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CONTENTS

Editorial

The dilemma of polypharmacy

Sarah N Hilmer, Departments of Clinical Pharmacology and Aged Care, Royal North Shore Hospital and University of Sydney

Key words: adverse effects, drug interactions, aged, quality use of medicines.

(Aust Prescr 2008;31:2–3)

The prevalence of chronic diseases, for which one or more medicines may be indicated, increases with age. Polypharmacy is usually defined as the use of five or more drugs, including prescribed, over-the-counter, and complementary medicines. It may be a useful prompt for medication review, as it is associated with problems of medication management and suboptimal prescribing. However, polypharmacy is not a clinically useful independent marker of the quality use of medicines. The type and dose of medications rather than the number of medications determine meaningful clinical outcomes.[1]

The more drugs a patient takes, the harder it may be to obtain an accurate medication history, which impedes informed medication review and prescribing. The incidence of adverse drug reactions increases with the number of medications used. Polypharmacy is a barrier to adherence because of the associated complex medication regimens, increased risk of adverse drug events and high medication costs. Poor adherence contributes to the increased risk of medication errors seen with polypharmacy.

In this issue…

Treatments should be safe and effective, but our assessment of safety and efficacy depends on understanding the outcomes of studies. Ian Scott therefore explains how to interpret the results of clinical trials.

When the findings of clinical trials are adopted into practice, they can result in some patients being prescribed multiple drugs. As polypharmacy is sometimes considered to be less than optimal prescribing, Sarah Hilmer explores the dilemma.

Another dilemma is whether chemotherapy causes cognitive impairment. Janette Vardy discusses the evidence.

There is evidence for the effectiveness of proton pump inhibitors, but Sam Al-Sohaily and Anne Duggan remind us what to consider before prescribing these drugs for long-term use.

Polypharmacy is associated with suboptimal prescribing. The more drugs a patient is exposed to, the more likely they are to be prescribed inappropriately.[2] 'Potentially inappropriate medications' in the elderly include those with sedative or anticholinergic effects and long-acting non-steroidal anti-inflammatory drugs.[3] Polypharmacy may occur when additional drugs are prescribed to treat the adverse effects of other drugs. This is known as the 'prescribing cascade'.[4] Other suboptimal prescribing associated with polypharmacy includes prescription of more than one drug in the same class or prescription of a drug that interacts with or is contraindicated in combination with another of the patient's medicines. Ironically, in a study of older patients the probability of under-prescribing – defined as lack of an indicated drug when no reason could be found for not prescribing it – also increased significantly with the number of drugs prescribed.[5]

The risk of falls is increased with polypharmacy. This association is partly due to the chronic diseases for which the multiple medications are prescribed.[6] With polypharmacy, the increased use of specific classes of drugs, especially centrally acting and cardiovascular medications, is also likely to be a factor in increasing the risk of falls.[7]

The key issue is whether each drug has been prescribed appropriately, both individually and in the context of the patient's total medication exposure, risk of drug interactions, comorbidities, physiology and quality of life. Some drugs, particularly those with anticholinergic and sedative effects, impair physical and cognitive function in older people. The more drugs with these effects that patients are exposed to, in number and in dose, the poorer the patients' overall function. A tool such as the drug burden index[1], which measures the patient's total exposure to anticholinergic and sedative medications using the principles of dose-response, provides a better indication of the risks of suboptimal prescribing than simply counting drugs.

There are several conditions in which the combined use of several drugs may be beneficial, appropriate, and advocated through evidence-based guidelines.[8] For example, primary prevention of macrovascular disease in diabetes may require one or more oral hypoglycaemics and/or insulin, one or more antihypertensives, lipid-lowering therapy, and aspirin. It is not clear how to apply treatment guidelines to frail older people with multiple comorbidities, because the evidence that supports them was not obtained from this population. Application of

published guidelines to a hypothetical 79-year-old woman with chronic obstructive pulmonary disease, type 2 diabetes, osteoporosis, hypertension and osteoarthritis led to recommendations for 12 medications, with high risks of interactions and adverse reactions.[9]

When prescribing for a frail older patient, co-ordinate prescribing with others involved in the patient's care and, if possible, aim for one prescriber per patient. Medications should be reviewed regularly with respect to the indication, therapeutic aims, dose, efficacy and safety. Consulting with a pharmacist for a home medication review may improve clinical outcomes.[10] The benefits and risks of treatment, including the overall impact on function and quality of life, should be discussed with the patient and/or their carer. The time required to achieve outcomes relative to the patient's life expectancy should be taken into account.

This clinical judgement approach contrasts starkly with the proposal to prescribe everyone over the age of 55 a 'polypill' for primary prevention of cardiovascular disease.[11] The polypill contains a lipid-lowering drug, three blood pressure-lowering drugs, aspirin and folic acid. Comorbidities, co-medications and age-related changes in pharmacokinetics and pharmacodynamics are not considered with this strategy.

Prescribing and managing multiple medications appropriately and effectively is important to optimise function and to avoid adverse health outcomes, especially in older patients. The overall effect of a person's medicines is like the sound of a group of musicians. A listener's perception of beautiful music does not depend on the size of the group, but on the quality and combination of the players, carefully selected and managed by the conductor, and tailored to the musical tastes of the specific audience.

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Conflict of interest: Dr Hilmer holds a patent for the drug burden index with Drs Abernethy and Mager.

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.

Prescribing exercise for diabetes

Editor, – In the article 'Prescribing exercise for diabetes' (Aust Prescr 2007;30:130–3), the author adequately takes into account cardiovascular and neurological concerns when advising, for example, jogging or running. However, relative adult weight gain (weight gain compared to weight on reaching maximum height and general maturity) is seemingly not addressed other than in very general terms.

Patients may be at risk of considerable irreversible weight-bearing joint damage if this issue is neglected, since even prolonged walks in obese individuals could result in aggravated ankle, knee and hip degeneration due to the load-bearing involved.

If 'losing a pound results in a four-pound reduction in knee-joint load for each step'[1], then surely adding weight might also potentially damage the weight-bearing joints in a fourfold manner as well.

Ted Arnold
Medical officer
Executive Health Management
Sydney

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Ms Bronwyn Penny, author of the article, comments:

I appreciate Dr Arnold's opinion and am in complete agreement regarding excessive joint loading in obese individuals who may be involved in significant weight-bearing activities.

In this situation, very obese patients may benefit from undergoing initial weight loss coupled with lower limb resistance training to increase lower limb strength and improve mobility before undertaking weight-bearing aerobic modalities.[1]

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Isomaltulose

Editor, – Food Standards Australia New Zealand (FSANZ) has recently approved a new sugar substitute called isomaltulose, but this product may pose a risk to individuals with disorders of fructose metabolism.

FSANZ has assessed isomaltulose and concluded that it is safe for the general population. It is not suitable for those very few people with disorders in fructose metabolism or people with sucrase-isomaltase deficiency. People with these conditions are recommended to avoid foods containing isomaltulose.

We want the medical and dietetic professions to be aware of this and so are informing the peak professional bodies and the medical media about this product. In addition, FSANZ has prepared a fact sheet on isomaltulose which is available on its website (http://www.foodstandards.gov.au/newsroom/factsheets/factsheets2007/informationaboutisom3627.cfm).

Bob Boyd
Chief Medical Advisor
Food Standards Australia New Zealand
Wellington, New Zealand

Extending prescribing rights

Editor, – In response to Professor Gullotta's letter about nurse prescribing (Aust Prescr 2007;30:88–90), I would stress that pharmacists are not the 'lesser-trained' professionals with regard to medications. How many doctors could claim they possess four years training in pharmacology and pharmaceutical care?

A few years ago I was approached to train as a pharmacist prescriber in the UK. Throughout my dispensing training, I worked alongside a general practitioner who was both mentor and assessor. My specific area of practice was hypertension management where I was valued, not as a 'pretend doctor', but as an expert on medicines. My remit was to conduct a hypertension clinic with previously diagnosed patients, monitor blood pressure, counsel on lifestyle, and review and discuss medication use. The range of prescription drugs I could prescribe was restricted to a formulary and I was entrusted to work within the level of my competency.

Contrary to Dr Gullotta's concern, I would argue that the well-managed introduction of non-doctor prescribers can actually enhance patient care.

Juanita Westbury
PhD candidate
University of Tasmania
Hobart

Editor, –The inference in the letter (Aust Prescr 2007;30:88–90), that only medical practitioners should be afforded prescribing rights, is in my view a somewhat myopic vision for the future health care of the country. Furthermore, the assertion that potential non-medical prescribers are 'lesser-trained' health professionals is misleading. They are not lesser trained in medicine, rather differently, yet highly, trained in their respective healthcare fields. The question is not whether we should consider alleged 'lesser-trained' doctors to prescribe, but whether we should allow other health professionals to extend their skills into the area of prescribing.

Patients often tell me that they could wait for a week before they are able to visit their doctor for their health complaint or regular prescription. The introduction of suitably qualified non-medical prescribers could afford general practitioners more time to focus in a more advanced diagnostic role.

Stephen Carbonara
Community pharmacist
Albion Park, NSW

Long-term management of patients taking proton pump inhibitors

Sam Al-Sohaily, Advanced trainee in Gastroenterology, Bankstown Hospital; and Anne Duggan, Consultant, Clinical Governance, Hunter New England Area Health Service, Conjoint Associate Professor, School of Medical Practice and Population Health, The University of Newcastle, and Senior Staff Specialist, Gastroenterology, John Hunter Hospital, Newcastle, New South Wales

Summary

Proton pump inhibitors have changed the management of acid-related upper gastrointestinal disorders. Other effective strategies for reducing upper gastrointestinal morbidity include lifestyle modification, *Helicobacter pylori* eradication for patients with present or past peptic ulcer disease and infection, and less potent therapy for mild dyspepsia and gastro-oesophageal reflux. Proton pump inhibitors have a definite role in the prevention of recurrence of oesophageal strictures. They can also be used to prevent the ulcerative complications of non-steroidal anti-inflammatory drugs in patients at high risk. In Barrett's oesophagus the efficacy of proton pump inhibitors in preventing disease progression and the development of adenocarcinoma is unclear.

Key words: dyspepsia, gastro-oesophageal reflux disease, *Helicobacter pylori*.

