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EDITORIAL

Quality use of medicines: ten years down the track

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Index words: drug utilisation, drug regulation.

(Aust Prescr 2001;24:106–7)

1991 was a significant year for medicines in Australia. The Baume Report was released foreshadowing major reform of the Therapeutic Goods Administration, with the expectation that the Australian market would have more timely access to new drugs of proven quality, safety and efficacy.[1]

Consumer groups were lobbying for improvements in the way medicines were prescribed, dispensed and used. In April 1991 the Consumers' Health Forum and the Australasian Society of Experimental and Clinical Pharmacologists and Toxicologists came together in a landmark workshop. 'Rational Prescribing: the challenge for medical educators' aimed to raise awareness of prescribing issues and was supported by the government of the day.[2]

In response, the Commonwealth Government established two advisory groups. Pharmaceutical education was the initial focus of the Pharmaceutical Health and Rational use of Medicines (PHARM) Working Party. This group went on to formulate the policy on the Quality Use of Medicines (QUM) in 1992.[3] To advise on policy and implementation, the Australian Pharmaceutical Advisory Council (APAC) was set up, representing the full range of professional and community organisations and the relevant parts of government.

The QUM policy went beyond rational prescribing to enshrine the goal of partnership between government, industry, consumers and the health professions. QUM became the fourth arm of a national medicinal drug policy, integrally linked to the other arms: timely availability of drugs through the Therapeutic Goods Administration, equity of access to drugs through the Pharmaceutical and Repatriation Benefits Schemes and a viable pharmaceutical industry through the Industry portfolio. By 2000, the revised policy had achieved bipartisan support at Commonwealth level. The new Australian Medicines Policy includes the non-prescription (self-medication) and complementary medicines industries.[4]

The Baume Report set out timelines for Consumer Medicine Information (CMI) to be produced for all drugs. Perhaps the first achievement of the new partnership under QUM policy was that consumers worked with government and the pharmaceutical industry to produce CMI leaflets. A decade later, CMI can be accessed by community and hospital pharmacies to print out at the time of dispensing. Use of the CMI by general practitioners is minimal but in the future the Royal Australian College of General Practitioners' web site will provide access to standard CMI.

Waste, hoarding, inappropriate demand and poor adherence to medicines regimens were all identified by the policy document as barriers to QUM. The government has funded many local projects* as well as successive national media campaigns to spread the catch cry of 'using medicines wisely' and the need for 'medicine check-ups'. National guidelines have been produced for medication management in aged care facilities and on hospital discharge. The National Medicines Disposal Program has also been put in place.

Gathering evidence from research was a key strategy for the new policy. By 1997, Australian trials funded by the QUM initiative had shown that effective educational techniques could influence general practitioner prescribing. A Cochrane review confirmed the importance of a social marketing approach, rather than one-off interventions.[5]

Evidence is one thing, putting it into practice is another. The original report of the PHARM Working Party recommended a national centre to co-ordinate quality use of medicines activity, to be set up outside government. Under the QUM

* See http://www.qummap.health.gov.au

In this issue

Ten years ago the Baume review set out to speed up the entry of new drugs into Australia. The new drug imatinib on page 129 is an example of a drug which has come quickly to the market because of a rapid evaluation. It is now also easier to market combination products, but Robert Moulds reminds us that these combinations do have some disadvantages.

The rapid approval of new drugs also means that their role in therapy may be unclear. Peteris Darzins shows us that the literature is not always helpful.

Government commitment to the quality use of medicines came at the same time as the Baume report. Andrea Mant reviews how this policy has developed over the past decade.

While there have been many changes in therapeutics these have been supported by changes in laboratory medicine. Don Bowden comments on the developments in testing for thalassaemia in the Australian population.

policy, PHARM undertook extensive consultation with general practitioners and other stakeholders. By March 1998, persistent and persuasive pressure led to the establishment of the National Prescribing Service (NPS), funded through the federal budget but with an independent board and constitution. The NPS has vigorously set about working with divisions of general practice (it has contracts with two-thirds of them) and has established its credentials through programs to support quality prescribing and use of medicines. The NPS has also pursued some long-hoped for initiatives to promote the quality use of medicines such as a national Therapeutic Advice and Information Service for health professionals. A nationwide Consumer Medicine Information Service is also close to being established.

An important part of the QUM policy is the production of professional drug information independent of industry sponsorship. Financial support was given to a joint venture to produce the *Australian Medicines Handbook* (www.amh.net.au). This reference, covering all pharmaceuticals marketed in Australia, has filled an essential gap. It complements *Australian Prescriber*, the national journal of therapeutics, and the *Therapeutic Guidelines* (www.tg.com.au) series. We are fortunate indeed in having these excellent resources. Finding time to use them, in a busy workplace, remains an issue, although information technology now makes them more readily accessible.

Ten years on, information technology has a greater role in encouraging the quality use of medicines in primary care through the use of electronic medical records and prescribing systems. An important step came earlier this year, with the requirement that the patient's Medicare number be recorded when a prescription is dispensed. Setting up electronic systems and solving the problems associated with them will take much energy in the next few years. It will take time before anticipated benefits flow.

What of the future? Continuation of government funding for the NPS promises that the social marketing of quality initiatives can be consolidated. A new prescribing course for medical schools developed by the NPS and universities is close to completion and will start to have an impact. QUM in pharmacy education will surely spread more widely. Collaboration between patients, pharmacists and doctors to manage multiple medication use is just beginning. In the information age, consumers and professionals already have access to more information and more marketing and promotion than ever before – will this lead to better health outcomes or just quality use of more medicines? A key research question will be to test whether better use of medicines achieves better health outcomes.

Partnership is at the heart of QUM and is likely to come under strain as society counts the cost of new and more expensive drugs. Looking back to see how much has been achieved encourages us to keep working at that partnership so as to minimise the harm and maximise the benefits from the use of pharmaceuticals. Much is at stake.

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REFERENCES

1. Baume P. A question of balance: report on the future of drug evaluation in Australia. Canberra: Australian Government Publishing Service; 1991.
2. Snell B, editor. Rational prescribing: the challenge for medical educators. Aust Prescr 1991;14 Suppl 1.
3. Commonwealth Department of Health, Housing and Community Services. A policy on the quality use of medicines. Canberra: Commonwealth Department of Health, Housing and Community Services; 1992.
4. National Medicines Policy 2000. Canberra: Commonwealth Department of Health and Aged Care; 2000.
5. Thomson O'Brien MA, Oxman AD, Davis DA, Haynes RB, Freemantle N, Harvey EL. Educational outreach visits: effects on professional practice and health care outcomes (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. Oxford: Update Software.

