge for their particular product. My understanding of the operation of this scheme was that it would follow the guidelines of the Australian Competition and Consumer Commission with respect to collusive pricing and price fixing. This would not appear to be the case, as many products today are obviously manufactured by the same company, their logo and name appearing on both the generic and premium-priced product (despite having a 'different' manufacturing code on the Pharmaceutical Benefits Schedule). An explanation of how brand price premiums are allowed, and calculated, would be appreciated.

Michael D. Rumpff
Pharmacist
Sale, Vic.

The Secretary of the Pharmaceutical Benefits Pricing Authority comments:

The Brand Premium Policy was introduced in December 1990 to reduce price controls where possible by allowing pharmaceutical suppliers to set their own price on multi-branded and therapeutically interchangeable brands listed on the Pharmaceutical Benefits Scheme, provided one brand was available at the subsidised price. This also encourages the development of the generic pharmaceutical industry in Australia.

Under the policy, suppliers of multi-branded items are able to set their own prices at a level they think the market will bear. At the same time, prescribers, pharmacists and patients can decide whether it is necessary to pay more for a particular brand when a cheaper equivalent and therapeutically interchangeable brand is available.

As the brand premium is not a government charge, it does not count towards a patient's safety net. The premium arises from the supplier's price setting and the majority of it goes to the supplier, with wholesalers and pharmacists receiving a percentage.

Under the competitive environment, it is up to the sponsor of the product to set the price at which it sells its brand. The government only sets the subsidised price. The pricing freedom that applies is similar to that of many other commodities such as food, clothing and cosmetics.

As of February 2000 there were 236 benefit items with a brand premium that could be therapeutically interchanged. The average brand premium was $1.45 and premiums ranged from $0.23 to $43.28.

The treatment of scabies

C. Commens, Department of Dermatology, Westmead Hospital, University of Sydney, Sydney

SYNOPSIS

Most experienced clinicians will miss the diagnosis of scabies at least once. As a result the patient's itch and discomfort will be prolonged and additional contacts needlessly infected. Scabies should be excluded in any patient with itch. The history, particularly itching of recent onset, and careful scrutiny of hands and wrists will usually establish the diagnosis. Scabies can be confirmed with skin scrapings. Treatment is effective provided it is done scrupulously. Permethrin cream is preferred in most cases, but severe cases may require oral ivermectin.

Index words: itch, infestations, permethrin, ivermectin.

(Aust Prescr 2000;23:33–5)

Introduction

Scabies is caused by *Sarcoptes scabiei,* a barely visible mite that is host specific for humans. Sarcoptes mites from other animals may also occasionally infest humans.

Mite movement is temperature dependent. The mite is almost immobilised below 20˚C. Transmission of mites between humans is therefore increased in a warm environment. Human to human contact of about 20 minutes allows the mite to transfer. Transmission also occurs via contaminated clothing, bedding, furniture and contaminated epithelial debris shed from scabetic patients.

The intraepidermal burrow is the pathognomonic clinical sign of scabies and contains the pregnant female mite, eggs, faeces and other discarded material from the mites. The eggs hatch in two weeks. The larvae form intraepidermal lesions whilst they mature into the adult form. This maturation takes only 2–3 weeks. Most humans develop a stable population of between 10–50 pregnant females in an ongoing infestation. Some forms of scabies have thousands of mites and are highly contagious.

Clinical settings

Scabies in the family setting usually means one or two other members of the family will also be affected. These patients usually have a low mite count (10–50) and appropriate treatment of the whole family is curative. In extended families, contact tracing is important to make sure that relatives and other people who had significant physical contact with the infested patient are also treated.

Scabies in a nursing home or institution is a difficult problem. The patients may be disabled, immobile or otherwise compromised and often have high mite counts. As a result they are more infectious. Nursing staff and patients in the surrounding areas will often become infected. Minor epidemics then result. The scabies may become long-standing despite treatment. Extensive contact tracing and treatment of affected patients and the immediate environment are therefore important.

Some patients develop severe scaling and crusting as a result of the infestation and have tens of thousands of mites. This has been described as Norwegian scabies (probably because it was first reported in Norway in 1848 when it was thought to be an endemic form of leprosy). Discarded crust and scale in bedding has hundreds of potentially infectious mites. Treating the patients' environment is particularly important.

Clinical features

Scabies should be considered in any patient with an unexplained itch of recent onset (Table 1). A definite diagnosis can be made with recognition of one major criterion (Table 2) and a likely diagnosis can be made with two or more of the minor diagnostic criteria.

Itch

Itch is the predominant feature in all but the most compromised patients. The itchy rash begins about four weeks after the beginning of the infestation coinciding with sensitisation. It is often worse at night.

Table 1

When should I think about scabies?

Unexplained pruritus especially if other contacts are also itchy
'Atopic or irritant dermatitis' of very recent onset
Persistent insect bite reactions
Recurrent impetigo with itch
Pustular lesions on the palms and soles particularly in the young
Unusual urticaria
Unusual pruritic psoriasiform rashes that are crusted and scaling or blistering

Table 2

Diagnosis

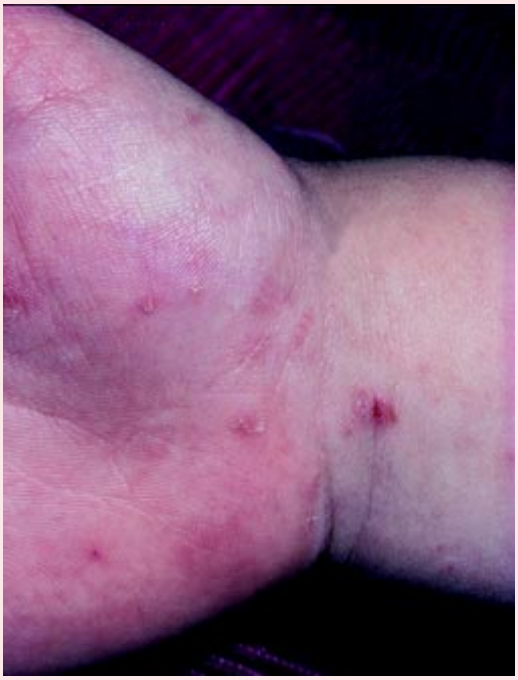
Major diagnostic criteria (presence of one confirms diagnosis)

- Identifiable typical burrow particularly associated with itchy rash
- Positive skin scrapings showing eggs or mite or faeces

Minor criteria (two needed for likely diagnosis)

- Typical itchy rash
- Sudden onset of unexplainable itchy rash
- Contact with a scabetic patient
- Papules on penis

Wrist showing lesions and intraepidermal burrow of the scabies mite



The itch is due to a combination of non-specific factors and specific immunological events as patients develop hypersensitivity to the mite and its products. A prickling irritation can be felt when mites move around on the warm skin.

Secondary dermatitis is widespread due to these immunological mechanisms, scratching and the irritation caused by the treatments applied by an increasingly desperate itchy patient.

Burrows

The diagnostic sign of scabies is the burrow (see picture). This is an intraepidermal track made by the egg laying female and is usually less than a centimetre long. The opening of the burrow may have a mild scale while the blind end contains the female. Most adult humans will have a burrow on the hands or wrists. Children will often have burrows on the feet as well. Burrows may also be found at other sites.