(Aust Prescr 2008;31:5–7)

Introduction

The discovery of *Helicobacter pylori* and the introduction of proton pump inhibitors (PPIs) in the 1980s were major advances in our understanding and management of upper gastrointestinal disorders. These advances made surgery for peptic ulcer disease largely obsolete. In Australia, general practitioners and gastroenterologists now prescribe PPIs to the extent that they are in the top 10 drugs, by prescription counts and cost.[1] Prescribing patterns reflect recent changes in the epidemiology of acid-related disorders, failure of a multi-pronged approach to chronic upper gastrointestinal disorders, uncertainty about the prevention of long-term complications and confidence about the relative safety of PPIs.

Clinical pharmacology

Gastric acid secretion by the parietal cells is controlled through food-stimulated and neuroendocrine pathways involving the activity of gastrin, histamine, acetylcholine, and pituitary adenylate cyclase activating peptide. PPIs irreversibly inactivate the final effector in the secretion pathway (gastric hydrogen potassium ATPase in the parietal cell). As PPIs suppress stimulated, as well as basal, acid secretion they are best taken before a meal. They are usually taken once daily as the recovery half-life of gastric acid secretion ranges from 15 to 46 hours. The anti-secretory effect increases within the first few days of oral dosing.

There are few clinically significant drug interactions with PPIs. Occasionally, the concentrations of drugs such as phenytoin and warfarin may be affected due to inhibition of the cytochrome P450 system. The absorption of other drugs (for example, quinolones, ketoconazole) may be affected by an increased gastric PH.

Indications

In the long-term management of patients taking PPIs, the initial indication for prescription always needs review. Persistent symptoms may require further investigation.

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease is probably the most frequent indication for prescribing PPIs. For patients with symptoms typical of gastro-oesophageal reflux disease, a therapeutic trial of PPIs can be started as a first step. If symptoms are relieved, this serves to support the diagnosis. After diagnosis, most of the controversy about the management of gastro-oesophageal reflux disease has been about pharmacological therapy. Should treatment be stepped up from the least potent towards the most potent therapy or stepped down from most towards least potent, with the end point being symptom control? This will be guided by the symptoms and, if indicated, endoscopy.

Whether the goal of therapy is symptomatic relief or reduction of adenocarcinoma risk, patients should be informed of the importance of risk factors for symptom generation and adenocarcinoma development. Obesity, smoking, alcohol and fatty foods all exacerbate gastro-oesophageal reflux disease and are risk factors for oesophageal carcinoma.[2] While the absolute risk of adenocarcinoma is small, overweight people and obese

people have about 1.5 and 4 times the risk of individuals with normal weight. Once lifestyle is addressed, the key questions determining the appropriate use of PPIs are:

- What is the natural history of gastro-oesophageal reflux disease?
- Does long-term treatment reduce complications?

Long-term studies of patients with dyspepsia and gastro-oesophageal reflux disease show that many patients' symptoms resolve and they stop treatment. While PPIs provide more effective symptom control than histamine (H_2) receptor antagonists there are also overwhelming long-term data that a substantial proportion of patients can control their symptoms with lifestyle interventions, antacids, H_2 receptor antagonists or PPIs taken when required.

PPIs should be prescribed regularly when there is a history of oesophageal stricture as, unlike H_2 receptor antagonists, they reduce stricture recurrence. The elderly also require regular therapy as they are more likely to have severe oesophagitis despite milder non-specific symptoms.[3]

Barrett's oesophagus

Long-term PPI therapy is currently recommended for all patients with Barrett's oesophagus although treatment is yet to be shown to reduce the risk of adenocarcinoma. A large randomised trial is investigating if a combination of low-dose aspirin and a PPI may reduce the development of adenocarcinoma in patients with Barrett's oesophagus.[4]

Gastric and duodenal ulcer disease

In patients who are not taking non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin, *H. pylori* is a key cause of peptic ulcer disease. Its eradication effects a cure. Everyone with a documented history of peptic ulcer disease and evidence of *H. pylori* infection should therefore be offered eradication therapy rather than be subjected to long-term PPI therapy. PPIs do have some antibacterial activity against *H. pylori*, but must be used in combination with antibiotics to achieve eradication. This simple and effective strategy is underutilised.

Patients taking long-term NSAIDs who also have *H. pylori* infection have a six-fold increase in the risk of ulcer bleeding, in contrast to a risk of less than two-fold for patients with *H. pylori* infection alone and almost five-fold for patients on NSAIDs with no *H. pylori* infection. The approach to primary prevention of ulcer disease in patients taking long-term NSAID and antiplatelet therapy will depend on clinical circumstances. Serious NSAID-induced gastrointestinal complications occur in about 1.5% of patients per year. This risk increases with the type of NSAID and dosage, concurrent warfarin or antiplatelet therapy, age and a past history of ulcer disease. Patients requiring NSAIDs, aspirin or clopidogrel, who are at increased risk of peptic ulcer complications should be considered for concurrent treatment with a PPI.[5]

Other indications

PPIs may be indicated in the prevention of stress-related mucosal injury in the critically ill. The long-term impact of PPIs on symptoms and quality of life in patients with functional dyspepsia is debatable. Empirical use of PPIs is not indicated in patients taking corticosteroids.

Zollinger-Ellison syndrome is a rare condition characterised by severe peptic ulceration resulting from the release of gastrin by a pancreatic tumour. High doses of PPIs may be needed.

Safety of long-term therapy

PPIs are well tolerated and most adverse effects are mild and transient. Common adverse effects, observed in up to 10% of patients, are headache, diarrhoea, gastrointestinal upset, constipation and flatulence. Rare but important adverse events include acute interstitial nephritis, hyponatraemia, hypokalaemia, hypomagnesaemia[6], pancreatitis and Stevens-Johnson syndrome. There are reports of an increased risk of pneumonia and *Clostridium difficile* colitis in long-term users of PPIs.[7]

Gastric atrophy and cancer

Long-term use of PPIs leads to hypergastrinaemia in most patients. The gastrin concentration is usually less than four times the upper limit of normal and quickly normalises after the PPI is stopped. Higher concentrations may be seen in patients with atrophic gastritis and with *H. pylori* infection. In these patients particularly, enterochromaffin-like cell hyperplasia may be seen, however there are no reported cases of dysplasia or carcinoid development. Fundic gland polyps may also be induced by prolonged hypergastrinaemia, but again despite their frequency dysplasia has rarely been reported.

Concern about the risk of gastric cancer with long-term PPI therapy largely relates to the interaction between the drugs and *H. pylori*. In infected patients PPI-induced changes in gastric pH drive the infection proximally and induce corpus gastritis and a progression to atrophic gastritis. There is currently no proof that this increases the incidence of gastric cancer among long-term PPI users, but in 2006 the Maastricht consensus panel recommended *H. pylori* eradication for patients with atrophic gastritis.

Enteric infection

Achlorhydria and hypochlorhydria increase the risk of enteric infections. A number of case control studies have investigated whether long-term PPI therapy increases the risk, particularly in the elderly. The results are inconclusive with some studies finding an increased risk of infection (for example with *Campylobacter* species) and others finding no significantly increased risk. Studies of community and of hospital-acquired *Clostridium difficile* infection have found PPI therapy to be a risk factor. This may be of particular relevance in hospitals where

high doses of PPI therapy are used, but further studies are needed to assess these findings.

Malabsorption

The effect of PPI therapy on the bioavailability of minerals, such as calcium, has been extensively studied. Although PPIs change pH and bioavailability this does not appear to be clinically relevant. A recent case control study found a higher incidence of hip fracture among long-term PPI users, but did not control for coeliac disease.[8]

Acid suppression therapy may inhibit B_{12} absorption as ingested B_{12} is protein bound and its release from foods is facilitated by gastric acid. Studies to date suggest only patients with profound acid suppression over many years, such as those treated for Zollinger-Ellison syndrome, are at risk of developing clinically relevant B_{12} deficiency and should be monitored.

Conclusion

The use of PPIs is widespread. Gastro-oesophageal reflux disease is a major indication but it should be addressed with lifestyle modification before acid suppression. For the majority of patients who remain symptomatic the objective is symptom control and this can often be achieved with intermittent treatment. Long-term maintenance therapy has a clear role in preventing NSAID/aspirin-induced ulceration and the recurrence of oesophageal strictures. Its capacity to reduce Barrett's oesophagus and adenocarcinoma development is less clear and awaits further studies.

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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 27)

1. Proton pump inhibitors reduce the recurrence of oesophageal strictures.
2. Most people with gastro-oesophageal reflux disease do not need continuous daily therapy with a proton pump inhibitor.

'Sulfur allergy' label is misleading

William B Smith, Senior Consultant, Clinical Immunology and Allergy, Royal Adelaide Hospital, Adelaide; and Constance H Katelaris, Professor, Clinical Immunology and Allergy, University of Western Sydney

Summary

The term 'sulfur allergy' is misleading and dangerous and should not be used. An allergy to a sulfonamide antibiotic may imply cross-reactivity with other sulfonamide antibiotics, but does not imply cross-reactivity with non-antibiotic sulfonamides or other drugs containing sulfhydryl or sulfate groups. Patients who suffer from an allergic reaction to the combination of sulfamethoxazole and trimethoprim should be considered potentially allergic to trimethoprim and/or sulfamethoxazole until proven otherwise, and not recorded simply as 'sulfur allergic'. Allergy to sulfonamides also does not imply cross-reactivity with sulfite preservatives, sulfates or elemental sulfur.

Key words: cross-reactivity, sulfonamide allergy.

(Aust Prescr 2008;31:8–10)

Introduction

Sulfonamides were the first class of antibiotics to be introduced in the 1930s. They remain important because they are effective, relatively safe and inexpensive, but adverse effects are relatively common.

Up to 8% of hospitalised patients and 1–2% of those in the community are reported to suffer adverse effects from the combination of sulfamethoxazole with trimethoprim, although only about 3% of these are thought to represent hypersensitivity. The situation is markedly different in patients with HIV as up to 60% experience allergic adverse reactions.

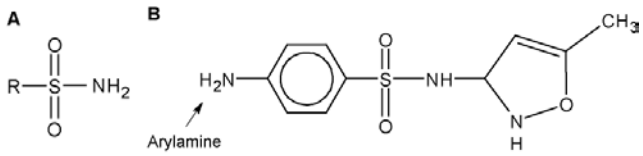
While most hypersensitivity reactions are relatively mild, sulfonamides account for a disproportionate number of cases of life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis.