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.

Prevention of deep vein thrombosis

Editor, – I refer to G. Weisz' recent letter 'Economy class syndrome' (Aust Prescr 2001;24:52). My understanding is that a recent meta-analysis demonstrated no value in the use of aspirin for venous thromboembolism as prophylaxis and treatment, and a reported 3% chance of some degree of gastrointestinal bleeding. It would seem that the use of this drug is best left to the management of arterial problems. Recommendation as a therapy for prevention of deep vein thrombosis is not supported by the *Australian Medicines Handbook* ('Aspirin is probably ineffective in the prevention of venous thromboembolism'), and in view of the incidence of adverse effects I would not advise its use for this purpose.

I would be interested to learn of any studies which support the view that there is a place for aspirin in this setting, or indeed in any situation with a recognised risk of venous thrombosis.

Ashley Collard
General Practitioner
Fairlight, NSW

Agnes Vitry, Senior Editor, Australian Medicines Handbook, comments:

A recent editorial in the *Medical Journal of Australia* concluded that the evidence on the risk of venous thromboembolism associated with air travel was, as yet, missing.[1] Most of the evidence comes from case series and

two conflicting prospective case-control studies.[2,3] Given the current uncertainty about possible increased risk, it seems common sense and harmless to give the usual advice about regular foot exercises, generous fluid intake and avoiding excessive alcohol. A recent randomised trial showed that compression stockings may prevent symptomless deep venous thrombosis but may cause superficial thrombophlebitis in varicose veins.[4]

The second edition of the *Australian Medicines Handbook* did not recommend the use of aspirin for prevention of venous thromboembolism on the basis of a meta-analysis, which suggested aspirin provided relatively little protection for postoperative patients compared to heparins or oral anticoagulants.[5] A recent large trial showed that aspirin (160 mg daily, started before surgery and continued for five weeks) slightly reduced the risk of pulmonary embolism and deep venous thrombosis, but not the overall mortality in patients with hip fracture.[6] Results of this trial are difficult to interpret, as only some of the patients received additional prophylaxis with heparin or low molecular weight heparins, and also as aspirin has not been directly compared with these first-line treatments.

Low-dose aspirin may be used in addition to first-line treatments in patients with hip fracture at low risk of bleeding. At present, low-dose aspirin cannot be recommended for the prevention of venous thromboembolism in other situations.

REFERENCES

1. Gallus AS, Baker RI. Economy class syndrome. Med J Aust 2001;174:264-5.
2. Ferrari E, Chevallier T, Chapelier A, Baudouy M. Travel as a risk factor for venous thromboembolic disease: a case-control study. Chest 1999;115:440-4.
3. Kraaijenhagen RA, Haverkamp D, Koopman MM, Prandoni P, Piovella F, Buller HR. Travel and risk of venous thrombosis. Lancet 2000;356:1492-3.
4. Scurr JH, Machin SJ, Bailey-King S, Mackie IJ, McDonald S, Smith PD. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. Lancet 2001;357:1485-9.
5. Collaborative overview of randomised trials of antiplatelet therapy – III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. Br Med J 1994;308:235-46.
6. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000;355:1295-302.

Medications which may lower seizure threshold

Editor, – I would like to offer another explanation for the apparent 'seizure activity' reported by Dr Loadsman (Aust Prescr 2001;24:51–2) when pethidine and tramadol were used concurrently. Both these drugs have serotonin reuptake inhibitor activity and have been implicated in serotonin toxicity when combined with other serotonergic drugs. Co-administration of pethidine and tramadol could certainly result in a pharmacodynamic interaction, leading to signs and symptoms of excess serotonin in the central nervous system such as 'twitching and anxiety'. These as well as the neuromuscular features, myoclonic spasms, tremor, clonus, hyperreflexia and hypertonia are included in Sternbach's diagnostic criteria for 'serotonin syndrome' and can easily be mistaken for 'seizure activity'. Physicians should be alert to the possibility of serotonin toxicity when pethidine is given to patients who have recently taken, or are still taking, serotonergic drugs (such as selective serotonin reuptake inhibitors and monoamine oxidase inhibitors). Concurrent use of pethidine and tramadol should be undertaken with caution or avoided when possible, because of the risk of serotonin toxicity.

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Oxaliplatin

Editor, – The new drug comment (Aust Prescr 2001;24:73–4) does not reflect the Australian trial experience with oxaliplatin. At the American Society of Clinical Oncology meeting in San Francisco we reported a phase II trial of oxaliplatin in conjunction with 5-fluorouracil and folinic acid in 40 patients with previously untreated advanced or metastatic colorectal cancer.[1] There was a low rate of severe (grade 3/4) toxicities and these included neuropathy (grade 3–17%), diarrhoea (grade 3–11%), mucositis (grade 3–4%) and neutropenia (grade 3/4–34%). Nausea and vomiting were not a major problem with the use of simple antiemetics. In addition the tumour response rate was 56% (95% CI 38–72%), which is very high for these conditions.

The comment that 'like other platinum-based drugs, oxaliplatin is very toxic' is therefore inaccurate, as is the following suggestion that 'most patients will have vomiting, diarrhoea, anaemia and altered liver function tests'. These comments cannot have been written by anyone who has ever used this compound.

Stephen Clarke

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REFERENCE

1. Goldstein D, Michael M, Mitchell P, Smith J, Clarke S. Improving patient convenience: a modification schedule of FOLFOX (oxalipatin combined with 5FU) with high activity and tolerability in untreated metastatic colorectal cancer (CRC). Proceedings of the Annual Meeting of the American Society of Clinical Oncology; 2001 May 12-15; San Francisco. Report No. 578.

Editorial comment

The Executive Editorial Board prepared the new drug comment before oxaliplatin was marketed in Australia. Prior to marketing there is obviously little information available about the use of any new drug in Australia. To ensure readers are presented with a balanced view of a new drug the Executive Editorial Board considers data from a variety of sources including information provided by the manufacturer. While the Executive Editorial Board is interested in the results of Dr Clarke's phase II study they do not negate the new drug comment.