Other presentations

Atypical clinical features are less common. Patients may develop urticarial or blistering rashes if they are very hypersensitive to the mite. Nodular lesions may develop from chronic scratching and infestation. Children may have a pustular eruption particularly around their hands and feet.

Investigations

In most patients, scraping a number of burrows will reveal the mite, eggs or faeces. This confirms the diagnosis and is a major diagnostic criterion (Table 2).

Treatment

There are some general principles (Table 3), but the treatment is influenced by the clinical setting.

Table 3

General strategies in scabies management

Confirm the diagnosis preferably by identifying a typical burrow or positive skin scrapings.
Trace all contacts and ensure appropriate treatment.
Co-ordinate treatment.
Apply antiscabetic cream thoroughly. This usually means the entire body from the neck down. In some individuals the head must also be treated. Repeat in one week.
Treat all contaminated clothing and bedding. In some circumstances the immediate environment may also need decontamination.
Follow up 4–6 weeks later to ensure clearance.

Table 4

Treatment of household scabies

- Treat the whole family simultaneously, even members who are not itchy. The initial strategy is to kill the mite. Once this is achieved then treatment for the itch and dermatitis can begin.
- Apply the acaricidal preparation to dry skin from the neck down emphasising treatment of all sites – e.g. under nails, soles of feet, natal cleft. Permethrin cream is a good primary treatment and the author advises patients to leave this on for 24 hours. The head requires treatment if involved. This should be looked for in the elderly, infants, compromised patients and those with Norwegian scabies.
- Family members with likely scabies should have a repeat permethrin treatment in one week.
- Wash all clothes and bed sheeting being used in hot water and either iron or put through a hot dryer. An alternative is to store bedding and clothing for 1–2 weeks.
- Advise patients that 'mite killing' cream will not immediately resolve the itch or the rash.
- Begin antipruritic dermatitis treatment immediately after each course of antiscabetic creams:
  - (a) moisturise before and after showering
  - (b) avoid irritants such as too much soap and excessive sweating
  - (c) apply appropriately potent topical corticosteroids to the rash for the next 2–3 weeks
  - (d) treat secondary infection

Family (Table 4)

An inviolable principle of scabies treatment is to treat all significant contacts. In practice this means all members of the family should have at least one treatment. Patients with definite or probable scabies should have two treatments. Caution should be exercised in treating infants, pregnant or lactating women, and the very elderly, as some preparations may be more toxic.

The treatment choice rests largely between topical permethrin or lindane applied to the skin. Permethrin is preferred because of its apparent lesser toxicity. A large number of other agents may be used in special circumstances (Table 5). The application must be done scrupulously. If one burrow is spared then the infestation will persist. The cream therefore needs to be massaged under nails and reapplied to any areas that are washed.

Table 5

Antiscabetic treatment

Treatment	*Comment*
Permethrin	A synthetic pyrethroid which is probably the safest antiscabetic treatment. Proven effectiveness. Probably safe in infants, pregnant and lactating women, and the elderly.
Benzyl benzoate	This is often irritating. Toxicity is uncertain. It can be used as a spray for furnishings and the environment where there is heavy contamination.
Lindane (gamma benzene hexachloride)	The potential for neurotoxicity limits the use of this agent particularly in infants, pregnant and lactating women, and in the elderly.
Ivermectin	Single dose may be effective. Simultaneous topical treatment is optional. Sometimes repeated doses are necessary. This drug is an important development in treating compromised patients, crusted Norwegian scabies, widespread unresponsive scabies and possibly some community epidemics in nursing home situations. Before prescribing, medical practitioners should be aware of the potential adverse effects and controversies in treating the young or the very elderly on multiple medications.
Miscellaneous other agents including maldison, and 6% precipitated sulphur cream	These agents require specialised experience and are not recommended as first line treatment. Some of these may also be used for spraying furniture.

Nursing homes and institutions (Table 6)

All cases in a nursing home must be identified and an assessment made of all their contacts who would be likely to be infested. This often means that 100 or more people may need assessment and counselling. There are protocols available from area health boards that spell out the importance of co-ordinated treatment.

Affected patients in nursing homes may have severe contractures and be compromised. Applying the antiscabetic agent thoroughly may be difficult. Failure to cure an epidemic may be because of a persistent, highly infectious patient or unrecognised contacts particularly amongst staff. All suspected patients should have two applications of topical antiscabetics, in the author's opinion. Those with high mite counts or persisting scabetic infections may require additional treatment with ivermectin (Table 5).

Norwegian scabies

Patients with severe scaling and crusting or who are very immunocompromised are highly infectious and are often difficult to cure with topical preparations. Ivermectin is indicated. Importantly, the patients' environment must be sterilised including bedding, chairs, carpets and curtains.

Table 6

Treatment of institutional scabies and those who are highly infectious

- Local Area Health Board can usually provide a scabies control protocol. Co-ordinated treatment is essential if patients belong to different general practitioners.
- Treat all infectious patients with stringent isolation procedures until cured. Multiple treatments may be necessary and consider adjunctive oral treatment such as ivermectin.
- Treatment of the entire body may be necessary including the head. Patients with Norwegian scabies will need exfoliation creams (e.g. salicylic acid 6% cream), and consultation with a dermatologist is recommended.
- All significant contacts should be evaluated with careful and, if appropriate, a full body examination. Scabies in affected staff, patients and contacts can look atypical. If possible the diagnosis should always be confirmed with microscopic scrapings or identification of typical burrows.
- Treat all affected contacts simultaneously.
- Nursing staff or attending carers should wear plastic disposable gloves and practise strict barrier nursing. They should be careful about excessive shaking of bedding and clothing that may disperse infected scale and debris widely into the environment.
- An acaricidal spray (e.g. benzyl benzoate) will help to decontaminate rooms with application of the spray to bedding, chairs, floors, pillows. Fumigation and closure of the area are other options.
- Shoes should be placed in a plastic bag for two weeks. Clothing and sheeting should be washed in hot water and ironed or put through a hot dryer. Storage for two weeks may be necessary for items that cannot be decontaminated.
- Follow-up with weekly treatments to highly infected individuals is important. Repeat scrapings may be necessary to ensure that these patients are finally clear.
- Contacts must be followed up at 4–6 weeks. Ensure that staff, relatives and contacts are fully aware of the implications of scabies and are warned to be suspicious of persistent or recurrent itchy rashes for the next few months.

Self-test questions

The following statements are either true or false (answers on page 47)

3. Norwegian scabies is not present in Australia.
4. The itch of scabies resolves within 24 hours of successful antiscabetic treatment.

New National Medicines Policy

The 2000 National Medicines Policy has been launched. Copies are available from the Department of Health and Aged Care: fax 02 6289 7746, phone 02 6289 7491.

Wanted: Rh D negative donors

Mark Dean, Assistant Director, Australian Red Cross Blood Service – NSW, Sydney

SYNOPSIS

Rhesus (Rh) D immunoglobulin is given to Rh negative women who have certain antenatal indications or give birth to an Rh positive baby. This prevents the development of maternal antibodies which could cause haemolytic disease of the newborn in future pregnancies.

The Australian Red Cross Blood Service (ARCBS) collects high titre anti-D plasma from donors to produce Rh D immunoglobulin. The supply is insufficient to meet all the indications and revised guidelines restricting the use of Rh D immunoglobulin have recently been released. These highlight the need to recruit more blood donors. Doctors are encouraged to refer donors with anti-D antibodies, or Rh negative donors who may be interested in being immunised, to the ARCBS.