Allergic mechanisms

The mechanisms of hypersensitivity to sulfonamides are not completely understood, but some principles are apparent.[1] The term sulfonamide applies to a sulfone group connected to an amine group (Fig. 1). All antibiotic sulfonamides are arylamines (Table 1).

Fig. 1

Sulfonamide structure



A Basic sulfonamide structure – present in many drugs.

B Sulfamethoxazole. The arylamine moiety, and also probably the 5-member ring containing a nitrogen atom, is thought to be important for hypersensitivity reactions.

Like most small chemical allergens, sulfonamides probably require metabolism or haptenation for immunogenicity. Hepatic oxidation of the arylamine group by the cytochrome P450 system results in the formation of a hydroxylamine intermediate metabolite which can be reduced by glutathione and excreted. However, the capacity for glutathione conjugation may be exceeded. The reactive hydroxylamine is capable of haptenating endogenous proteins and has been shown to be associated with hypersensitivity. Other reactive metabolites have also been identified. These may act by forming immunogenic structures (epitopes) for antibodies or T cells and also by direct cytotoxicity to lymphocytes and other immune cells.

Cross-reactivity

Many commonly used drugs, such as thiazide diuretics, gliclazide, frusemide and celecoxib, contain a sulfonamide moiety, but none contain the arylamine group. While it has long been considered that allergic cross-reactivity may exist between sulfonamide antibiotics and other sulfonamide drugs, this is actually unlikely because of the structural differences. Reports of cross-reactivity are based on single cases or small series.[2] The co-existence of hypersensitivity reactions to several drugs does not prove cross-reactivity between them. A review of all available relevant studies concluded that the dogma of cross-reactivity between sulfonylarylamines and other sulfonamide drugs cannot be supported by the evidence.[3] In patients who have had an allergic reaction to one drug, allergic reactions to other drugs, even if entirely unrelated, occur more commonly. In support of this concept, a very large cohort study showed

Table 1

Common examples of arylamine and non-arylamine sulfonamides

Drug groups	Cross-reactivity
Sulfonamide antibiotics (sulfonylarylamines) sulfamethoxazole sulfadiazine sulfadoxine sulfacetamide sulfasalazine (contains sulfapyridine)	Allergic cross-reactivity within this group is possible
Sulfonamide antiretrovirals (sulfonylarylamines) amprenavir fosamprenavir	Allergic cross-reactivity with sulfonamide antibiotics is likely on structural grounds but has not been established
Non-antibiotic sulfonamide drugs (non-sulfonylarylamines) frusemide hydrochlorothiazide gliclazide celecoxib	Current evidence suggests that allergy to sulfonamide antibiotics is not associated with increased risk of allergy to these drugs
Sulfhydryl drugs penicillin piroxicam captopril	No relationship to sulfonamide allergy
Sulfate drugs morphine sulfate heparin sulfate hydroxychloroquine sulfate glucosamine sulfate	No relationship to sulfonamide allergy

that the association between allergy to sulfonylarylamines and other sulfonamide drugs was no stronger than that between sulfonylarylamines and the completely unrelated penicillins.[4] The evidence therefore suggests that non-antibiotic (non-arylamine) sulfonamide drugs need not be considered as contraindicated in those with a history of hypersensitivity to antibiotic (sulfonylarylamine) sulfonamides. This conflicts with the product information of many drugs.

Trimethoprim with sulfamethoxazole

The most common sulfonamide antibiotic used in Australia is sulfamethoxazole in combination with trimethoprim. This combination has synergistic antimicrobial activity, however, when hypersensitivity reactions occur, the patient might be allergic to trimethoprim or sulfamethoxazole (or possibly both). Trimethoprim, on its own, has been reported to cause type 1 allergy (anaphylaxis)[5] and even to cause fatal toxic epidermal necrolysis.[6] There are cases in which patients who had anaphylaxis after trimethoprim-sulfamethoxazole were labelled 'sulfur allergic' and subsequently had anaphylaxis after receiving trimethoprim alone, indicating that the patient was actually allergic to trimethoprim, not sulfamethoxazole.

Patients who suffer from hypersensitivity reactions to trimethoprim-sulfamethoxazole should avoid both sulfonamide antibiotics **and** trimethoprim. If the original reaction to trimethoprim-sulfamethoxazole was mild, a cautious challenge with trimethoprim under observation is reasonable, but if the original reaction was severe, trimethoprim should not be used unless proven safe by testing or a careful graded dose challenge under the supervision of a clinical immunology and allergy specialist.

Sulfur

Sulfur is a natural element and exists in many forms. There are many substances which have names stemming from 'sulfur' such as sulfites (preservatives in food and drugs) and sulfates (common compounds found in drugs, soaps and cosmetics). Some patients who have suffered from hypersensitivity reactions to sulfonamide antibiotics are unfortunately labelled 'sulfur allergic'. This term creates confusion for the patient and often for health professionals. Many patients believe that having been labelled 'sulfur allergic' they are also at risk of adverse reactions or allergies from sulfites, sulfates and even elemental sulfur and may attempt to avoid them. Sulfates are sometimes mildly irritant and sulfites can cause respiratory reactions in patients with asthma and, rarely, non-immunoglobulin E-mediated

anaphylactic reactions, but there is no relationship between these reactions and hypersensitivity to sulfonamides. Patients who have had allergic reactions to sulfonamide drugs do not need to avoid sulfites, sulfates or sulfur.

Conclusion

As a general principle, all allergic adverse reactions to medications should be recorded in the patient's file with the specific name of the drug or drugs to which the patient has reacted and the nature of the reaction. Allergies should not be attributed to classes or groups of drugs unless proven because assumptions about cross-reactivity may later be found to be incorrect. The term 'sulfur (or sulphur, sulpha, sulfa) allergy' should not be used.

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Conflict of interest: none declared

Self-test questions

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

3. A patient who has an allergic reaction to the combination of trimethoprim and sulfamethoxazole may have a similar reaction to trimethoprim.
4. Patients who are allergic to sulfonamides should avoid food containing sulfites.

Medicinal mishap

Neutropenia with quetiapine

Prepared by Jacqueline Landau, Pharmacy Department, Ken Lu, Department of General Medicine, Cheng Choo, Pharmacy Department, and Peter Greenberg, Department of General Medicine, The Royal Melbourne Hospital

Case

An 85-year-old woman was admitted to hospital with an exacerbation of heart failure secondary to cardiac arrhythmia. Her past history included atrial fibrillation, diastolic heart failure, emphysema, gastritis, Alzheimer's disease and anxiety. She was taking quetiapine, sertraline, donepezil, omeprazole, tiotropium, salbutamol and diltiazem.

Examination revealed rapid atrial fibrillation, with no systemic or focal signs of sepsis, and she was afebrile. Haemoglobin, thyroid function, liver function and serum creatinine were normal. Her chest X-ray showed changes consistent with pulmonary oedema and bilateral pleural effusions. She was treated with frusemide and aspirin.

On the day before admission her white cell count was normal (5.5×10^9/L) with a neutrophil count of 4.1×10^9/L. However, on admission her white cell count was low (2.9×10^9/L with a neutrophil count of 1.9×10^9/L). The day after admission her white cell count fell to 2.7×10^9/L and her neutrophil count to 1.5×10^9/L.

Following a detailed review of all her drugs and in consultation with the psychiatry team, we decided to start risperidone and cease her quetiapine as it could have been the cause of the neutropenia. She had started quetiapine 200 mg twice a day four months earlier for the control of psychotic behaviour related to Alzheimer's disease. Her white cell counts were normal before she started quetiapine.

Five days after admission, the white cell count had increased to 4×10^9/L and the neutrophil count to 2.6×10^9/L (see Table 1). Given her improvement, bone marrow biopsy was not performed. Her psychotic symptoms remained controlled with the switch to risperidone, and she was discharged from hospital.

Comment

Quetiapine is an atypical antipsychotic drug with a similar chemical structure to clozapine and olanzapine. Clozapine was the first atypical antipsychotic drug, but the risk of significant agranulocytosis requires rigorous monitoring.

Table 1

White cell and neutrophil counts

Time of tests	White cell count (x 10^9/L)	Neutrophil count (x 10^9/L)
3 months before admission	4.2	2.6
Day before admission	5.5	4.1
Admission	2.9	1.9
Day 2	2.7	1.5
Day 4	3.9	2.6
Day 6	4.0	2.6
2 months after admission	6.8	4.5

The risk of neutropenia and agranulocytosis associated with antipsychotics such as clozapine is reported to be between 1% and 10%. With quetiapine, premarketing and smaller postmarketing studies suggest the risk of neutropenia is less than 0.01%. By November 2007 the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[1] had received two possible and eight probable case reports of neutropenia associated with quetiapine. Seven of the eight patients were known to have recovered after stopping the drug.

The onset of neutropenia with quetiapine is variable. In the ADRAC series, neutropenia was reported to have occurred from one week to one year after starting therapy. The dose of quetiapine ranged from 50 mg daily to 1000 mg daily. The effect did not appear to be dose dependent. Published case reports include patients who developed neutropenia two days[2] and two months[3] after starting quetiapine. Other reports of quetiapine-associated neutropenia have been confounded by the simultaneous use of clozapine[4] or valproate.[5,6]

The exact mechanism(s) by which quetiapine causes neutropenia is unknown. From the clozapine literature, proposed mechanisms are direct bone marrow suppression or toxicity from the drug or its metabolites.[7] Immmunologically mediated destruction of granulocytes or granulocytic precursors has also been proposed. Given the related chemical structure and pharmacological profile of quetiapine and clozapine, quetiapine-induced neutropenia may have similar mechanisms.[3]

Our patient was taking multiple medications before admission, but sertraline and omeprazole were the only other drugs suspected to cause neutropenia. However, as she had taken sertraline and omeprazole for more than one year, it was thought that quetiapine was the more likely explanation. In addition, after stopping quetiapine, the neutropenia resolved, despite the continuation of both sertraline and omeprazole.

The World Health Organization definition of 'probable/likely' causality assessment of a suspected adverse reaction is:

> a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.[8]

Based on these criteria, it appears our patient had a 'probable' response to the development of neutropenia associated with quetiapine, with a rapid recovery after the drug was stopped and replaced by risperidone.