The comment was based on the pivotal clinical trials which used different regimens from the phase II study. In these trials symptoms of neuropathy developed in 85–95% of patients. Anaemia occurred in more than 80% of patients and neutropenia and thrombocytopenia were very common. The comment that most patients will have vomiting and diarrhoea is also consistent with the manufacturer's product information.

In Dr Clarke's trial 83% of the patients required a dose reduction and toxicity resulted in 25% ceasing treatment. While the frequency of severe adverse effects may be low from an oncology perspective, it is important that patients decide what is acceptable to them. The Executive Editorial Board hopes that the favourable response rate seen in the trial will lead to improved survival for the patients.

Medicinal mishap

Statin-fibrate combination therapy

Prepared by Ian Hamilton-Craig, Senior Visiting Cardiologist, Repatriation General Hospital, Adelaide, and David Miller, Senior Visiting Nephrologist, Flinders Medical Centre, Adelaide

Case 1

After coronary bypass five years ago this patient was treated with atorvastatin 40 mg daily and gemfibrozil 600 mg twice daily for combined hyperlipidaemia. He also took extended-release diltiazem for hypertension and aspirin 100 mg daily. He complained of minor, tolerable muscle aches but his creatine kinase levels were normal.

In March, cerivastatin 0.3 mg daily was substituted for atorvastatin. Three weeks later, the patient noticed flu-like symptoms with aching of the neck, shoulders and limbs. He persisted with his therapy in spite of severe muscle aching and stiffness, weakness, lethargy and decreasing urinary output. When he presented in April he had signs of acute renal failure and his urine contained pigmented casts typical of myoglobinuria. His creatine kinase peaked at over 30 000 U/L with a high creatinine (0.75 mmol/L) and urea (49.7 mmol/L). His liver function was also affected (LDH 2727 U/L, ALT 1089 U/L, AST 1827 U/L). After haemodialysis for 15 days, his initially profound muscle weakness improved and his strength returned to normal over subsequent weeks, as did his renal function.

Case 2

A 63-year-old woman with combined hyperlipidaemia (total cholesterol 7.5 mmol/L, triglycerides 10.2 mmol/L) was prescribed cerivastatin 0.4 mg daily. Three years previously she had been treated with atorvastatin, but ceased this after six months because of severe muscle aches and pains. Gemfibrozil 600 mg daily was subsequently added to cerivastatin when her total cholesterol and triglycerides were 5.4 and 5.7 mmol/L respectively. Three weeks later, she developed stiffness and pain in the lower back, with severe impairment of mobility. She ceased medications and her symptoms had largely resolved on presentation two days later. Her plasma concentrations were: creatine kinase 14 500 U/L, LDH 647 U/L, AST 352 U/L, ALT 191 U/L. Glucose, creatinine and urea concentrations were normal. TSH was marginally elevated (4.7 mIU/L) and free T4 borderline (11 pmol/L). Two days later her creatine kinase was 45 600 U/L. Her symptoms and creatine kinase concentrations were normal one week later.

Comment

Rhabdomyolysis has been a frequent adverse drug reaction with cerivastatin-gemfibrozil combination therapy. Fatalities have led to the withdrawal of cerivastatin from the market, other than in Japan where gemfibrozil is not available.

High plasma concentrations of 'statins' predispose to rhabdomyolysis with either high doses or co-administration of cytochrome P450 inhibitors, including calcium channel blockers[1] (see Case 1).

Conditions predisposing to myopathy include severe hypoxia, hyperthermia, hypotension, hypothyroidism (see Case 2), recent major surgery, severe acute infections, severe endocrine, metabolic and electrolyte disturbances, uncontrolled seizures and possibly underlying genetic myopathies.[2] Patients experiencing myopathy with one statin are likely to experience it with another (see Cases 1 and 2).

Severe myopathy may occur without elevation of creatine kinase, and therapy should be withdrawn in patients, especially elderly women, complaining of muscle weakness.[3] Patients should have normal thyroid function before starting treatment with lipid-lowering therapy. Adverse drug reactions should be reported to the Adverse Drug Reactions Advisory Committee to ensure adequate post-marketing surveillance.

REFERENCES

1. Martin J, Fay M. Cytochrome P450 drug interactions: are they clinically relevant? Aust Prescr 2001;24:10-2.
2. Ucar M, Mjorndal T, Dahlqvist R. HMG-CoA reductase inhibitors and myotoxicity. Drug Safety 2000;22:441-57.
3. England JD, Walsh JC, Stewart P, Boyd I, Rohan A, Halmagyi GM. Mitochondrial myopathy developing on treatment with the HMG CoA reductase inhibitors – simvastatin and pravastatin. Aust N Z J Med 1995;25:374-5.

Muscle disorders with statins – to August 2001

Statin	*Total number of reports*	*Reports of myalgia, myopathy and myositis (% of total)*	*Reports of rhabdomyolysis (% of total)*
Cerivastatin	148	68 (45.9%)	27 (18.2%)
as monotherapy			7 (4.7%)
with gemfibrozil			20 (13.5%)
Simvastatin	2248	427 (19.0%)	32 (1.4%)
Atorvastatin	679	130 (19.1%)	3 (0.4%)
Pravastatin	339	85 (25.1%)	3 (0.9%)
Fluvastatin	242	62 (25.6%)	1 (0.4%)

Table provided by Adverse Drug Reactions Advisory Committee

Alternatives to cisapride

Geoff Hebbard, Senior Consultant, Gastroenterology, and Joy Gailer, Drug and Therapeutics Information Service, Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia; and Graeme Young, Professor, Gastroenterology, Flinders University of South Australia, Flinders Medical Centre, Adelaide

SYNOPSIS

Cisapride has the potential to cause arrhythmias, particularly in susceptible patients, at higher doses and when combined with drugs or foods that inhibit its metabolism. Meta-analyses suggest that the efficacy of cisapride may have been overestimated in the past. Many currently available medications have equivalent or greater efficacy than cisapride for indications such as gastro-oesophageal reflux disease, functional dyspepsia, oesophageal dysmotility and constipation. The alternatives include acid suppressing drugs, domperidone, metoclopramide and laxatives. Several drugs currently under development, especially the new $5HT_4$ agonists and GABA-B agonists, may also be of value. Cisapride still has a limited role in gastroparesis.