Index words: blood donation, rhesus, antenatal care.

(Aust Prescr 2000;23:36–8)

Introduction

Women with a Rhesus (Rh D) negative blood group carrying a Rhesus positive fetus can develop antibodies against the fetus. Isoimmunisation may occur if fetal red blood cells enter the maternal circulation either during pregnancy or following birth. The antibodies, once formed, can cross the placenta and bind to the fetal Rh D positive cells and destroy them. This causes haemolytic disease of the newborn. These antibodies may also affect future pregnancies. To prevent isoimmunisation Rh D immunoglobulin (anti-D) is given to Rh D negative women who have Rh D positive babies.

An anti-D antibody can only develop if the mother is negative for the Rh D antigen. There are ethnic variations in the frequency of Rh D negative individuals with approximately 17% of women in Australia being negative for the Rh D antigen. They are, therefore, at risk of developing anti-D if they give birth to an Rh D positive baby. There will not be a problem if the father is also Rh D negative, as the fetus will be Rh D negative.

Rh project in Australia

In the 1960s it was discovered that it was possible to prevent the body's immune response to the D antigen by giving anti-D post partum.[1] A joint project was established in 1966 by the Australian Red Cross Blood Service (ARCBS) and Commonwealth Serum Laboratories to provide high titre anti-D plasma. This became known as the Rh Project. The first donors had been either immunised by previous exposure, e.g. by transfusion or pregnancy, or were deliberately immunised by being given Rh D positive cells intravenously by the Blood Transfusion Service.

In order to maintain the donors' anti-D titres it was necessary to boost their antibody production by giving them further injections of D positive cells. They were injected with 1 mL of red cells when the titre of anti-D fell (about every six months). Each donor was fully informed about the risks of boosting and advised to discuss it with their own doctor.

Boosting however was electively ceased in November 1991 as it was believed there were sufficient stockpiles of Rh D immunoglobulin and an adequate input of high titre anti-D plasma for processing. Following the cessation of boosting, the titres of anti-D in the plasma received for processing progressively declined. Boosting had to recommence in late 1994 as it became evident that the country was in fact facing a supply crisis. At first, boosting involved only those donors who had previously been boosted, however in December 1995 boosting was extended to donors with preformed anti-D who had not previously been boosted. Boosting in women was limited to those who were postmenopausal or who had had a hysterectomy. This decision was made because Australia was still unable to meet its requirements. These boosted donors now provide 95% of the plasma available for processing.

Despite these efforts and the Royal Australian College of Obstetricians and Gynaecologists Interim Guidelines to reduce usage of Rh D immunoglobulin, Australia ran out of immunoglobulin in 1995. A worldwide shortage of plasma for Rh D immunoglobulin production currently exists.

Donor recruitment

The Rh Project donors are now an elderly group. Many of them are retiring from the boosting program, some are forced to cease donating due to health reasons and others will have to leave because of their age. The success of the project means it is becoming increasingly difficult to find new donors with anti-D because there is a much smaller number of women developing anti-D in the community.

The ARCBS is currently boosting donors across Australia. Despite the maximisation of anti-D collection over the last two years by recruiting and boosting all possible acceptable donors, the Australian supply is only just sufficient to meet the current indications. We would need to increase the supply three times to be able to provide routine antenatal prophylaxis at 28 and 34 weeks of pregnancy.

Guidelines

The National Health and Medical Research Council (NHMRC) has recently released new guidelines for using the limited supply of Rh D immunoglobulin in obstetrics.[2] The main document and a summary as well as a consumer leaflet are available on the NHMRC internet web site http://www.nhmrc.health.gov.au (under Publications, Women's Health).

General

For successful immunoprophylaxis, Rh D immunoglobulin should be given as soon as possible after the sensitising event, but always within 72 hours. If Rh D immunoglobulin has not been given within 72 hours, a dose offered within 9–10 days may provide protection. Blood should be taken from the mother, before administration of the Rh D immunoglobulin, to assess the magnitude of fetomaternal haemorrhage. The blood group of the father is not taken into consideration when determining immunoprophylaxis. This is because the important end point is whether the baby is Rh D positive and the mother is Rh D negative. It is not possible to know the baby's group exactly by knowing the mother's and father's blood groups. In this situation there may also be uncertainty about who the father is.

Postpartum administration

A dose of 125 microgram (625 IU) Rh D immunoglobulin should be offered to every Rh D negative woman following the delivery of an Rh D positive baby.

Rh D immunoglobulin should not be given to women with pre-formed anti-D antibodies, except where the preformed anti-D is due to the antenatal administration of Rh D immunoglobulin.

The magnitude of the fetomaternal haemorrhage should be assessed by a method capable of quantifying a haemorrhage of at least 6 mL of fetal red cells (12 mL of whole blood). The traditional method was the Kleihauer test although several centres are now using flow cytometric assays. The choice of test does not matter significantly as long as the laboratory can accurately quantify the amount of fetomaternal haemorrhage. One dose of 125 microgram Rh D immunoglobulin will protect against a haemorrhage of 6 mL of fetal red cells. If the fetomaternal haemorrhage is assessed as being greater than 6 mL of fetal red cells then additional doses of Rh D immunoglobulin should be given, i.e. another 125 microgram of Rh D immunoglobulin for every extra 6 mL of fetal red cells.

Antenatal administration for potentially sensitising events

First trimester

Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D antibodies to ensure adequate protection against immunisation for the following indications up to and including 12 weeks gestation:

- miscarriage
- termination of pregnancy
- ectopic pregnancy
- chorionic villus sampling

A dose of 50 microgram Rh D immunoglobulin is sufficient. However, until this dosage size becomes available in Australia, 125 microgram should be used.

There is insufficient and conflicting evidence about whether or not women having a threatened miscarriage should receive Rh D immunoglobulin. Until further evidence is available it would seem prudent to give Rh D immunoglobulin if the clinician was aware of the threatened miscarriage.

After the first trimester

A dose of 125 microgram Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D antibodies to ensure adequate protection in the following situations after 12 weeks gestation:

- genetic studies (chorionic villus sampling, amniocentesis and cordocentesis)
- abdominal trauma considered sufficient to cause fetomaternal haemorrhage
- each occasion of revealed or concealed antepartum haemorrhage (where the patient suffers unexplained uterine pain the possibility of concealed antepartum haemorrhage should be considered, with a view to immunoprophylaxis)
- external cephalic version (performed or attempted)

It is recommended that the magnitude of the fetomaternal haemorrhage be assessed after the event and following any further procedures or trauma.

Antenatal prophylaxis

Universal prophylaxis with Rh D immunoglobulin to Rh D negative women with no preformed anti-D antibodies at 28 and 34 weeks gestation is generally regarded as best practice. However, due to supply constraints, routine antenatal prophylaxis should not be given until further notice.

Future supply

To secure future supply of anti-D, the NHMRC recommends recruiting more donors to the Rh Project and in the interim, registering and importing anti-D from overseas.