Although the risk of agranulocytosis is low it needs to be balanced against any benefit of treatment. There is currently no strong evidence to support the use of quetiapine for psychological and behavioural problems in patients with dementia.[9]

Conclusion

The risk of agranulocytosis with quetiapine is significantly lower than with clozapine, so regular estimations of white cell and neutrophil concentrations are not indicated. However, vigilance is required, as blood dyscrasias can still occur.

We would like to acknowledge the advice received from Dr Sam Robson, Psychiatric registrar, Royal Melbourne Hospital.

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Conflict of interest: none declared

Interpreting risks and ratios in therapy trials

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Summary

To appreciate the significance of clinical trial results, clinicians need to understand the mathematical language used to describe treatment effects. When comparing intervention and control groups in a trial, results may be reported in terms of relative or absolute risk (or probability), or as more statistically sophisticated entities based on odds and hazard ratios. When events in the intervention group are significantly less frequent than in the control group, then relative risk, odds ratio and hazard ratio (and their confidence intervals) will be less than 1.0. If the converse holds true, these values will be greater than 1.0.

Key words: clinical trials, number needed to treat, odds, statistics.

(Aust Prescr 2008;31:12–16)

Introduction

In randomised trials and systematic reviews of trials, the effects of new treatments on dichotomous outcomes (such as death vs survival) can be expressed in several ways including relative risk, absolute risk, odds ratio and hazard ratio. These figures help to determine if the new treatment has an advantage over other treatments or placebo.

Ways of expressing treatment effects

The absolute risk, number needed to treat, relative risk and odds ratio can be calculated by compiling a 2x2 table of study data. Values can then be derived using the equations shown in the box.

Absolute risk

Absolute risk reduction, also termed risk difference, is the difference between the absolute risk of an event in the intervention group and the absolute risk in the control group.

In a trial of 441 patients at risk of developing pressure ulcers, patients were randomised to receive a sheepskin mattress overlay (intervention group) or usual treatment (control group) during their hospital stay.[1] The data from the trial can be represented in a 2x2 table (see Table 1).

Box

Calculations

	Bad outcome	Good outcome	Total patients
Intervention group	*a*	*c*	*a+c*
Control group	*b*	*d*	*b+d*

Measure	Equation
Absolute risk	$\left(\frac{b}{b+d}\right) - \left(\frac{a}{a+c}\right)$
Number needed to treat	$\frac{1}{\left(\frac{b}{b+d}\right) - \left(\frac{a}{a+c}\right)}$
Relative risk	$\left(\frac{a}{a+c}\right) \div \left(\frac{b}{b+d}\right)$
Odds ratio	$\left(\frac{\frac{a}{a+c}}{\frac{c}{a+c}}\right) \div \left(\frac{\frac{b}{b+d}}{\frac{d}{b+d}}\right) = \left(\frac{a}{c}\right) \div \left(\frac{b}{d}\right)$

Table 1

Trial data

	Patients with ulcer(s)	Patients with no ulcers	Total patients
Sheepskin group	21	197	218
Control group	37	186	223

The absolute risk reduction can then be calculated by subtracting the proportion of patients with ulcers in the sheepskin group from that in the control group.

$$\left(\frac{37}{223}\right) - \left(\frac{21}{218}\right) = 0.07 \text{ (or } 7.0\%)$$

Almost 17% of patients in the control group developed ulcers compared to 10% in the sheepskin group after 20 days of observation. This means that the absolute risk of developing ulcers in the sheepskin group was 7% less than in the control group.

If a treatment is effective and reduces the risk of an unwanted event, we see an absolute risk reduction. Conversely, if the treatment does not work and in fact increases the risk of the event, then we see an absolute risk increase.

It may be difficult to conceptualise the clinical relevance of the absolute risk reduction. The reciprocal of this value (1/absolute risk reduction) gives the number of patients who need to be treated for a certain period of time to prevent one event.

This is termed the number needed to treat and can be useful for comparing the effectiveness of a number of different interventions. So in the ulcer trial, 14 patients need to have a sheepskin overlay for 20 days to prevent one of them from getting an ulcer.

It is important to appreciate that absolute risk will vary according to the event rates in both patient groups, whereas the relative risk usually remains unchanged across the spectrum of disease severity (see Table 2). Putting this another way, in 'low risk' patients (those with mild hypertension in Table 2) the absolute risk reduction will be small whereas in 'high risk' patients (those with moderate hypertension) absolute risk reduction will be larger. For both groups the relative risk (and relative risk reduction) is the same.[2]

Relative risk

Relative risk, also known as risk ratio, is the risk of an event in the experimental group divided by that in the control group. For the sheepskin trial, this can be calculated from the data in Table 1.

$$\left(\frac{21}{218}\right) \div \left(\frac{37}{223}\right) = 0.58$$

In the trial, 10% of patients in the sheepskin group developed ulcers compared to 17% in the control group. So the risk of getting ulcers with a sheepskin overlay was 0.58 of that in the control group.

In most trials where the treatment intends to prevent an undesirable outcome such as death or complication (prevention trials), efficacy will be denoted by a relative risk of less than 1.0. Treatment harm, reflecting an increased risk of an event (including adverse effect), will be denoted by a relative risk of more than 1.0. However, in trials where the treatment intends to reduce active disease (treatment trials) and promote a positive event, such as disease remission or symptom abatement, a relative risk of more than 1.0 confirms treatment efficacy. A relative risk of 1.0 indicates no difference between comparison groups. In all cases, statistical significance is assumed if the 95% confidence interval (CI) around the relative risk does not include 1.0.

The relative risk reduction equals the amount by which the relative risk has been reduced by treatment and is calculated as 1 – relative risk. For example in the sheepskin trial, sheepskin overlays reduced the risk of patients getting ulcers by 0.42 (1 – 0.58) or 42%.

Odds ratio

Odds are the number of times an event happens divided by the number of times it does not within a group. Odds can also be expressed as the risk (or probability) of an event occurring over the risk of an event not occurring. To provide a numerical example: if 1/5 of the patients in a study suffer a stroke, the odds of their having a stroke is (1/5) ÷ (4/5) or 0.20/0.80, or 0.25. As the denominator is the same in both top and bottom expressions, it cancels out, leaving the number of patients with the event (1) divided by the number of patients without the event (4).

The odds ratio is the odds of an event occurring in one group divided by the odds of the same event in another group. In the sheepskin trial, the odds ratio can be calculated by dividing the odds of getting an ulcer in the sheepskin group by the odds in the control group.

$$\left(\frac{21}{197}\right) \div \left(\frac{37}{186}\right) = 0.54$$

The odds were about 0.11 in the sheepskin group and 0.20 in the control group. This means that the odds of developing an ulcer in the sheepskin group were 0.54 of that in the control group. Put another way, patients with a sheepskin overlay were half as likely to develop ulcers as patients given usual treatment.

Odds ratio is similar to relative risk. In the sheepskin trial the relative risk was 0.58 and the odds ratio was 0.54. For most clinical trials where the event rate is low, that is less than 10%

Table 2

Relation between relative risk, absolute risk and odds ratio [2]

In an overview of randomised controlled trials of hypertension management, rates of stroke were measured in patients randomised to receive the experimental treatment or control. Results were analysed according to the severity of hypertension.

Disease severity	Event rate in control group (or AR)	Event rate in experimental group (or AR)	RR (RRR)	ARR	NNT	OR
Moderate hypertension	20%	12%	0.60 (0.40)	8%	13	0.54
Mild hypertension	1.5%	0.9%	0.60 (0.40)	0.6%	167	0.60

AR absolute risk
RR relative risk
RRR relative risk reduction
ARR absolute risk reduction
NNT number needed to treat to prevent one stroke
OR odds ratio

Table 3

Hazard ratio and time-to-event analysis [1]

In a randomised controlled trial, 441 patients assessed on admission as having low to moderate risk of developing pressure ulcers were randomised to receive a sheepskin mattress overlay for the duration of hospital stay or usual treatment (control group) as determined by ward staff. Patients were followed for up to 20 days after randomisation and assessed daily for the onset of pressure ulcers. The results were reported as follows:

	Sheepskin group	Control group
a. Total number of patients	218	223
b. Total number of bed days observed	1728	1561
c. Total number of ulcers	27	58
d. Number of patients with ulcer(s)	21	37
e. Mean bed days per patient	7.9	7.0
f. Cumulative incidence risk (95% CI)	9.6% (6.1%–14.3%)	16.6% (12.0%–22.1%)
g. Relative risk	0.58 (0.35–0.96)	1.0 (referent group)
h. Incidence rate per 100 bed days (95% CI)	1.6 (1.0–2.3)	3.7 (2.8–4.8)
i. Incidence rate ratio (95% CI)	0.42 (0.26–0.67)	1 (referent group)
j. Hazard ratio	0.39 (0.22–0.69)	1 (referent group)

CI confidence interval

Cumulative incidence risk (f) is the total number of patients who developed one or more ulcers (d)/number of patients for each group (a).

Relative risk (or risk ratio) (g) is the ratio of cumulative incidence risk (f) in sheepskin vs control group (9.6%/16.6% = 0.58).

Incidence rate (h) per 100 bed days is the total number of ulcers (c)/total number of bed days observed (b).

Incidence rate ratio (i) is the ratio of incidence rate per 100 bed days (h) in sheepskin vs control group (1.6/3.7 = 0.42).

Hazard ratio (j) is estimated using Cox proportional hazards regression applied to Kaplan-Meier time-to-event curves for ulcer-free survival (Fig. 1).

of all participants have an event, the odds ratio and relative risk can be considered interchangeable. The relative risk and odds ratio will also be closer together when the treatment effect is small (that is, odds ratio and relative risk are close to 1) than when treatment effect is large. However, as the event rate increases above 15% or as the treatment effect becomes huge, the odds ratio will progressively diverge from the relative risk.

Fortunately, this is rarely a problem. Consider a meta-analysis of ligation versus sclerotherapy for oesophageal varices, which demonstrated a re-bleeding rate of 47% with sclerotherapy, as high an event rate as one is likely to find in most trials.[3] The odds ratio associated with treatment with ligation was 0.52, a large effect. Despite the high event rate and large effect, the relative risk was 0.60, not very different from the odds ratio. Thus choosing one measure or the other is unlikely to have an important influence on most treatment decisions.

The odds ratio is gradually losing favour as a measure of treatment effect[4], particularly as data from which relative risk is derived can also be used to calculate absolute risk reduction and number needed to treat, which are more clinically useful.