Index words: dyspepsia, gastroparesis, gastro-oesophageal reflux disease.

(Aust Prescr 2001;24:110–2)

Introduction

The recognition that cisapride may be associated with cardiotoxicity has led to a significant re-evaluation of its role in the therapy of gastrointestinal motility disorders. In addition, several recent meta-analyses have identified flaws in the literature concerning cisapride, suggesting that the benefits of cisapride may have been overestimated by publication bias.[1] The concerns about toxicity have resulted in some countries withdrawing cisapride altogether, whereas in others it has been restricted to specific indications or prescribing groups.

In Australia, the Therapeutic Goods Administration now only approves cisapride for a few indications and the product information carries a boxed warning about the risk of arrhythmia. The listing of cisapride on the Pharmaceutical Benefits Scheme (PBS) is even more restricted. Cisapride is only available, with an authority prescription, for the treatment of gastroparesis diagnosed by a consultant physician.

Pharmacology

Cisapride is a prokinetic agent with actions throughout the gastrointestinal tract. It acts as an agonist at muscarinic (M_2) and some serotonergic ($5HT_4$) receptors, and as an antagonist at other serotonergic ($5HT_3$) receptors. Cisapride increases smooth muscle tone, strength and possibly the co-ordination of contractions. This results in improved transit of gastrointestinal contents. Cisapride has therefore been widely used in disorders due, or believed to be due, to disordered gastrointestinal motility.

Toxicity

The cardiac toxicity of cisapride is attributed to its inhibition of potassium channels in the myocardium. This concentration-dependent effect leads to prolongation of the QT interval which increases the risk of torsade de pointes and sudden death. Toxicity is seen in all age groups, and is enhanced by higher doses, individual susceptibility due to disease or genetic factors, co-administration of drugs inhibiting the metabolism of cisapride via cytochrome P450 3A4 (e.g. macrolides, azole antifungals, grapefruit juice)[2], or other drugs which prolong the QT interval (e.g. quinidine, sotalol).

By early 2001, the Australian Adverse Drug Reactions Advisory Committee had received 58 reports of cardiac adverse events in both adults and children. These included 24 arrhythmias (one fatal) in which cisapride was the sole suspected drug.

Alternatives to cisapride

There are a number of currently available drugs which are alternatives to cisapride (Table 1), and several new drugs are under investigation.

Metoclopramide is a dopamine (D_2) antagonist, an agonist at $5HT_4$ receptors and an antagonist at $5HT_3$ receptors. Its peripheral effects improve gastric emptying, and its central effects on dopamine receptors are antiemetic. The central effects are also responsible for most of the therapy-limiting adverse effects including drowsiness and dystonic reactions.

Domperidone is a peripherally acting dopamine (D_2) antagonist with antiemetic effects. These are mediated through the chemoreceptor trigger zone which is situated in the area postrema, outside the blood-brain barrier. Domperidone does not cross the blood-brain barrier, and hence does not have the same range of central effects as metoclopramide, but it may still cause galactorrhoea. A difficulty with prescribing domperidone is the PBS restriction of 25 tablets with no repeats available on a standard prescription.

Two new serotonin ($5HT_4$) agonists – tegaserod, a partial agonist, and prucalopride, a full agonist – have recently been developed. Although they were developed for the treatment of

disorders of colonic motility, these drugs may have actions throughout the gastrointestinal tract. (At present clinical trials with prucalopride have been suspended.)

Erythromycin is the prototype drug of the motilides. These drugs act as agonists at the motilin receptors in the stomach and small intestine. In patients with diabetic gastroparesis, the administration of erythromycin results in an improvement in gastric emptying. However, this may be associated with unwanted gastrointestinal symptoms and other adverse effects. Other motilides have been developed, but have not been adequately evaluated and are not available commercially.

Gastroparesis

Gastroparesis is the sole remaining indication for prescribing cisapride on the Australian PBS. This reflects the relative lack of effective alternative treatments.

Diabetes mellitus and idiopathic gastroparesis account for the majority of cases. If simple dietary modification with small, frequent, low fat meals is unsuccessful, prokinetic drugs can be considered. There are few comparative trials of prokinetics in gastroparesis, and the trials that do exist are of relatively poor quality. The endpoints of the majority of trials assessed acceleration in gastric emptying alone, and few have assessed improvement in symptoms and/or quality of life scores.

A recent systematic analysis found that erythromycin appears to accelerate gastric emptying more than other prokinetic drugs (44% improvement in gastric emptying time compared to domperidone 28%, cisapride 27% and metoclopramide 21%). In terms of improving the symptoms of gastroparesis in this systematic analysis, erythromycin, domperidone, metoclopramide and cisapride (in descending order of apparent efficacy) were all found to be of value.[3] However, their clinical usefulness is limited by their modest efficacy, poor tolerability and toxicity.

Any patient prescribed cisapride should have an ECG to check for pre-existing QT prolongation, and at least one ECG while on therapy. The use of cisapride in patients with diabetic gastroparesis requires consideration of specific problems. Diabetic autonomic neuropathy may be associated with prolongation of the QT interval, and care must be taken to ensure that patients do not become hypokalaemic (for example because of hypoglycaemia or vomiting) as this could predispose to ventricular arrhythmias. Patients with diabetic nephropathy and renal impairment have a reduced clearance of cisapride, and will require lower doses.

If any of the motilides become available they may play an important role in the management of gastroparesis. Although the newer $5HT_4$ agonists (tegaserod and prucalopride) will not initially be marketed for treatment of upper gastrointestinal motility disorders they may have beneficial effects on the upper gastrointestinal tract. The efficacy of tegaserod in the treatment of diabetic gastroparesis will be examined in clinical trials in the near future.

Two small uncontrolled trials have suggested that there is some benefit from injecting botulinum toxin into the pyloric sphincter in idiopathic and diabetic gastroparesis. Controlled studies are required before this treatment can be recommended.

If drug therapies are unsuccessful, gastric electrical stimulation (a therapy which is commercially available, but still undergoing clinical evaluation) or alternative methods of feeding such as a surgically or endoscopically placed jejunostomy may be required.