There is no prospect in the medium term of the availability of a monoclonal anti-D and hence we will continue to need volunteer blood donors. Anyone with anti-D is potentially valuable as a blood donor. The ARCBS is currently re-introducing primary immunisation. Rh D negative male donors and postmenopausal Rh D negative females who may be interested in being immunised should be referred to the ARCBS. For further information please contact your local ARCBS Collection Centre or call 131495.

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Self-test questions

The following statements are either true or false (answers on page 47)

5. First trimester abortion is no longer an indication for giving anti-D to a Rhesus negative woman.
6. Rhesus immunoglobulin should be given within 72 hours of a sensitising event.

Prescribing by numbers

Eve Hurley, Senior Editor, Australian Medicines Handbook, Adelaide

The results of clinical studies are often presented in terms of the relative risk reduction achieved with an active treatment over a control. The relative risk reduction is usually expressed as a percentage and can appear impressive but, as it is isolated from the underlying incidence of the event being prevented, it has little value in the clinical situation.

Absolute risk reduction is the difference in event rates between active and control groups, but it can be difficult to visualise its clinical relevance. The reciprocal of the absolute risk reduction gives the number of patients who need to be treated to prevent one event. This is the **number needed to treat** and is a more useful measure which can be used to compare a range of interventions.[1]

Calculations

$$\text{Event rate} = \frac{\text{events in group}}{\text{number of subjects in group}}$$

$$\text{Relative risk reduction \%} = \left(\frac{\text{event rate control} - \text{event rate active}}{\text{event rate control}}\right) \times 100$$

$$\text{Absolute risk reduction} = \text{event rate control} - \text{event rate active}$$

$$\text{Number needed to treat to prevent one event} = \frac{1}{\text{absolute risk reduction}}$$

The results of the Helsinki heart study[2] (see box) were generally presented as a reduction of 34% in the incidence of coronary heart disease with gemfibrozil treatment.

Expressing results as the number of patients who need to be treated to prevent one event (or for one patient to benefit) is much more meaningful. It can be useful when discussing treatment options with patients.

Example

Helsinki heart study

Subjects: 4081 asymptomatic men aged 40–55 with dyslipidaemia (total cholesterol minus HDL ≥5.2 mmol/L).

Treatment: gemfibrozil 600 mg twice daily (2051 men) or matched placebo (2030 men) in a five year randomised double-blind study.

Results: number of events (fatal, non-fatal myocardial infarction or cardiac death)
gemfibrozil – 56 events, placebo – 84 events.

Calculations

Event rate placebo = $\frac{84}{2030}$ = 0.041 (4.1%)

Event rate active = $\frac{56}{2051}$ = 0.027 (2.7%)

Relative risk reduction % = $\frac{0.014}{0.041} \times 100$ = 34%

Absolute risk reduction = 0.041 – 0.027 = 0.014 (1.4%)

Number needed to treat for five years to prevent one event = $\frac{1}{0.014}$ = 71 men

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Treating acute sinusitis

Peter John Wormald, Professor and Head, Department of Otolaryngology Head and Neck Surgery, University of Adelaide and Flinders University, Adelaide

SYNOPSIS

Infections in the nose involve the sinuses because the lining of the nose and the paranasal sinuses is continuous. The major sinuses drain through a common tract – the ostiomeatal complex, which is located under the middle turbinate. Acute sinusitis usually follows a cold and presents with nasal obstruction, facial pain, dental pain, purulent rhinorrhoea, sinus tenderness and in some cases fever and malaise. The diagnosis is made on the history, the patient's lack of response to topical decongestants and on finding pus in the nose with associated sinus tenderness. Treatment consists of combining topical or systemic decongestants with saline irrigations and an antibiotic, usually amoxycillin. Referral to a specialist should be considered if patients fail to respond to second line antibiotic therapy and for those who get recurrent episodes of sinusitis.

Index words: decongestants, rhinitis, rhinosinusitis.

(Aust Prescr 2000;23:39–42)

Introduction

The lining of the nose and the paranasal sinuses is continuous and inflammation which affects the lining of the nose will spread, to a variable extent, into the sinuses (Fig. 1). An inflammatory process that is primarily sited in the sinuses will in turn extend to the nasal cavity and result in a variable amount of rhinitis. Most conditions in the nose therefore affect both the nasal cavity and the sinuses (rhinosinusitis). Acute sinusitis is defined as an infection of the nose which has spread to the paranasal sinuses, with a duration of between one day and three weeks. Chronic sinusitis is defined as a patient having two or more of the symptoms of nasal obstruction, rhinorrhoea, facial pain or headache or anosmia for longer than three months. The treatment of chronic sinusitis is different from that of acute sinusitis.

Anatomy

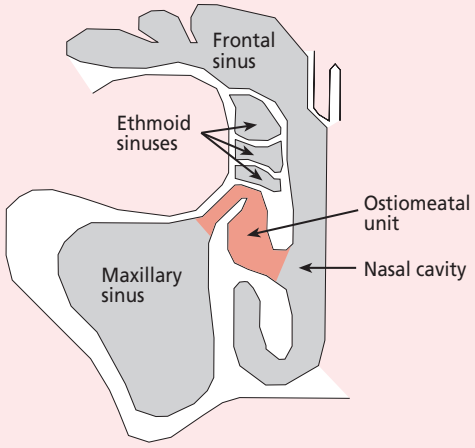
The paranasal sinuses consist of four pairs of sinuses. These are the maxillary, frontal, ethmoid and sphenoid sinuses (Fig. 1). The maxillary, frontal and anterior ethmoid sinuses open into the ostiomeatal unit under the middle turbinate while the posterior ethmoid and sphenoid sinuses open into the superior meatus above the middle turbinate.

The nose and sinuses are lined by pseudostratified columnar epithelium similar to that in the lower respiratory tract. This epithelium is covered by a mucous blanket which is made up of two layers: the liquid layer in which the cilia move (the sol layer) and a thin more viscous layer (the gel layer) which is moved by the cilia. Inhaled particles normally adhere to the gel layer and are moved out of the sinuses and nose to the nasopharynx before being swallowed. The health of the nose and paranasal sinuses is primarily dependent on this self-cleaning action of the mucociliary pathways. In the sinuses these pathways always lead towards the ostiomeatal unit. Blockage of the ostia results in sinus disease.

Fig. 1

The epithelium lining the nasal cavity and the sinuses is continuous. Infections of the nose will usually affect the sinuses to some degree and infections of the sinuses will affect the nose. (The sphenoid sinus is not shown.)

The ostiomeatal unit is the final common pathway for muco-ciliary drainage of the maxillary, frontal and anterior ethmoid sinuses.



Prevalence

Symptoms of rhinosinusitis are prevalent in 16% of the general population.[1,2] Acute sinusitis accounts for up to 4.6% of consultations with young adults.[3] Approximately 0.5% of common colds are complicated by sinusitis and the average number of colds for an adult per year is 2–3, so many patients will present with signs and symptoms of sinusitis.

Pathogenesis of acute sinusitis

Acute sinusitis usually follows an acute upper respiratory tract infection (common cold). As the viral infection spreads in the nasal mucosa, swelling and oedema of the mucosa results. As the mucosal surfaces of the ostiomeatal unit are in close proximity to one another (Fig. 1), obstruction of the sinus ostia results. In addition, the viral infection may reduce normal

cilial motility. This prevents normal mucociliary clearance resulting in an accumulation of mucus in the sinuses and the development of the symptoms of sinusitis. If this mucus becomes secondarily infected by bacteria, acute bacterial sinusitis develops.