Hazard ratio

Hazard ratio is a measure of relative risk over time in circumstances where we are interested not only in the total number of events, but in their timing as well. The event of interest may be death or it may be a non-fatal event such as readmission or symptom change.

Table 3 shows results of the study on pressure ulcers in hospitalised patients.[1] Results were expressed in several ways including:

- relative risk (row g), which is based on comparing the proportions of patients between groups who developed ulcers by study end (which the authors of the study termed cumulative incidence risk)
- incidence rate ratio (row i), which is a time-dependent relative risk comparing the rates of ulcers over time (in this case, per 100 bed days) between groups.

Note that the relative risk and the incidence rate ratio were different, 0.58 versus 0.42, with the time-dependent relative risk suggesting a greater benefit from intervention than the overall relative risk, and which is also fairly close to the estimated hazard ratio of 0.39 (row j).

In contrast to the overall relative risk, both the time-dependent relative risk and hazard ratio take into account the timing of events which may not be evenly distributed throughout the study period.

The hazard ratio equals a weighted relative risk over the entire

duration of a study and is derived from a time-to-event curve or Kaplan-Meier curve. This curve describes the status of both patient groups at different time points after a defined starting point. In the sheepskin study, events in the intervention group are not only less frequent overall than in the control group but they are delayed in time (Fig. 1). As some patients will be followed for a longer period of time than others (because they were recruited or randomised into the trial at an earlier time or because they remained in the study while others dropped out), the time-to-event curve usually extends beyond the mean follow-up duration.

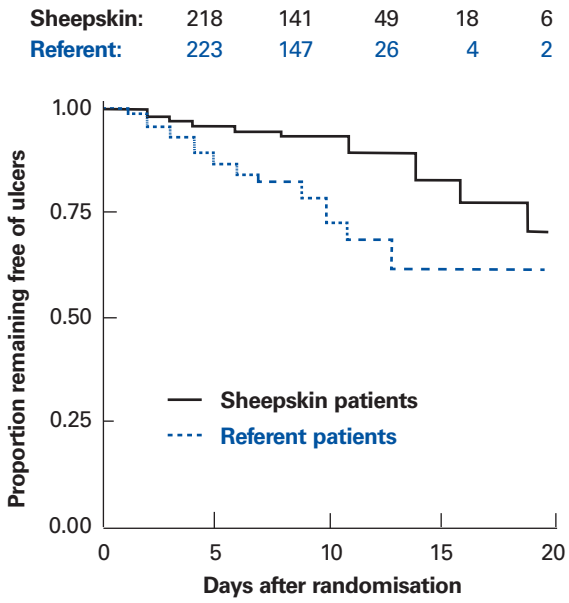
As the trial progresses, at some point prediction of treatment effect becomes very imprecise (in our example at 20 days) because there are few patients available to estimate the probability of the outcome of interest. Confidence intervals around the survival curves would capture the precision of the estimate. Ideally then, we would estimate relative risk by applying an average, weighted for the number of patients available, over the entire study duration. Statistical methods allow just such an estimate which is the hazard ratio.

This derived (or 'crude') hazard ratio then needs to be 'adjusted' or corrected for differences in the two groups at baseline that might influence the outcome of interest. This issue is less of a concern if randomisation has rendered both groups similar in terms of their baseline characteristics. In our example, patients in the intervention group compared to control were older (mean age 63.2 years vs 61.1 years), more acutely ill (51% were emergency admissions vs 43%), and had greater prevalence of medical, as opposed to surgical, diagnoses (35% vs 27%). Applying the Cox proportional hazards regression model produces an adjusted hazard ratio which takes account of such imbalances.

In every other way the hazard ratio is similar to odds ratio and relative risk wherein treatment efficacy is denoted by a hazard ratio of less than 1.0 in prevention trials and a hazard ratio of more than 1.0 in treatment trials.

Fig. 1

Kaplan-Meier curve for time to onset of first pressure ulcer *



* Jolley DJ et al. Preventing pressure ulcers with the Australian medical sheepskin: an open-label randomised controlled trial. MJA 2004;180:324–327. ©Copyright 2004. The Medical Journal of Australia – reproduced with permission.

Kaplan-Meier estimates show the time to onset of first pressure ulcer in 441 hospitalised patients at risk of developing pressure ulcers. Patients were randomised to receive either a sheepskin mattress overlay or usual treatment (referent group).

Predicting the effect of the sheepskin intervention becomes very imprecise as the number of patients in each group decreases with time.

Statistical significance

If there is a statistically significant difference in outcomes between treatment and control groups, the observed difference is very unlikely to have occurred due to the play of chance, even after accounting for imprecision in the difference related to the total number of events in both groups.

P values

Statistical significance is defined arbitrarily in terms of a p value of less than 0.05. The p value however does not directly indicate the chance of an effect being present or not being present. Instead it tells us how often chance alone would give apparently favourable results. A p value of less than 0.05 tells us that there is less than 5% probability that chance alone would lead to such favourable results, but it says nothing directly about whether chance is the best explanation for the results.

Confidence intervals

Confidence intervals give us an estimate of the precision of the results. Conventionally 95% confidence intervals are used which, if the same trial were to be repeated many times over, define the range of values within which the true estimate would be found in 95% of occasions. The confidence interval represents the range of values within which we are 95% confident that the true population estimate lies. If the number of events such as death occurring over time is fairly small (as occurs with small samples and/or low case fatality rate), then the precision with which the true probability of the event can be estimated is relatively low, as reflected in wider confidence intervals. Narrower confidence intervals indicate more precise results. The 95% confidence intervals represent almost two standard deviations around the mean.

It is important to remember that the result is statistically significant if the confidence intervals do not cross the null value, such as 1.0 for relative risk and 0 for absolute risk reduction.

Conclusion

An understanding of the commonly used statistical measures of benefit is necessary if clinicians are to gain an appreciation of the efficacy of different therapies. For the majority of clinical trials, relative risk and odds ratio can be considered interchangeable as a measure of the relative change in the risk of a preventable event. The hazard ratio is a related measure that weights the risk change according to when events occur over time. Absolute risk reduction represents the absolute change in risk (expressed in percentage points) and its reciprocal represents the number of patients who would need to be treated over a given period of time to prevent one event.

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Conflict of interest: none declared

On the correct use of eye drops

Michael Steiner, Eye Surgeon, Sydney

Summary

Drops are a common vehicle for administering drugs to the eye, but they must be instilled correctly. To limit wastage and systemic absorption a single drop should usually be prescribed. If the patient needs to use two types of drop their instillation should be separated by at least three minutes. Most eye drops contain a preservative, but they should not be kept beyond the expiry date on the label.

Key words: expiry dates, instillation, ophthalmic solutions.

(Aust Prescr 2008;31:16–17)

Introduction

Patients should be instructed on how to use their eye drops. They need to know about the frequency and the method of administration, and how the drops should be stored.

One drop or two?

Only one drop should be used at a time. A second drop may wash out the first or increase the possibility of systemic absorption and toxicity. A second drop can often end up on the skin of the eyelids and the patient is then more likely to develop a contact allergy. Using two drops also doubles the cost of the medication.

How often?

The type of drug and the patient's condition determine the frequency of instillation. In some serious infective or inflammatory conditions the drops may need to be used as frequently as half hourly (although generally only while the patient is awake). In contrast, the most commonly used treatments for glaucoma only need to be instilled once a day.

How to use eye drops

The method of instilling the drops is important. If it is not done properly, the drops have almost as much chance of landing on the cheek as in the eye.

It is important that patients wash their hands and remove any contact lenses before using the drops. Many eye drops contain the drug in suspension rather than in solution. These drops should always be shaken before use.

The cap should be removed from the bottle but never put down on the table in such a way that it may become contaminated. It should either be put on its side or held carefully in the other hand.

During instillation it is very important that patients do not touch their eye with the tip of the bottle. This could both abrade the cornea and contaminate the remaining drops.

In the traditional method of instilling drops (see Fig. 1) the bottle is held upside down in one hand between the thumb and index finger and with the other hand the lower eyelid is gently pulled

down to form a pouch. The head is tilted back, the patient looks up and, placing the tip of the bottle close to their lower eyelid, gently squeezes the bottle to release one drop into the pouch formed between the eye and lid.

An alternative technique (see Fig. 2) is for the patient to hold the bottle between the thumb and index finger of their dominant hand then rest their little finger below the lower lid and use it to pull the lid out and create a pocket. Then, tilting their head back, they look up and squeeze the bottle. It is almost impossible to miss as the tip of the bottle is within two or three centimetres of the eye.

After entering the eye the drop will pass through the nasolacrimal duct into the nasopharynx. In some cases the amount of systemic absorption can be significant, especially with the beta blocker eye drops used for glaucoma. After the drop is instilled the patient should therefore close their eyes and place their index fingers against the inner corner of the eyes, pressing against the nose for one or two minutes. This punctal pressure will reduce the amount of drug that reaches the nasopharynx and thus reduce any systemic absorption.

Only one drop should be used at a time

If the patient is instilling more than one medication they should wait at least three minutes before putting in the next medication. Generally, they should wait at least 15 minutes before inserting contact lenses if they are worn.

Storage

Eye drops should generally be stored in a cool dry place and for some drugs, especially chloramphenicol, the most commonly used ocular antibiotic in Australia, it is preferable to keep the bottle in the fridge.

Patients should not keep their eye drops beyond the printed expiry date. The current policy is that once eye drops have been opened they should be disposed of after 28 days. This is based on research from earlier times when drops were dispensed in glass bottles with glass pipettes, and many eye drops did not contain preservatives. To my knowledge none of this research is current, using modern dropper-type bottles. This policy seems a terrible waste and causes increased expense to the patients and the health system.

Although evidence is needed to support the practice, some ophthalmologists allow patients who are using drops regularly to keep the bottle for up to two months (although most of them run out after about six weeks). Of course when patients have drops that they use only from time to time, such as artificial tears or other drops used purely for comfort, then these drops should not be kept long term as the risk of contamination may then be significant.

Patients who develop an allergy or other reaction to the preservative in eye drops may need to use a formulation without a preservative. Many eye drops are also available in this form in single-use disposable containers.

Safety

Patients should check the label every time they use their eye drops. Unfortunately, there are some glues and hardeners which are sold in bottles very similar to eye drops. Many doctors have seen patients who have accidentally used these drops in their eye, often with significant resulting morbidity.