Gastro-oesophageal reflux disease

Cisapride is effective in the treatment of mild gastro-oesophageal reflux disease because of its effects on oesophageal motility. However, its potential risks, lack of PBS listing and the availability of acid suppressing drugs mean that cisapride is unlikely to have a significant role in future. Most cases of gastro-oesophageal reflux disease can be managed adequately with lifestyle changes and acid suppression, using H_2 receptor antagonists or proton pump inhibitors, according to severity.

Cisapride has sometimes been used in reflux disease as an adjunct when the clinical response to acid suppression is inadequate. If inadequate suppression of gastric acidity is the problem (demonstrated for example by measuring ambulatory pH), increasing acid suppression (by either dose escalation or changing to an alternative drug) is likely to be more effective than cisapride. Continuing regurgitation of non-acid gastric contents will not be improved by further acid suppression and, although this has not been examined formally, it is arguable whether cisapride has any role to play in this group of patients. Surgery is likely to be their best option.

There is a sub-group of patients with symptoms of reflux that respond to cisapride. Their symptoms recur when it is ceased and cannot be adequately controlled using other medications. In this group, continued therapy with cisapride is reasonable, provided low doses are used, with appropriate care and patient education. An ECG should be recorded during treatment with cisapride to check for QT prolongation. This treatment is outside the PBS authority prescribing restrictions unless the patient also has concurrent gastroparesis (delayed gastric emptying is common in patients with gastro-oesophageal reflux disease).

Table 1

Alternatives to cisapride

Indication	*Current alternatives*
Adult	
Gastroparesis	Erythromycin Metoclopramide Domperidone
Gastro-oesophageal reflux disease	Acid suppression with H_2 receptor antagonist or proton pump inhibitor
Functional dyspepsia/gas/bloat	Acid suppression Domperidone Metoclopramide *H. pylori* eradication (limited value)
Paediatric	
Gastro-oesophageal reflux disease	Acid suppression

Another class of drugs, GABA-B agonists (prototype drug baclofen), is under investigation for the treatment of reflux disease. These drugs reduce the number of transient lower oesophageal sphincter relaxations (the major mechanism of gastro-oesophageal reflux) in healthy subjects, and trials are being conducted in patients with reflux disease. The use of baclofen itself is not appropriate for reflux disease because of its adverse effects. Efforts are under way to develop new GABA-B agonists with a more favourable adverse effect profile.

Functional dyspepsia

The use of cisapride in functional dyspepsia or for non-specific upper gastrointestinal symptoms is difficult to justify because of its potential toxicity, even though the absolute risks are low if appropriate care is taken. Alternative drugs such as domperidone, metoclopramide or acid suppressing drugs (especially in reflux-type functional dyspepsia) should be used if simple dietary advice is ineffective and more serious disorders have been excluded. In patients infected with *Helicobacter pylori*, eradication therapy can be tried, but is unlikely to be of benefit in the majority of patients with functional dyspepsia.[4]

Patients with upper gastrointestinal symptoms (e.g. gas/bloating) which are currently controlled on cisapride, and which recur on cessation of cisapride, should probably be re-evaluated for the presence of gastroparesis.

Oesophageal motility disorders

Cisapride has been used to treat disordered oesophageal motility, after disorders such as achalasia have been excluded by oesophageal manometry. Given the lack of convincing evidence of clinical benefit, this use of cisapride is now difficult to justify. The new $5HT_4$ agonists may have a role to play, but this requires considerable further research.

Paediatric conditions

In children cisapride has been most widely used for gastro-oesophageal reflux disease. However, clinical trials have failed to show that cisapride has a clinical benefit.[5,6] Some children's hospitals have introduced significant restrictions on the prescription of cisapride, including the requirement for neonatology and/or gastroenterology review, and for ECGs to monitor the QT interval.

Simple alternatives such as thickening of feeds and posturing have usually been tried and proven ineffective by the time a drug is required, and acid suppression may be an alternative in this situation.

REFERENCES

1. Soo S, Moayyedi P, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia (Cochrane Review). In: The Cochrane Library, 3, 2001. Oxford: Update Software.
2. Martin J, Fay M. Cytochrome P450 drug interactions: are they clinically relevant? Aust Prescr 2001;24:10-2.
3. Sturm A, Holtmann G, Goebell H, Gerken G. Prokinetics in patients with gastroparesis: a systematic analysis. Digestion 1999;60:422-7.
4. Talley NJ, Lam SK, Goh KL, Fock KM. Management guidelines for uninvestigated and functional dyspepsia in the Asia-Pacific region: First Asian Pacific working party on functional dyspepsia. J Gastroenterol Hepatol 1998;13:335-53.
5. Cohen RC, O'Loughlin EV, Davidson GP, Moore DJ, Lawrence DM. Cisapride in the control of symptoms in infants with gastroesophageal reflux: A randomized, double-blind, placebo-controlled trial. J Pediatr 1999;134:287-92.
6. Gilbert RE, Augood C, MacLennan S, Logan S. Cisapride treatment for gastro-oesophageal reflux in children: a systematic review of randomized controlled trials. J Paediatr Child Health 2000;36:524-9.

Dr Hebbard has been sponsored to attend scientific meetings by Novartis (tegaserod) and AstraZeneca (omeprazole, esomeprazole). He is a member of an expert advisory team on esomeprazole and has met with Pharmacia regarding pantoprazole.

Professor Young and Ms Gailer: no conflict of interest declared.

Self-test questions

The following statements are either true or false (answers on page 131)

1. Erythromycin should not be prescribed for a patient who is taking cisapride.
2. Erythromycin may improve gastric emptying in patients with diabetic gastroparesis.

Anaphylaxis Wall Chart

Included in this issue is an updated version of the *Australian Prescriber* Wall Chart 'Medical management of severe anaphylactoid and anaphylactic reactions'. This version replaces the previous wall chart which was published in 1994, but which can be still found in many clinics and treatment rooms across Australia.

The new wall chart has been produced with the assistance of the postgraduate organisations which contributed to previous versions (the Australasian College for Emergency Medicine, the Australasian Society of Clinical Immunology and Allergy, the Australian and New Zealand College of Anaesthetists, the Royal Australasian College of Physicians and the Royal Australian College of General Practitioners). In addition, the Executive Editorial Board of *Australian Prescriber* welcomes the contribution of the Royal Australian and New Zealand College of Radiologists.