Diagnosis

The symptoms and signs of acute sinusitis are nasal obstruction, facial pain, dental pain, purulent rhinorrhoea, sinus tenderness and in some cases systemic manifestations such as fever and malaise. A review of the literature found that the most sensitive symptoms and signs for the diagnosis of acute sinusitis were maxillary toothache, a poor response to decongestants, a coloured nasal discharge (symptoms), purulent nasal discharge and abnormal maxillary sinus transillumination (signs).[4] One of the common problems facing the doctor is differentiating an acute upper respiratory tract infection (the common cold) from acute sinusitis as there is considerable overlap of the symptoms and signs (Table 1).

The gold standard for the diagnosis of acute bacterial sinusitis remains aspiration of pus from one of the major sinuses. As the maxillary sinuses are the most accessible to aspiration and also the most commonly involved sinus in acute sinusitis, they were the most commonly aspirated sinuses. Nowadays maxillary sinus puncture and aspiration is seldom performed as the procedure can be painful.

Examination

After taking the history, the next step is to perform anterior rhinoscopy. In the normal nasal cavity, a patent nasal airway and the normal inferior and middle turbinates can be seen (Fig. 2). Note the lining of the nose is not inflamed or oedematous and there is no intranasal discharge. In the case of the common cold, the lining of the nose is erythematous and oedematous and there are clear or pale yellow nasal secretions (Fig. 3). In patients with acute sinusitis, often all that can be seen is copious yellow or green nasal discharge (Fig. 4). If this is cleared, the underlying nasal mucosa is erythematous and oedematous.

Table 1

Similarities and differences between the common cold and acute sinusitis

Symptoms & signs	*Common cold*	*Acute sinusitis*
Nasal obstruction	+++	+++
Rhinorrhoea (clear or pale yellow)	++++	±
Facial pressure	++	++++ (especially when bending forward)
Poor response to topical decongestants	–	++
Purulent rhinorrhoea (yellow/green)	–	+++
Facial pain	–	+++
Dental pain	–	+
Sinus tenderness	–	++
Fever	–	+

Frontal sinus or maxillary sinus tenderness is checked by tapping over the forehead just above the eyebrows or on the cheeks below the eyes. Pressure can also be applied in the roof of the orbit, which is the floor of the frontal sinus. The other sinuses are inaccessible for the examination of tenderness.

Maxillary sinus transillumination is not commonly used as it requires experienced personnel and a completely darkened room. Only a negative finding (i.e. normal transillumination) is useful. The light is held on the lower rim of the orbit and the palate examined through the patient's open mouth. The palate lights up with normal transillumination.

Fig. 2

Normal inferior turbinate with middle turbinate just visible in the distance

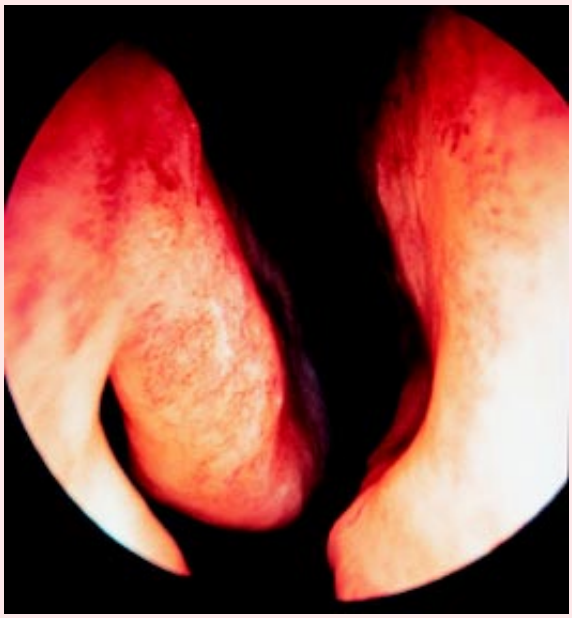


Fig. 3

Mucus coming from the ostiomeatal unit under the middle turbinate

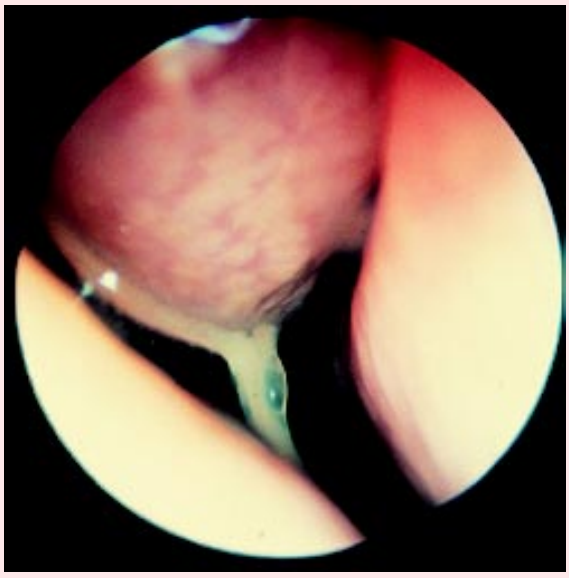
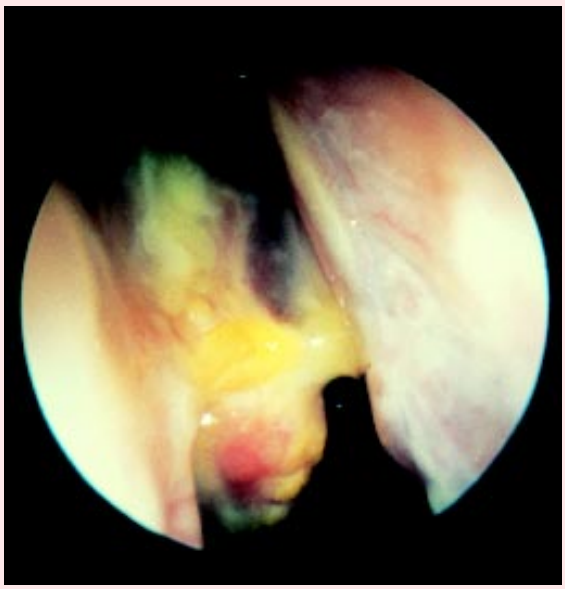


Fig. 4

Thick mucopus from the ostiomeatal unit lying on the anterior end of the middle turbinate



Investigation

When the patient has all the clinical features the diagnosis of acute sinusitis is clear. It is also usually quite clear when the patient does not have acute sinusitis if only one symptom or sign, or none, is present. However, the difficulty in the diagnosis of acute sinusitis comes when there are two or three symptoms and signs present. In these patients plain x-rays of the sinuses can be useful. A Waters (straight anteroposterior) view of the skull will allow the maxillary sinuses to be evaluated while a Caldwell (occipitomental) view will allow evaluation of the frontal sinuses. Lateral x-rays can help evaluate the sphenoid sinuses. The patient should be upright in all radiographs so that air-fluid levels can be seen. As the maxillary sinuses are involved in nearly 90% of patients with acute sinusitis, a single Waters view may be all that is required to confirm the diagnosis of acute sinusitis.[4] If this is inconclusive the other views may be added.