Conflict of interest: none declared

Fig. 1

'Traditional' method of instilling eye drops

Fig. 2

'One-handed' method of instilling eye drops

Diagnostic tests

Emerging indications for magnetic resonance imaging in neuroradiology

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Summary

When imaging is needed to investigate a patient's neurological problem, computerised tomography is the initial modality to use. Magnetic resonance imaging is increasingly used, but like the other imaging modalities it has strengths and weaknesses that need to be understood if it is to be used efficiently. The main strength of magnetic resonance imaging is its inherently superior soft tissue contrast because of its ability to image many different tissue characteristics. The emerging indications in neurology are based on imaging additional tissue characteristics.

Key words: angiography, multiple sclerosis, stroke.

(Aust Prescr 2008;31:18–20)

Introduction

The role of medical imaging is to maximise the conspicuousness of a disease process, in contrast to the normal background anatomy. To accomplish this most imaging modalities measure, at most, only one or perhaps two tissue characteristics, for example the reflectivity of sound in ultrasound scans or the absorption of X-rays in radiography or CT scanning. Magnetic resonance imaging (MRI) is unique in its ability to image many different tissue characteristics.

Mechanisms of MRI

Originally, magnetic resonance was developed as a biochemical technique. It was used to differentiate the chemical bonds occurring in pure samples of compounds studied *in vitro*. It was found that it was possible to align the hydrogen nuclei contained in organic compounds in a strong magnetic field. Under these conditions the nuclei would absorb and then retransmit radio waves with the frequencies and time constants of these transmissions depending on the differing elements that the hydrogen was bonded to. In order to scale up this technique to image whole patients, rather than just biochemical samples in test tubes, many technical difficulties had to be overcome, however, the underlying biochemical nature of MRI remains.

The signal from the hydrogen incorporated into long carbon chains and other groups is the basis for T1 imaging. This is effectively a map of the position of fat and protein in an organ so T1 imaging provides information about the structural components of an organ and is used to show structural changes. T2 imaging obtains its signal predominantly from the hydrogen in water. T2 images tend to show pathology to the greatest advantage because most pathological processes (for example trauma, infarction or neoplasia) involve an inflammatory reaction with oedema (increased water content).

The original tissue characteristics have now been expanded. New techniques have the ability to image:

- capillary disruption and leakage using MRI contrast materials
- moving fluids (as used in MRI angiography and flow quantification)
- water diffusion across cell membranes (used in diffusion imaging in acute stroke as well as to define white matter tracts)
- frequency shifts in various metabolites (magnetic resonance spectroscopy and fat saturated imaging)
- oxygen concentration of the haemoglobin molecule (used for brain activation and functional MRI).

Strengths and weaknesses of MRI

The main strength of MRI is its ability to delineate soft tissues throughout the body. Other benefits are the lack of ionising radiation and the multi-planar capabilities of MRI. However, MRI does have some weaknesses. Tissues which have a limited hydrogen content, for example cortical bone, produce no signal and so cortical fractures are better imaged with X-rays. Air and soft tissue interfaces produce artefacts which degrade the signal so the lung parenchyma is also not routinely imaged with MRI.

There are some contraindications to MRI. Strong magnetic fields and rapidly changing magnetic gradients produce movement in ferrous metallic materials and can heat up and induce currents in metallic wires and foreign bodies. Patients with metallic foreign bodies of unknown composition, for example bullet fragments or older iatrogenic implants such as aneurysm clips, heart valves and prostheses, should not have MRI. Newer

prostheses are usually manufactured to be MRI compatible, but pacemakers, implanted defibrillators, cochlear implants and nerve stimulators are all absolute contraindications. Satisfactory images can usually be obtained without contrast media, but if it is considered, there may be a risk of harm in patients with impaired renal function.

Neuroimaging

For many years MRI has been a mainstay of neurological imaging. It is often important to define the site and size of brain lesions which may be very small or subtle on CT. The eloquent* nature and specificity of function of many neural structures means that a 5 mm infarct in the brainstem may be of much more importance than a similar lesion elsewhere in the body.

Stroke

In recent years it has been recognised that a stroke is not an 'all or none' phenomenon and that there is some scope for reversing the damage.[1] When a vessel, such as the middle cerebral artery, is acutely occluded, there is cell death in the infarct core within minutes. However, there remains a region of tissue surrounding the core where blood flow from collaterals can maintain the neurons for some time (typically 3–6 hours). These so-called penumbral areas are often of considerable size and it is now known that if the blood flow can be reinstated then this tissue can be saved. The previous nihilism surrounding acute stroke medicine has now changed with the advent of magnetic resonance diffusion/perfusion imaging.

Diffusion imaging is designed to define the infarcted and non-treatable core region. This technique measures the rate of water flow across a cell membrane. Dead cells do not maintain their water and solute pumps and dead tissue can be defined within a few minutes of infarction (it typically takes 1–2 days for infarcted tissue to be defined by CT).[2]

Perfusion imaging uses a bolus of MRI contrast material, which is tracked at one second intervals across the entire brain volume to detect the poorly perfused penumbra surrounding the core. The penumbra has a reduced and delayed perfusion pattern. The relative size of the core and the penumbra is the information required by a neurologist to make a decision as to whether a thrombolytic drug should be given.

Diseases of white matter

Diffusion and perfusion studies are aimed predominantly at grey matter disease, but an offshoot of diffusion imaging also allows a more comprehensive investigation of the white matter.[3]

Myelin is the lipid insulator surrounding the axons making up the white matter tracts and because water can diffuse along an axon much easier than across the myelin sheath, there is a difference in the diffusion signal along an axonal tract compared to across it. This difference in the diffusion signal along the fibres compared to across them is the so-called fractional anisotropy. Imaging using this technique is beginning to find uses in defining axonal damage in white matter diseases (such as multiple sclerosis) where the changes in the water diffusion are apparent much earlier than with the traditional imaging. It is also sometimes important to know the exact position of a white matter tract, for example a tract adjacent to a brain tumour, as resection of vital tracts, such as the corticospinal tract, can be avoided if they can be visualised despite being displaced or obscured by oedema.

Functional MRI

The scanner has the ability to detect differences in the signal produced by haemoglobin molecules depending on their state of oxygenation. The blood in the capillary bed in areas of the brain which are actively processing information has a different amount of oxygenated versus deoxygenated haemoglobin compared to the background areas.[4] These differences can be detected and maps of brain activation during tasks such as reading, talking or practically any mental activity can be provided. This is a valuable research tool.

Clinical indications are emerging for this technique. These include mapping brain functions (for example where surgery will possibly disrupt an eloquent structure) to minimise functional loss and it has applications in surgery for epilepsy. There is early research to suggest that functional MRI could have a role after a stroke to try and predict the improvement a patient may expect from rehabilitation.

Angiography

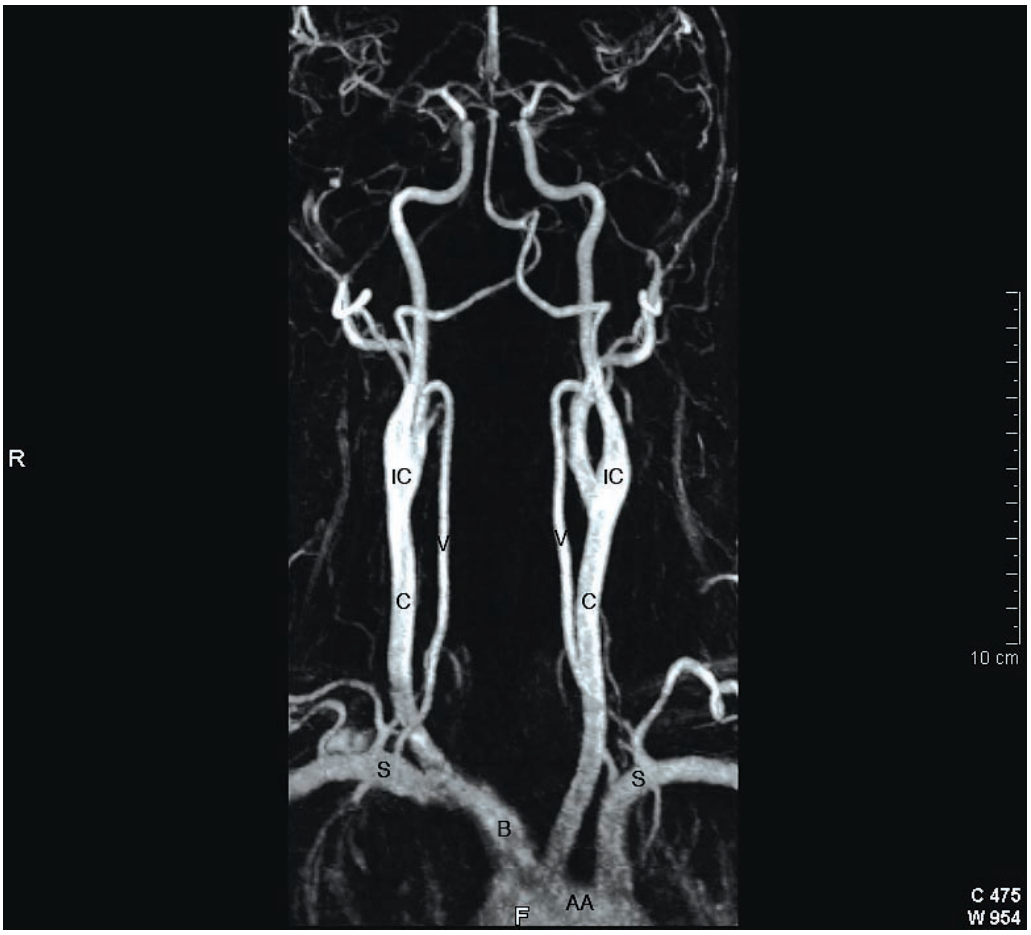
Many techniques are available to image the arterial tree. While ultrasound can provide information about superficial arteries, it is very operator dependent and time consuming. Multi-detector CT can quickly image large areas of the vascular tree, but artefacts from calcified plaque in the walls of arteries and the large contrast boluses required remain significant limitations.

MRI has long been able to image arterial or venous structures in a specified region (for example the head or neck) using only the inherent signal changes brought about by the flowing blood. Newer techniques utilising boluses of 10–20 mL of contrast can image much larger regions (even total body angiography is possible with this technique). The practical uses in neuroradiology of this technique, however, are to provide a review of the entire arterial tree supplying the brain from the aortic arch to the cortical branches, as part of a comprehensive

* The term 'eloquent' describes how essential a portion of brain is to normal activities. The eloquent areas of the brain are so specialised that their functions are very difficult to transfer and so damage to these areas leads to permanent loss of function.