The main change in the wall chart is an increase in the paediatric dose of adrenaline. Our consensus was that the first dose should be 10 microgram/kg. The doses for adults are unchanged.

The Executive Editorial Board believes that the wall chart will be useful in an emergency, but hopes that it does not have to be used too often.

Undernutrition in the community

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SYNOPSIS

Patients who are undernourished may benefit from dietary modifications, including eating foods with a high energy and protein content. A varied diet including all food groups should ensure adequate intakes of vitamins and minerals. Some patients may need to include nutritional supplements as part of their usual dietary intake and others may require enteral nutrition. A full dietary assessment should be conducted by a dietitian especially if the patient has long-term nutritional problems. Simple nutritional screening assessments, particularly for patients considered at risk of undernutrition, can be effective in reducing the consequences and complications of malnutrition.

Index words: nutritional supplements, food, ageing.

(Aust Prescr 2001;24:113–5)

Introduction

Good nutrition consists of adequate amounts of macronutrients such as protein, fat and carbohydrates, and micronutrients such as vitamins and minerals. Malnutrition is associated with a high burden of illness, poor wound healing and increased morbidity and mortality. It is a hidden financial burden to the community. Screening and early intervention are the key to the management of malnutrition.

Patient groups most at risk of undernutrition

Poor nutritional status usually results from inadequate dietary intake or malabsorption. It may be related to neurological, psychiatric and other medical problems including polypharmacy. Social factors are also important. The patients most at risk of nutrition-related complications are the elderly (including those with Alzheimer's disease, Parkinson's disease or chronic obstructive pulmonary disease), the disabled who are house-bound, people with chewing and swallowing problems, and patients with HIV/AIDS or cancer. A significant risk factor is living alone, especially for men.

The elderly are particularly at risk of protein-energy malnutrition. The development of a suboptimal nutritional status is a major problem in frail elderly people. Another group of undernourished patients may be young women with restrictive dietary practices. Their diets may be nutritionally inadequate, particularly if they omit all animal products.[1]

Statistics

Malnutrition is a critical healthcare problem among all age groups, but especially in the elderly where it is a major issue affecting the allocation of resources in primary care. Approximately 14% of the Australian population are aged 65 years or over, representing almost two million people who may require additional health care as time progresses. Consequently, early intervention may save considerable financial resources in addition to increasing the number of healthy, as opposed to frail, aged people.

In the elderly, poor nutrition is a major health problem which contributes greatly to morbidity and mortality. Poor nutritional status has also been linked with diminished cognitive and physical performance, and a reduced overall sense of physical and mental well-being.[2] Studies on hospitalised elderly patients have shown that early intervention with nutrition support has a positive impact on nutritional status, length of hospital stay/re-admission rates, and clinical outcomes.[3]

Screening for undernutrition

In the community a full nutritional assessment is not practical but simple screening tools can identify patients at increased risk of poor nutrition (see box). Identification and assessment of patients who are malnourished, or those who are at increased risk, should include clinical assessment and a brief dietary history.[4]

Several assessment tools have been designed including the Nutrition Screening Initiative, Subjective Global Assessment (SGA)[5], and the Australian Nutrition Screening Initiative. The SGA is a screening tool which has been used in the community. It encompasses previous history and symptomatic and physical

Nutritional risk screening and monitoring tool
Obvious underweight – frailty?
Unintentional weight loss?
Reduced appetite or reduced food and fluid intake?
Mouth or teeth or swallowing problem?
Follows a special diet?
Unable to shop for food?
Unable to prepare food?
Unable to feed self?
Obvious overweight affecting life quality?
YES to one or more questions indicates nutritional risk. Consider more detailed assessment.

Reprinted with permission. Aged, Community and Mental Health Division, Victorian Department of Human Services. Identifying and planning assistance for home-based adults who are nutritionally at risk: Executive Summary, Appendix 1. In press 2001.

parameters. This helps to determine whether nutrient assimilation has been restricted as a result of decreased food intake or due to a medical condition. The SGA is one of the most well established and validated nutrition assessment tools and is an appropriate gold standard against which other nutrition screening tools may be compared. There is good correlation between the SGA and other parameters such as biochemical and anthropometric measures of nutrition.

Other screening tools with high sensitivity may not demonstrate specificity and may assess some well-nourished patients as being at risk of malnutrition (false positives) and a full nutritional assessment would be required. Hence the Australian Nutrition Screening Initiative is a checklist developed to raise awareness of the importance of nutrition and to identify independent older people who may be at risk of poor nutrition. It consists of the 12 most common factors contributing to risk of malnutrition in the older adult.[2] People who are identified as being at risk need an accurate nutrition assessment involving a combination of clinical examination and anthropometric and biochemical measurements.

Assessment of nutritional status

Body Mass Index (BMI) can be calculated as weight in kilograms (kg) divided by height in metres squared (m^2). BMI of 20–25 kg/m^2 is acceptable. BMI under 19 kg/m^2 is considered underweight and BMI under 18.5 indicates a significant risk of malnutrition. Although BMI is widely accepted as a measure of body fatness, its use is limited in some groups.

BMI overestimates body fat in very muscular people and can underestimate body fatness in underweight people. Moreover the cut-off points may not be appropriate for different racial groups given that they were originally developed for people of European origin. Measurement of body weight in some patients can also be confounded by changes in body water as a result of underhydration, oedema and ascites.

Changes in weight should also be taken into consideration. A 10% change in body weight in six months is a significant indicator of the risk of malnutrition.

Plasma proteins may be used as markers of malnutrition, but concentrations may be influenced by non-nutritional factors, such as liver disease, sepsis and inflammatory bowel disease. Albumin is a routine marker of undernutrition (chronic protein deficiency) in hospitalised patients. As albumin has a relatively long biological half-life (approximately 20 days), it is not considered a good indicator of short-term protein and energy deprivation.

Other factors in assessment include recent changes in food intake, persistent diarrhoea or vomiting, and a change in the way that clothes fit. Unintentional weight loss is also an important indicator of future nutritional deficiencies.

Management

Some patients will benefit from non-nutritional interventions, such as medication review. Dental problems may also contribute to poorer nutrition. Reports show that the majority of those who are edentate experience more eating problems than those who are dentate. Checking if the patient's dentures fit is a simple remedy.