Microbiology

Acute sinusitis is thought to be caused by the secondary bacterial invasion of inflamed sinuses that can occur in an acute viral upper respiratory tract infection. However, the presence of bacteria in the sinuses can only be confirmed by direct aspiration of the sinus. This is only possible in the maxillary sinus and can only be done with some discomfort to the patient.

The most commonly involved organisms are *Haemophilus influenzae* and *Streptococcus pneumoniae*. Other organisms involved include other streptococci, anaerobes, *Moraxella catarrhalis* and *Staphylococcus aureus*.[5] Beta-lactamase production by *Haemophilus influenzae* has dramatically increased over the last 15 years and is found in up to 50% of organisms in certain areas of the world.[5]

Treatment

There are no good data on the treatment of sinusitis. Common practice includes decongestants which shrink the nasal mucosal oedema and help open the natural ostia of the sinuses and allow re-aeration and muco-ciliary drainage. For example oxymetazoline 0.5% in the form of a nasal spray gives good nasal mucosal decongestion with symptomatic relief. In addition, irrigation of the nose with normal saline nasal spray has also been found to improve symptomatology and outcome. Antihistamines, topical and systemic steroids have not been shown to give any additional benefit.

The use of antibiotics to treat all suspected cases of acute sinusitis is controversial. Many of the studies have had conflicting results. In general practice it can be difficult to be certain that the patient's symptoms are caused by sinusitis. If the diagnostic criteria are strict, acute bacterial sinusitis should be treated with antibiotics as they are significantly more effective than placebo alone.[6] Amoxycillin is still considered first-line treatment. The adult dose is amoxycillin 500 mg three times a day for a period of between 10 and 14 days.[7] Patients allergic to penicillin should be treated with either trimethoprim-sulfamethoxazole or cefaclor. Should the patient fail to respond to this regimen, second line therapy should be selected from an amoxycillin-clavulanate combination, cefaclor, cefuroxime axetil, loracarbef or cefixime.

Surgical intervention

This is usually only considered if complications of acute sinusitis develop. These include periorbital cellulitis, intra-orbital abscesses, osteitis or intracranial sepsis. Surgery would include drainage of affected sinuses plus management of the complication.

Specialist referral

Most cases of acute sinusitis can be managed by the general practitioner. However, referral should occur if complications develop or if the patient fails to respond to second-line therapy. Referral should also be made for patients with recurrent acute sinusitis.

The specialist will perform nasal endoscopy with a rigid nasal telescope to confirm the presence of pus in the middle meatus and/or spheno-ethmoidal recess. An endoscopically guided pus swab will be taken for culture and sensitivity. This will guide further antibiotic therapy. In addition to the antibiotics, a history of possible contributing factors such as allergy will be sought. If tests confirm the presence of an allergy, additional therapy will be needed. If the patient still fails to respond, a CT scan of the sinuses will be performed and endoscopic sinus surgery may be offered to the patient.

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7. Casiano RR. Azithromycin and amoxicillin in the treatment of acute maxillary sinusitis. Am J Med 1991;91(suppl):27S-30S.

Self-test questions

The following statements are either true or false (answers on page 47)

7. Amoxycillin is the drug of first choice for patients with sinusitis who are not sensitive to penicillin.
8. Antihistamines have a significant effect on the symptoms of acute bacterial sinusitis.

Book review

Cancer facts: a concise oncology text
Edited by James F. Bishop. London: Harwood Academic Publishers; 1999. 411 pages.
Price $65.00 soft cover; $120.00 hard cover

Ian Kerridge, Hunter Haematology Unit, Mater Misericordiae Hospital, Newcastle, NSW

Approximately 25–30% of the Australian population will die from cancer or its various complications and one in four will be diagnosed with cancer by age 75. An understanding of the basics of clinical oncology and of the impact of the major scientific advances in oncology is therefore of critical importance to all practising clinicians. For not only must clinicians suspect, investigate, diagnose and manage cancer – they must also transmit accurate information to patients and their carers in a respectful, empathic and collaborative manner.

Cancer facts is a concise text written by 55 experts in the field, collated and edited by an international authority in clinical and academic oncology. The stated objective of the text is to provide a concise but comprehensive summary of the essentials of oncology and cancer management.

In general terms the text succeeds admirably in achieving its stated aim and provides an accessible, clinically relevant overview of clinical oncology and the related sciences. The book comprises 62 chapters divided into 14 parts covering symptom control and quality of life, lung cancer, breast cancer, gastrointestinal cancer, urogenital cancers, gynaecological cancers, head and neck cancers, melanoma, haematological malignancies, miscellaneous cancers, complications in cancer patients and psychosocial issues in cancer. Each chapter provides an evidence-based synopsis of the field and includes a reading list designed to allow wider, more detailed reading on the essential elements of each chapter.

Cancer facts provides an overview of an extremely broad and complex area of medicine and as such is more likely to be of benefit to the non-oncologist than the specialist oncologist. The structure of the text is generally clear and consistent, but at times seems to be determined more by the organisation of medical specialties than by the need to provide a precise, coherent integration of cancer management. One must wonder whether having separate chapters on the surgical, radiation and chemotherapy management of non-small cell lung cancer would be more ambiguous or confusing to the non-oncologist than a single chapter on non-small cell lung cancer written collaboratively by a radiation oncologist, medical oncologist and surgeon.

The book concludes with nine colour plates of skin cancers, an essential part of any substantive review of cutaneous malignancies. However, aside from a single mammogram, there are no colour illustrations, reproductions of medical imaging or diagrams to help readers gain an understanding of anatomy, pathology or staging. As with all similar multi-authored texts, there is some unevenness in the quality and referencing of the chapters, and inevitably there will be questions raised about those topics omitted from the text. Research and clinical ethics, patient education resources, evidence-based medicine, decision-analysis, oncology on the internet and environmental/occupational oncology could all arguably be included within an expanded text.

For the most part, however, these are minor objections and *Cancer facts* is likely to find a valued place in many doctors' library or desk. James Bishop has taken on an ambitious task and his text is highly recommended for all oncologists and non-oncologists, be they students, trainees or practising clinicians.

Australian Prescriber web site news

The full text of each issue is now available in PDF format as well as in HTML. This means you can now read and print *Australian Prescriber* exactly as it appears in the printed copy. Click on 'print version' for individual articles or the full issue. PDF format is not available for issues prior to December 1999.

Dental implications

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

Treating acute sinusitis (page 39)

Treatment of acute dental pain involving the maxillary teeth requires careful diagnosis. While an acute apical infection or acute pulpitis needs treatment, in the absence of a clear dental or alveolar cause, maxillary sinusitis should be considered in the differential diagnosis.

Characteristically dental pain related to maxillary sinusitis is not related to one tooth. Where the dental/sinus pain has persisted for some time it may be referred to the mandibular teeth. Often those with acute maxillary sinusitis experience a bad taste and smell early in the morning related to pharyngeal sinus drainage. Tenderness of teeth to percussion, increased sensitivity of the maxillary teeth to cold food or drink, or when tested with ice, are distinctive signs. To assist in the diagnosis, an appropriate x-ray e.g. an orthopantomograph (OPG), may be very useful to demonstrate the anatomy of the dentition and the maxillary sinus.

Where pain is being experienced and in the absence of any dental or dento-alveolar pathology, local anaesthesia can be used to assist the diagnosis. A dose of 1 mL of 4% prilocaine without a vasoconstrictor, placed in the buccal fold adjacent to the first maxillary molar generally brings relief of maxillary sinus pain in approximately two minutes.