Fig. 1

A contrast-enhanced magnetic resonance angiogram of the arterial supply to the brain



AA aortic arch
B brachiocephalic artery
C common carotid arteries
IC internal carotid arteries
S subclavian arteries
V vertebral arteries

The internal carotid arteries branch within the brain (at the top of the figure) to supply blood to the anterior and middle cerebral arteries. The two vertebral arteries join to form the basilar artery in the midline.

investigation which replaces several separate tests with a single examination (Fig. 1).

Conclusion

The role of MRI in neuroimaging continues to expand. The ability of MRI to image many differing tissue characteristics and the continued research into new applications means that MRI will continue to evolve at a rapid rate.

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Conflict of interest: none declared

Self-test questions

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

5. Following a stroke it takes 1–2 days for the lesion to be detected by MRI.
6. Cochlear implants are a contraindication to MRI.

Medicinal mishap

Cabergoline-induced valvulopathy

Prepared by Simone Headrick, Neurology Advanced Trainee, Department of Neurology, Royal Brisbane Hospital; Michael Adsett, Consultant Cardiologist, Queensland Cardiovascular Group; and Cecilie Lander, Consultant Neurologist, Department of Neurology, Royal Brisbane Hospital, Brisbane

Case

A 36-year-old female, who had been taking low-dose cabergoline for incapacitating restless legs syndrome, presented with symptoms that she ascribed to increasing restless legs syndrome. For more than two months she had complained about increasing ankle swelling, abdominal discomfort and worsening leg discomfort.

She had been prescribed cabergoline five years earlier because other treatments had not helped her restless legs. Biperiden helped slightly but for a limited time, while levodopa/benserazide (up to 600 mg/150 mg per day) helped considerably until a rebound effect occurred. She had been prescribed 0.5 mg cabergoline daily and told about possible fibrotic reactions. The symptomatic response was excellent, but she had gradually required an increase in the dose to 2 mg daily in order to achieve relief. The woman did not return for neurological review and also changed her general practitioner.

On examination she had a regular pulse of 70 beats per minute. Her blood pressure was 140/85 mmHg and her jugular venous pressure was elevated with prominent V-waves. Heart sounds were dual with ejection and early diastolic murmurs. Her liver edge was pulsatile and there was severe pitting oedema to her mid calves. These clinical findings were suggestive of right heart failure.

ECG showed sinus rhythm and an incomplete right bundle branch block. There was some T wave inversion over the right precordial leads.

A chest X-ray showed borderline cardiomegaly with clear lung fields. There was no evidence of interstitial oedema or fibrosis or pleural effusions. Blood tests were normal.

Echocardiography showed severe (grade 4/4) tricuspid regurgitation, moderate aortic stenosis with moderate regurgitation, mild pulmonary stenosis, mild mitral stenosis and regurgitation.

Cabergoline was ceased. Frusemide and spironolactone produced a diuresis with a 5 kg reduction in weight. There was an excellent clinical response to this diuretic regimen and echocardiographic surveillance will be maintained. There may yet be a requirement for corrective surgery.

Comment

Ergot-derived dopamine agonists, such as pergolide and cabergoline, are used in the treatment of Parkinson's disease. Although the indications may not be approved, lower doses are used for restless legs syndrome and hyperprolactinaemia.

Pulmonary fibrosis is a recognised, if uncommon, complication of these drugs.[1] Two recently published studies[2,3] have found increased frequencies of significant cardiac valvulopathy in patients taking the ergot-derived dopamine receptor agonists pergolide and cabergoline. The excess risk was 33 cases per 10 000 patients per year with pergolide and 21 cases per 10 000 patients per year with cabergoline.[3] Pergolide has now been withdrawn from the market in the USA.

Pergolide and cabergoline are agonists of the 5-HT_{2B} receptor found on heart valves. This could cause valvular hyperplasia. Fenfluramine, ergotamine and methysergide have all been reported to cause cardiac valvulopathy, probably by similar mechanisms.

Conclusion

This case shows severe multi-valvular pathology probably as a result of cabergoline. Prescribers need to be aware of the risk of cardiac valvulopathy associated with the use of ergot-derived dopamine agonists. Patients should be warned about the potential adverse events, particularly if the drugs are prescribed for 'off-label' indications. They must be advised to report any unusual symptoms and to have regular clinical reviews to look for possible fibrotic complications. Baseline and periodic echocardiography may be needed.

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Conflict of interest: none declared

Neurocognitive effects of chemotherapy in adults

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Summary

A subset of patients complain that their memory and concentration is not as sharp after receiving treatment for solid tumours. This problem persists in some patients, but there is no correlation between self-reported impairment and cognitive impairment detected on formal neuropsychological testing. Self-reported cognitive impairment is strongly associated with fatigue, anxiety and depression, but these symptoms are not correlated with objective impairment. Cross-sectional studies found that 15–50% of oncology patients have impairment after chemotherapy, with prospective studies reporting that up to 30% of patients have cognitive impairment before chemotherapy. Apart from the treatment of anxiety and depression, there is no proven intervention to prevent long-term impairment or to treat it once it has occurred.

Key words: cancer, cognitive impairment.

(Aust Prescr 2008;31:22–4)

Introduction

There is growing evidence that a subset of people who survive cancer suffer cognitive impairment after chemotherapy.[1,2,3,4,5,6] Survivors have coined the terms 'chemobrain' and 'chemofog' to describe this symptom, although recent studies have found that some patients' cognitive impairment may predate the chemotherapy[7], and hormonal treatment for cancer may also impact on cognitive function.[6,8] Fortunately, the problem is generally subtle and often improves after ceasing chemotherapy. However, for some survivors the symptoms are sustained and can impact significantly on their quality of life and ability to function in their everyday activities.[5]

Overview of the literature

Most of the cognitive research has been in breast cancer survivors although there are currently ongoing studies investigating cognitive function in patients with colorectal, testicular and prostate cancer. Studies have reported a 15–50% incidence of cognitive impairment in patients who received chemotherapy for solid tumours.[1,2,3,4,5] The studies were mainly cross-sectional in design with no evaluation of cognitive function before treatment and no longitudinal data. Comparison between studies is hampered by lack of clear definition of cognitive impairment and standardisation of neuropsychological tests used. Despite methodological problems and small sample size, the studies consistently showed a sub-group of people who suffered subtle cognitive impairment, with diffuse yet patchy deficits after chemotherapy. The cognitive domains most consistently impaired were attention, concentration, verbal and visual memory and processing speed.[1,2,3]

A lack of assessment before chemotherapy means that patients who have been functioning at a very high level may have a substantial decline in cognitive function but still formally test within normal limits, so that the true degree of their cognitive decline is not realised. Conversely, cognitive impairment that may have been present before treatment may be incorrectly attributed to chemotherapy.

Longitudinal studies with baseline cognitive assessments have been published in the last few years. These have reported that up to 30% of patients with solid tumours may have cognitive impairment before receiving chemotherapy.[9,10,11]

Self-reported impairment

Multiple studies have reported no significant association between cognitive impairment after chemotherapy on formal cognitive testing and patients' self-report of their cognitive function. The patient's perception of cognitive impairment is generally worse than that detected by objective assessment.[1,2,3,5,6] The literature indicates consistently that there is a strong association between self-reported cognitive impairment and fatigue, anxiety and depression.[2,6,11] However, no association has been found between these symptoms and objective cognitive impairment.[1,2,3,4,6,9,11] Regardless of the reason for the dissociation between self-reported cognitive impairment and cognitive impairment detected on formal neuropsychological tests, any impairment can cause substantial distress.[5]

Potential mechanisms

The cause of cognitive impairment in cancer patients after chemotherapy is unknown, but is likely to be multifactorial. Possible mechanisms by which chemotherapy might lead to cognitive dysfunction include:

- direct neurotoxic effects
- oxidative damage

- induced hormonal changes
- immune deregulation with release of cytokines
- blood clotting in small vessels of the central nervous system.

Some patients may have a genetic predisposition to developing cognitive impairment (for example, due to problems with DNA or neuronal repair, changes in neurotransmitter activity or apolipoprotein ε4 genotype).[12] Preliminary results of two studies suggest that elevated cytokines may be associated with increased cognitive dysfunction and fatigue.

Chemotherapy regimen and dose-related toxicity

It is likely that the regimen, the dose and the duration of chemotherapy influence the incidence and severity of cognitive impairment.[12] The different regimens may account for the varying rates of incidence reported in the published studies. In particular, objective rates of impairment have been higher following treatment with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) than after anthracycline-containing regimens in which methotrexate is generally replaced by doxorubicin or epirubicin.

Studies comparing high-dose chemotherapy for breast cancer with standard-dose chemotherapy or no chemotherapy have generally found higher rates of cognitive dysfunction in patients who received high doses. One breast cancer study reported cognitive impairment in 32% of patients after high-dose chemotherapy, 17% after standard doses and in 9% of those who did not have chemotherapy. The odds ratio of cognitive impairment was 8.2 for high-dose chemotherapy when compared with local cancer treatment alone and 3.5 when compared with standard-dose chemotherapy.[2] However, another study found no significant difference between high-dose and standard-dose chemotherapy.[13]

Duration of impairment

The duration of cognitive impairment after anticancer treatment is uncertain. One study of breast cancer and lymphoma found more cognitive dysfunction in patients up to 10 years after chemotherapy, compared to patients who had surgery or radiotherapy without chemotherapy.[1] A Dutch study reported impairment in breast cancer patients at a median of 1.9 years after chemotherapy[3], but no difference between groups four years after treatment.[14] Longer-term follow-up of longitudinal studies is required to determine the duration of impairment.

Treatment of cognitive impairment after chemotherapy

There are no proven interventions to prevent chemotherapy-associated cognitive impairment or to treat it once it has developed. Randomised controlled trials have investigated the use of prophylactic erythropoietin and methylphenidate, however all trials were essentially negative. Other small intervention studies are ongoing, but it is difficult to design an intervention until we have a better understanding of mechanisms. At present the mainstay of treatment for patients with self-reported cognitive impairment is to treat any existing depression and anxiety.