Patients with chewing and swallowing problems should be referred to a speech pathologist for assessment and to a dietitian for advice regarding texture modification of food and drink. People who have problems preparing food should be referred to occupational therapists for advice regarding appropriate use of utensils and equipment. Home delivered meals may also help.

Patients with severe or excessively restrictive dietary practices may need psychiatric intervention.

Nutrition intervention

The dietary guidelines for older Australians[6] do not recommend a reduction in total fat intake, as this may not be in the best interests of this group of patients who become frail. They tend to be underweight, and consume foods in smaller quantities than younger age groups. Although energy needs may be lower in this age group than in younger adults due to reduced energy expenditure, it is important to provide advice on foods with a high energy density to help older people meet their dietary requirements.

Nutrition intervention may include modification of the usual diet with high energy and high protein foods, as well as the use of commercial products including dietary supplements. Energy dense foods include margarine, oil, butter and cream. Foods high in protein and energy include full-fat dairy products, eggs, meat and nuts.

Poor dietary intake may also result in vitamin and mineral deficiencies, particularly folate, calcium, iron and zinc. Prolonged or poor storage of fresh foods can lead to a reduction in nutrient content but 'convenience' foods are a useful alternative since frozen, chilled, or packed fruits and vegetables can be a good source of vitamins and minerals.

The amount of iron absorbed from food depends on the source of iron and also on other constituents in the diet. Haem iron is found in food such as meat, liver, kidney, poultry and seafood. Non-haem iron is found in legumes, egg yolk, wholemeal/wholegrain breads and cereals, green leafy vegetables, nuts and seeds.

Haem iron is better absorbed than non-haem iron. Iron absorption is reduced in the presence of tannins (in tea, coffee) and phytates (in unrefined cereal foods). To increase the absorption of non-haem iron it is recommended that foods rich in vitamin C (a reducing agent) should also be consumed at the same time (for example a glass of orange juice with a wholegrain breakfast cereal would substantially increase iron absorption from the cereal).

Low intakes of thiamin (B_1), riboflavin (B_2) and niacin have been reported in the elderly. The ability to absorb vitamin B_{12} and folic acid also decreases with age. Thiamin is found in cereal foods, meat, pulses, nuts and milk. Riboflavin is found in milk, cheese, eggs, pulses and green vegetables. Nicotinic

acid is found in meat, fish, wholegrain cereals, pulses and nuts. Pyridoxine (B_6) intakes in the elderly have also been reported to be low although vitamin B_6 is widely distributed in foods such as liver, cereals, pulses, leafy vegetables, and fruits. Vitamin B_{12} is found in only animal foods so strict vegans may require a supplement.

As breakfast cereals are now fortified with folate, increasing cereal intake would be a useful suggestion, especially a fibre-enriched variety. Other good sources of folic acid are green leafy vegetables, liver, citrus fruits such as oranges and grapefruit, and nuts.

Calcium absorption can be impaired by fibre and phytate in cereals and vegetables. As vitamin D is also required for the absorption of calcium, house-bound or institutionalised people may not be able to obtain vitamin D by the action of sunlight on the skin. They will need a good supply of vitamin D in their diet from sources such as oily fish, and fortified cereals and margarines.

Marginal intakes of calcium contribute to osteoporosis, a disease already prevalent in the elderly. Good sources of calcium include dairy products, calcium-fortified soy products, fish with edible bones and green leafy vegetables.

If the intake of zinc is marginal it can have a major impact on food intake by reducing taste sensation. As taste is already impaired in the elderly this can seriously affect food choice. Zinc is readily available in animal foods especially red meat, liver, fish and eggs. If this is not feasible, then the use of a multivitamin and minerals supplement may be a suitable alternative. However multiple medication use is prevalent in this population and another 'pill' may add to the confusion.

Fruits and vegetables are the main sources of vitamin C in the diet. Potatoes contain moderate amounts but as potatoes are eaten in relatively large quantities, they provide a major and significant amount of vitamin C. Some food products have vitamin C added to them (e.g. dehydrated potatoes, fruit drinks).

Nutritional supplements

One of the simplest ways to increase the energy and nutrient content of the conventional home diet is by the use of nutritional supplements.

A range of supplements is available in the form of liquids and powders; some products can provide a single nutrient, whereas others are nutritionally complete and provide both macro- and micronutrients. Most supplements are available in a variety of flavours to aid compliance and help avoid flavour fatigue.

Some supplements are available as thickened liquids and texture-modified semi-solids in order to meet the nutritional requirements of patients who have difficulty in swallowing. Specialised supplements are also available such as those which provide semi-elemental nutrition for patients with impaired gastrointestinal function. Some oral dietary supplements can also be used as a complete tube feed.

Enteral nutrition

If daily nutritional requirements cannot be met orally, then enteral feeding may be considered. Oral intake may still occur simultaneously with tube feeding and some patients may prefer overnight tube feeding with food intake during the day. Enteral feeding may be continued until oral intake is considered adequate. Standard enteral feeds provide 1 kcal/mL and more energy dense alternatives are also available.

The most commonly used methods for providing enteral nutrition are via nasoenteral and gastrostomy feeding. Patients who require long-term enteral feeding can be considered for gastrostomies such as percutaneous endoscopic gastrostomy which has become a safe and well established technique.

Monitoring

Multidisciplinary team management with regular review and continued monitoring are important in any nutritional intervention. As weight gain is achieved, dietary nutritional supplements may need to be gradually reduced, provided adequate nutrition can be maintained by food intake. Changes in food intake should be noted and advice from a dietitian should be sought for a complete nutritional assessment.

REFERENCES

1. Donovan UM, Gibson RS. Dietary intakes of adolescent females consuming vegetarian, semi-vegetarian, and omnivorous diets. J Adolesc Health 1996;18:292-300.
2. Lipski PS. Australian Nutrition Screening Initiative. Aust J Ageing 1996;15:14-6.
3. Larsson J, Unosson M, Ek AC, Nilsson L, Thorslund S, Bjurulf P. Effect of dietary supplement on nutritional status and clinical outcome in 501 geriatric patients – a randomised study. Clin Nutr 1990;9:179-84.
4. Schneider SM, Hebuterne X. Use of nutritional scores to predict clinical outcomes in chronic diseases. Nutr Rev 2000;58:31-8.
5. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA. What is subjective global assessment of nutritional status? J Parenter Enteral Nutr 1987;11:8-13.
6. NHMRC. Dietary guidelines for older Australians. Canberra: AGPS;1999.