Dental treatment of pain from maxillary sinusitis is similar to that outlined in 'Treating acute sinusitis', however where the maxillary teeth are excessively sensitive to cold a short course, over four to six days, of a non-steroidal anti-inflammatory drug is useful. Ibuprofen 400 mg three times daily is an effective measure. Where there is persistent sinusitis the patient should be referred for medical management of the condition.

Australian Pregnancy Register for Women on Antiepileptic Medication

The Centre for Clinical Neuropharmacology at St. Vincent's Hospital in Melbourne is researching links between pregnancy, epilepsy and antiepileptic medications. The Australian Pregnancy Register for Women on Antiepileptic Medication was launched in 1999. It aims to research the incidence of birth defects in children born to women with epilepsy. This will help to establish whether certain drugs or drug combinations are safer than others.

Previous research shows a slightly higher risk of birth defects for women with epilepsy who take antiepileptic drugs. Information collected through the register will help determine whether this elevated risk is due to drugs or to the epilepsy itself.

Women who become pregnant while taking antiepileptic drugs are encouraged to contact the register. Participation is voluntary. Health professionals involved in caring for these women can encourage them to contact the register.

Participation in the register takes the form of four telephone interviews during and after pregnancy. A consent form is signed before any information is collected. Women taking antiepilepsy medication for an indication other than epilepsy are also encouraged to contact the Centre.

Telephone 1800 069 722.

Australian Medicines Handbook
Second edition, March 2000

When you want up to date, practical and reliable drug information quickly in an easy to use format, the Australian Medicines Handbook (AMH) is a good choice.

Compared with sources reliant on product information, the AMH also contains often difficult to locate information including comparisons between members of a drug class, well-established non-approved indications for use, summaries of areas of newer evidence and areas of therapeutic uncertainty.

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The restructured second edition book has fewer pages, more information, improved design and index and over 60 therapeutic areas have been updated. New therapeutic areas including breast cancer, prostate cancer, depression, substance abuse and attention deficit disorder are covered.

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Perils and pitfalls of methotrexate prescription

S. Kanagarajah, Consultant Physician in Geriatric Medicine, Illawarra Area Health Service, Warrawong, NSW

Methotrexate is a folic acid antagonist which can be used as an antineoplastic drug or as an immunomodulator. While it has a well established role in specialist oncology practice, it is increasingly being used in general medical practice for immunomodulation. Methotrexate is prescribed as a 'steroid-sparing' drug for conditions in which glucocorticoids have been used to suppress inflammatory activity. These conditions include rheumatoid arthritis, asthma, psoriasis, inflammatory bowel disease, myasthenia gravis and inflammatory myositis. This list of indications continues to grow.

Methotrexate is used in an attempt to minimise the dose of long-term oral corticosteroids and reduce their adverse effects. However the somewhat atypical dose regimen for low-dose methotrexate has presented some difficulties. The toxic adverse-effect profile of methotrexate is well known. However, the weekly dosage regimen of low-dose therapy (e.g. 7.5–10 mg) has caused confusion and errors for prescribers and patients. The risk of misadventure is increased by the current tablet formulations available.[1]

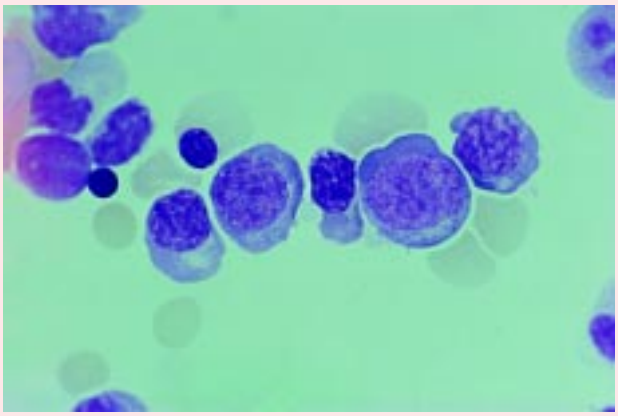
There have been six reports to the Adverse Drug Reactions Advisory Committee (ADRAC) of serious consequences resulting from toxic doses of methotrexate. Three of these patients died from complications of bone marrow suppression. Four of the six people were more than 70 years old and three of them misunderstood clear written instructions about taking the drug **weekly**, instead of daily. One patient took extra doses to relieve arthritic symptoms. Two of the cases were patients in a hospital and the methotrexate dose was incorrectly charted and/or dispensed daily, instead of weekly.

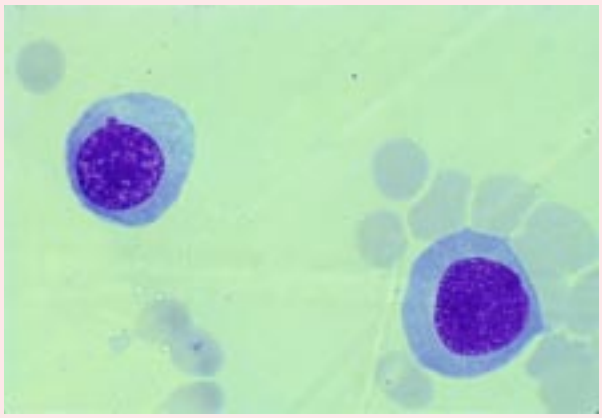
In elderly patients, other factors can contribute to the adverse outcome. Sensory and cognitive impairment may increase the chance of patient-related errors. In one of the cases cited above, there was clearly a misunderstanding of the mechanism of effect of methotrexate; it is not for symptom relief. The drug is renally cleared and may therefore accumulate in the older patient with reduced renal function.

So what can both the prescriber and 'the system' do to reduce the chance of adverse effects due to errors? Common sense measures include the following:

- give clear written instructions that **name a specific weekday** for taking the tablet[2]
- prepare instructions in big print to assist people with poor eyesight
- have a clear protocol for monitoring appropriate clinical and blood parameters such as full blood count, liver and renal function tests
- take special care in those with known renal/hepatic impairment
- ensure the patient has a good understanding of how and when to take the drug and the dangers of taking too much
- explain that extra or irregular doses are dangerous

Photomicrographs illustrating features of red cell precursors in bone marrow rendered megaloblastic by treatment with methotrexate. Normal red cell precursors on the left (slide 1) are a mixture of larger immature cells, and smaller mature forms with red cytoplasm and very dark small round nuclei. In the bone marrow of the patient affected by methotrexate on the right (slide 2), the red cell precursors are larger, tend to appear immature, and have a characteristically abnormal appearance of the nucleus.





Pictures provided by Dr Frank Firkin, St Vincent's Hospital, Melbourne

- advise the patient not to take a catch up dose if one dose is missed; the flare-up of disease is unlikely
- make a carer responsible for giving the drug if the patient appears to have cognitive or severe sensory difficulties

Most of these principles are relevant when advocating unusual or atypical regimens. The consequences of incorrect dosage can be fatal but are often preventable.[3]

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New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Board 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 Board is prepared to do this. Before new drugs are prescribed, the Board 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.