Although there is no published research of cognitive rehabilitation programs in cancer survivors, cognitive rehabilitation has been shown to be effective in treating other patient groups with cognitive impairment.[15,16] Different interventions have been developed, but the majority of methods focus on either restoration of a specific cognitive function (for example, attention training) or compensatory training to help patients adapt to the presence of deficits, rather than trying to treat the underlying deficit.[16] A small interim analysis of a behaviour therapy program has shown some potential benefit, however further results are awaited.

Conclusion

Approximately a third of cancer patients have cognitive impairment before receiving chemotherapy and possibly 20–30% have cognitive impairment after chemotherapy. The underlying mechanism of the impairment is currently unknown. Once we have insight into the mechanisms that might cause cognitive impairment, strategies for preventing or minimising chemotherapy-induced cognitive impairment can be devised.

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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 27)

7. The cognitive impairment reported by some patients after chemotherapy may be caused by depression.
8. Erythropoietin prevents the cognitive impairment associated with chemotherapy.

New drugs

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

Nitric oxide

INOmax (Delpharm)

2 and 10 litre gas cylinders containing 800 parts per million

Approved indication: neonatal respiratory failure

Australian Medicines Handbook Appendix A

Nitric oxide has a physiological role in several systems of the body. One of its actions is to cause vasodilation. When it is administered as a gas it dilates the vessels in the lung. There is little effect on the systemic circulation as nitric oxide is inactivated when it binds to oxyhaemoglobin. This has led to the study of inhaled nitric oxide in conditions where there is pulmonary vasoconstriction.

Pulmonary hypertension can cause hypoxic respiratory failure in neonates. The pulmonary vascular resistance causes deoxygenated blood to be shunted from the right to the left heart through the foramen ovale. In severe cases extracorporeal membrane oxygenation is needed, but this procedure is very specialised and mortality remains high. If nitric oxide can reduce the pulmonary hypertension it could reduce the need for extracorporeal membrane oxygenation.

The Neonatal Inhaled Nitric Oxide Study (NINOS) involved 235 babies, of at least 34 weeks gestation, who needed ventilation for hypoxic respiratory failure. In about half the cases this resulted from meconium aspiration while 16–18% of the babies had persistent pulmonary hypertension of the newborn. There was a significantly greater improvement in the oxygenation of the babies randomised to receive nitric oxide. Extracorporeal membrane oxygenation was needed by 39% compared with 55% of a control group who received 100% oxygen.[1]

Another study randomised 58 full-term neonates with persistent pulmonary hypertension of the newborn, confirmed by echocardiography, to receive either nitric oxide or nitrogen. Extracorporeal membrane oxygenation was needed by 12 of the 30 babies given nitric oxide and by 20 of the 28 babies in the control group.[2]

The Clinical Inhaled Nitric Oxide Research Group studied 248 babies, born after 34 weeks gestation, who had clinical or echocardiographic evidence of pulmonary hypertension. Extracorporeal membrane oxygenation was needed by 38% of the babies given low-dose nitric oxide and 64% of the control group. The median duration of successful treatment was 44 hours.[3]

Nitric oxide should not be used if the baby is dependent on a right to left shunt. It should also not be stopped suddenly as the pulmonary artery pressure may rebound, reducing oxygenation.

A complication of ventilating patients with nitric oxide is the formation of methaemoglobin. As neonates have a limited amount of methaemoglobin reductase they need to be monitored to avoid methaemoglobinaemia. Some of the toxicity of nitric oxide may be the result of oxidation to nitrogen dioxide. Monitoring is needed to ensure that nitrogen dioxide concentrations are minimised.

Adverse events are common in sick neonates. Those reported in trials of nitric oxide include hypotension, haematuria, infection and atelectasis. Hypokalaemia and thrombocytopenia occur frequently.

While nitric oxide may spare babies from extracorporeal membrane oxygenation it does not improve their survival. In NINOS 14% of the nitric oxide group and 16% of the control group died.[1] With low doses the mortality in the first 30 days of life was 7% with nitric oxide and 8% in the control group.[3]

A Cochrane review has evaluated the evidence for giving nitric oxide for respiratory failure in infants born at or near term. It found that nitric oxide improves oxygenation in approximately 50% of cases. A combined end point including extracorporeal membrane oxygenation and death was less frequent with treatment, but this was mainly accounted for by a reduced need for extracorporeal membrane oxygenation. Babies with diaphragmatic hernias did not benefit.[4]

Nitric oxide is only approved for babies over 34 weeks gestation. Trials in preterm babies have not shown a clear benefit and in this group nitric oxide has been described as a therapy in search of an indication.[5]

T manufacturer provided only the product information

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Varenicline tartrate

Champix (Pfizer)

0.5 mg and 1 mg film-coated tablets

Approved indication: smoking cessation

Australian Medicines Handbook section 18.7

Smoking is addictive. Although many smokers try to stop, very few succeed without assistance. Some people need nicotine replacement therapy or bupropion to help them quit.[1]

Varenicline is a drug which binds to nicotinic receptors. It is a partial agonist so it provides some stimulation at the receptor, but also blocks nicotine. These actions may help to reduce withdrawal symptoms and the craving smokers have for nicotine.

Once someone has committed to stop smoking, they begin varenicline one or two weeks before the date they have set to quit. They gradually increase the dose from 0.5 mg daily to 1 mg twice daily which they continue until the end of the 12-week period of treatment.

The tablets are well absorbed and undergo little metabolism. Most of the dose is excreted in the urine with an elimination half-life of approximately 24 hours.

Varenicline has been compared with placebo and bupropion. In one trial, which randomised 1025 people, 44% of those given varenicline had stopped smoking by the end of the 12-week treatment period. This was significantly better than the 30% of the bupropion group and the 18% of the placebo group who stopped smoking. The patients were followed for a further 40 weeks. At the end of the year, the continuous abstinence rates were 22% for varenicline, 16% for bupropion and 8% for placebo.[2]

Using the same design, another trial randomised 1027 smokers. In the last month of treatment (weeks 9–12 of the study) 44% of the varenicline group, 30% of the bupropion group and 18% of the placebo group were no longer smoking. When followed up at 52 weeks the continuous abstinence rate was 23% with varenicline, 15% with bupropion and 10% with placebo.[3]

Many of the people who restarted smoking resumed soon after stopping treatment. Another trial therefore investigated if abstinence rates could be improved by a longer duration of treatment. People who had stopped smoking after a 12-week course were randomised to continue varenicline for another 12 weeks or take a placebo. During this maintenance phase 71% of the varenicline group did not smoke compared with 50% of the placebo group. After a year the rates were 44% and 37%.[4]

Many people dropped out of the smoking cessation trials.[2,3] In the varenicline group 4–9% of people discontinued because of adverse effects. Nausea is the most common problem, affecting approximately 30% of those taking varenicline compared to approximately 10% of the placebo group. Other adverse effects which occurred more frequently with varenicline than placebo included vomiting, constipation, abnormal dreams and insomnia. Patients who cannot tolerate these adverse effects could try a reduced dose. It is not known if the elderly are more prone to adverse effects as few people over 65 years old were included in the trials of varenicline. It is not recommended for people under 18 years old. Following the marketing of varenicline in the USA, there have been reports of patients experiencing suicidal thoughts and aggressive and erratic behaviour.

Varenicline does not prevent the weight gain associated with stopping smoking. After 12 weeks of treatment, patients taking varenicline gained 2–3 kg.[2,3] The safety of varenicline in pregnancy and breastfeeding is unknown.

All the participants had weekly counselling[2,3] so it may not be possible to achieve the same results in routine practice. Although varenicline achieved higher rates of abstinence than bupropion, the difference was not statistically significant in the long term. There do not appear to be any published comparisons of varenicline and nicotine replacement therapy.

T T T manufacturer provided clinical evaluation

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Zoster virus vaccine

Zostavax (Merck Sharp & Dohme)

vials containing lyophilised virus for reconstitution

Approved indication: prevention of herpes zoster infection

Australian Medicines Handbook section 20.1

Herpes zoster (shingles) results from a reactivation of varicella zoster virus, which primarily causes chickenpox. Shingles is characterised by a painful blistering skin rash. Over half of all cases involve people over 60 years of age as viral reactivation is associated with waning cellular immunity.

Complications associated with herpes zoster are common. From June 1999 to July 2000, there were 1918 admissions to Australian hospitals due to herpes zoster; 1142 of these patients had complications.[1] The most frequent complication is postherpetic neuralgia, a painful condition which can persist for years and diminish the quality of life.

The vaccine, which has been registered in Australia, is a live attenuated strain of varicella zoster virus. It is to be given as a single subcutaneous dose.

The safety and efficacy of the vaccine have been assessed in a single placebo-controlled trial of 36 716 adults aged 60 years or older in the USA. Most of the participants (95%) were actively followed for three years after vaccination for signs of herpes zoster. There were 642 confirmed cases of herpes zoster in 18 357 control patients compared with only 315 confirmed cases in 18 359 vaccinated patients. The median duration of pain was 21 days in the vaccine group compared with 24 days in the control group. Similarly, the severity of disease was less in the vaccine group compared to the control group. There were 107 cases of postherpetic neuralgia; 27 in the vaccine group and 80 in the placebo group.[2]

The numbers of deaths and serious adverse events were similar in the vaccine and control groups. Safety was more closely monitored for 42 days following injection in a sub-group of 6616 people. In the vaccine group, 1604 people (48%) had at least one adverse event at the injection site compared with 539 people (16%) in the placebo group. Systemic adverse events related to the intervention were more frequently reported by vaccinated individuals than by people who received the placebo (209 vs 160).[2]

People for whom the vaccine is not recommended include:

- immunodeficient patients or patients on immunosuppressive therapy, such as high-dose corticosteroids
- patients with a history of anaphylaxis to neomycin
- patients with untreated tuberculosis.

There is a theoretical risk that the vaccine virus could be transmitted from a vaccinated person, who has developed a varicella-like rash, to a susceptible contact.

Although this vaccine will decrease the incidence of herpes zoster, its efficacy is only around 51%. Its duration of protection beyond four years is unknown, so it is unclear if people will need to be revaccinated.

Most of the efficacy data for this vaccine are from people aged 60 years or over. However, the vaccine has also been approved for individuals aged 50–59 based on immunogenicity data alone.

T manufacturer provided only the product information

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The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2007;30:26–7.

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

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

Answers to self-test questions

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

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