Anagrelide

Agrylin (Orphan)

0.5 mg capsules

Approved indication: essential thrombocythaemia

Australian Medicines Handbook Section 7

Essential thrombocythaemia is an uncommon abnormality of the bone marrow. This clonal stem cell disorder results in the production of abnormal platelets and an increased platelet count. Patients are not only at risk of thrombosis, but also bleeding.[1]

Patients require treatment if they develop complications or if their platelet count exceeds 1000 x 10^9/L. While some patients require plateletpheresis, many patients are treated with hydroxyurea. This drug can have serious adverse effects so anagrelide will offer an alternative treatment.

Anagrelide was originally developed as an inhibitor of platelet aggregation, but was found to cause thrombocytopenia. It is thought to impair the maturation of megakaryocytes.

A clinical trial investigated anagrelide in 577 patients with conditions such as polycythaemia vera and chronic granulocytic leukaemia. The trial included 335 patients with essential thrombocythaemia, but only 262 were evaluable. After completing at least four weeks of treatment, 247 had a platelet count which had reduced by half or fallen below 600 x 10^9/L.[2]

Patients begin treatment with 0.5 mg four times a day or 1 mg twice a day for at least a week. The dose is adjusted to the lowest dose able to keep the platelet count under control. The platelet count should be measured every two days in the first week, then weekly until the maintenance dose is found. In clinical studies the mean duration of treatment was 65 weeks, but more than 20% of patients took anagrelide for two years.

The drug is rapidly absorbed. Although food reduces bioavailability the effect is not significant. Anagrelide has a half-life of 1.3 hours and is extensively metabolised. Most of the metabolites are excreted in the urine. Patients with liver or kidney disease must be monitored carefully as anagrelide may alter liver function and possibly cause renal failure.

Anagrelide causes vasodilatation. Patients may develop hypotension, palpitations, tachycardia and heart failure. These symptoms led to the withdrawal of some patients from the clinical trials. In total 15% of the patients withdrew. Other reasons for withdrawal included headache, diarrhoea and abdominal pain which are common adverse reactions to anagrelide.

Anaemia is common and thrombocytopenia can develop. In addition to full blood counts, renal and liver function should also be checked during treatment.

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2. Anagrelide Study Group. Anagrelide, a therapy for thrombocythemic states: experience in 577 patients. Am J Med 1992;92:69-76.

Varicella vaccine

Varilix (SmithKline Beecham)

vials containing a powder pellet for reconstitution

Approved indication: immunisation

Australian Medicines Handbook Section 20.1

Chickenpox is usually a mild childhood infection. It can, however, be fatal in immunocompromised patients. In the USA the cost of managing chickenpox is estimated to be US$400 million.[1] Universal vaccination is now recommended for all American children.

The vaccine which has been approved for use in Australia is a live attenuated strain of the varicella-zoster virus. A single dose is recommended for children more than nine months old. Older children and adults have two doses at least six weeks apart. The deltoid area is the preferred site for the subcutaneous injection.

In children a single dose of vaccine has an efficacy of 88%. Children who catch chickenpox despite vaccination appear to develop an attenuated infection.

Injection site reactions occur in 27% of cases. Some vaccinees develop a mild varicella-like disease within a month.

Although varicella vaccines have been available overseas for

several years, there are unanswered questions about their role. The duration of immunity is unknown; will immunising children result in more infections in later life? It will be many years before we know if the vaccine influences the incidence and severity of shingles. An economic analysis in the USA has found that the vaccine may not be cost-beneficial from the perspective of 'payers' such as governments or health funds. For every dollar spent the payer only saves US 90 cents. However, from a societal perspective, including costs such as time lost from work, the community saves US$5.40 for every dollar spent.[1] A New Zealand study found similar results. For every dollar spent the payer saves NZ 67 cents, but society saves NZ$2.79.[2]

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NEW FORMULATIONS

Phytomenadione

Konakion MM Paediatric (Roche)

2 mg/0.2 mL in glass ampoules

Approved indication: prevention of haemorrhagic disease of the newborn

Australian Medicines Handbook Section 7.4

Injecting neonates with vitamin K (phytomenadione) has been an effective method of preventing haemorrhagic disease of the newborn. In the early 1990s a possible link between these injections and childhood cancer was reported.[1] Although other studies have not confirmed this link, the National Health and Medical Research Council advised that vitamin K could be given orally as an alternative to injection. The intramuscular formulation was not ideal for oral use and has now been replaced by a formulation which is approved for oral and intramuscular use.

Health professionals need to be aware that the new formulation has different regimens. Not only are repeat oral doses required for babies given vitamin K by mouth, but also for babies who are breast-fed following an injection. The regimens for prophylaxis are:

Healthy breast-fed neonates

2 mg orally at birth, at 3–5 days and every two weeks thereafter while breast feeding

OR

1 mg intramuscularly at birth followed by either 1 mg intramuscularly or 2 mg orally at 6–8 weeks (if the second dose is given orally, further doses every two weeks should be considered)

Healthy formula-fed neonates

2 mg orally at birth and at 3–5 days

OR

1 mg intramuscularly at birth

Neonates at risk of haemorrhagic disease

- 1 mg intramuscularly at birth
- second dose if fully breast-fed:

  1 mg intramuscularly at 6–8 weeks

  OR

  2 mg orally at 6–8 weeks and 2 mg orally every two weeks thereafter while breast feeding

To reduce the risk of late-onset bleeding, it is important to remind parents to ensure that the recommended repeat doses are given.

REFERENCE

1. Golding J, Greenwood R, Birmingham K, Mott M. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. Br Med J 1992;305:341-6.

Ocreotide

Sandostatin LAR (Novartis)

10 mg, 20 mg and 30 mg modified-release intramuscular injection

NEW STRENGTHS

Desferrioxamine mesylate

Desferal (Novartis)

2 g powder for injection

NEW PROPRIETARY BRANDS

Clomipramine

DBL Clomipramine (Faulding)

25 mg tablets

Diltiazem

DBL Diltiazem (Faulding)

60 mg tablets

Gemfibrozil

DBL Gemfibrozil (Faulding)

600 mg tablets

Gliclazide

Glyade (Alphapharm)

80 mg tablets

Moclobemide

DBL Moclobemide (Faulding)

150 mg and 300 mg tablets

Prazosin hydrochloride

DBL Prazosin (Faulding)

1 mg, 2mg and 5 mg tablets

Ticlopidine hydrochloride

Ticlohexal (Hexal)

250 mg tablets

Therapeutic Guidelines: Respiratory
Version 2, January 2000

The new edition of the popular Respiratory Guidelines has just been published. All chapters have been revised and updated, with several new chapters added.

New chapters and appendices include a range of topics, such as:

- patients with respiratory disease undergoing surgery
- respiratory fitness to scuba dive
- guide to pulmonary function testing
- a list of major studies on which recommendations are based
- patient support organisations and sources of information
- the use of respiratory drugs for pregnant or breastfeeding women

There has been extensive revision of the chapters on asthma (prevention, acute attacks and long-term asthma), pulmonary tuberculosis, venous thrombosis and pulmonary embolism, rhinitis and sinusitis, and smoking assessment and treatment.

Recommendations in the Guidelines are based on the best available scientific evidence tempered by the knowledge, experience and opinion of Australia's foremost experts and practitioners in respiratory medicine.

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Did you know that all Therapeutic Guidelines titles are now available electronically? A second opinion could be just a mouse click away!

Answers to self-test questions

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

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