FURTHER READING

Bunney C, Bartl R. Reduce the risk – a common sense guide to preventing poor nutrition in older people. Gosford, NSW: Nutrition Department, Central Coast Area Health Service; 1996.

Wahlqvist ML, Wattanapenpaiboon N. Antioxidant nutrients. Aust Prescr 1999;22:142-4.

Self-test questions

The following statements are either true or false (answers on page 131)

3. Zinc deficiency can alter taste sensation.
4. A low serum albumin is not a good indication of short-term protein deprivation.

Are we there yet? – Travel along the information highway seeking evidence-based medicine

Peteris Darzins, Senior Lecturer in Geriatric Medicine, University of Melbourne, National Ageing Research Institute; and Majella Pugh, Librarian, Melbourne Extended Care and Rehabilitation Service, Melbourne

SYNOPSIS

Health professionals are encouraged to practise evidence-based medicine. Ideally patients should be treated according to good quality evidence. This evidence is often lacking and can be difficult to find. Even using the latest technology, searching the published literature is time-consuming and may not answer a specific question. Clinical decisions, therefore, frequently have to be made without good supporting evidence.

Index words: medical informatics, systematic reviews, birth defects.

(Aust Prescr 2001;24:116–9)

Introduction

To practise evidence-based medicine doctors must have access to the evidence when they need it. The vast increase in healthcare information makes it difficult to do this.

The National Health and Medical Research Council (NHMRC) classifies the strength of evidence into four levels. These levels reflect the research methods used in clinical trials (Table 1). Ideally all treatment decisions would be based on Level I, the highest level of evidence. Failing this, lower levels of evidence need to be used to guide the decisions.

To help people access the higher levels of evidence the Cochrane Collaboration is collating all randomised-controlled trials and systematically reviewing the results. The Cochrane Collaboration makes this information available electronically through its subscription databases, and via State government initiatives such as the Clinical Information Access Program of New South Wales, and Victoria's Clinicians Health Channel.

Table 1

The four levels of evidence of the National Health and Medical Research Council[1]

Level I	evidence obtained from a systematic review of all relevant randomised-controlled trials (includes Cochrane reviews, and other systematic reviews and meta-analyses)
Level II	evidence obtained from at least one properly designed randomised-controlled trial
Level III	evidence obtained from well designed controlled trials without randomisation; or from well designed cohort or case controlled analytic studies preferably from more than one centre or research group; or from multiple time series with or without intervention
Level IV	evidence obtained from case series, either post-test or pre-test and post-test

It is impossible to keep up with all the developments in medicine. Inevitably patients will present clinical problems to which their doctors do not know the solutions. Advice can be sought from colleagues, but it must be remembered that the opinion of respected authorities, based on clinical experience, descriptive studies or reports of expert committees is considered to be the lowest form of evidence.

Case – to immunise or not to immunise?

A fit, 35-year-old woman who is 30 weeks pregnant consults you in mid-winter because she wants advice about influenza vaccination. She has heard that last year a woman died of 'flu' late in pregnancy. Indeed, just recently one of her friends had 'the flu', was off work for a week, and even some weeks later her friend has not regained full strength. Your patient does not wish to lose time from work with the flu as she has a large information technology consulting project to finish before she delivers; she plans to work up until the end of the 37th week of pregnancy. She thinks it might be a good idea to be immunised, but does not want to harm her unborn child. One of her friends has given her the Consumer Medicine Information part of an influenza vaccine package insert (Fig. 1).

Action

Next steps

After reading the Consumer Medicine Information leaflet it appears there are no definite contraindications to the influenza vaccine. Although there is a general note of caution relevant to pregnancy, there is no recommendation for or against immunisation of healthy pregnant women. Your well-educated patient reiterates her desire to be protected from influenza but also her concern for the well-being of her unborn child. She seeks your advice.

To attempt to address her question, you and the patient read the medical part of the information in the package insert. This information is also silent on pregnancy as an indication for use. The only note regarding pregnancy states that there is no convincing evidence of risk to the fetus from immunisation of pregnant women using inactivated virus vaccines, bacterial vaccines or toxoids.

Fig. 1

Selected extracts from the 2000 Consumer Medicine Information for influenza vaccine

Who should be vaccinated?

Annual vaccination against influenza is recommended for the following individuals:

- People over 65 years of age
- Aboriginal and Torres Strait Islander people over 50 years of age
- Adults with chronic illness, especially chronic heart, lung or kidney disorder or diabetes
- Children with heart disease
- People living in nursing homes and other long term care facilities
- People receiving medicines that reduce natural immunity

Annual vaccination against influenza should be considered for the following individuals:

- People who work in medical or health science

Who should not be vaccinated?

Influenza vaccine should not be given to:

- Anyone who has an allergy to eggs and/or chicken feathers, neomycin, polymyxin, gentamicin and any other component of the vaccine
- Anyone who has a severe infection with a high temperature

Before you have the vaccination

Before you receive the injection you must tell your doctor if:

- You are pregnant or likely to become pregnant or if you are breastfeeding so that you can discuss the risks and benefits of vaccination (Australian use in pregnancy Category B2)

Where can I get more information?

You can get more information from your doctor or pharmacist.

Table 2

Doctor's electronic search for information about the risks and benefits of influenza vaccination in pregnancy

Time	*Information source and search strategy used*	*Information found*
2 minutes	NHMRC web site. Browsed and searched using the terms 'vaccination' and 'guidelines' separately	Immunisation guidelines not found
8 minutes	Clinicians Health Channel/ Guidelines and protocols/ Victorian sources/Infection Control/Victorian Infectious Diseases Bulletins	Bulletins browsed, but no relevant information found
3 minutes	Clinicians Health Channel/ Guidelines and protocols/ Guidelines for the control of infectious diseases/ The Blue Book (Victorian Department of Human Services, 1997)	The Blue Book (Victorian Department of Human Services, 1997) - but contents not available electronically
1 minute	Medical Journal of Australia Guidelines site	No information on immunisation
5 minutes	Cochrane Collaboration. Searched using MeSH term 'vaccination'	7 reviews found, but none relevant
6 minutes	Best Evidence 1991–2000. Searched using MeSH term 'vaccination'	13 articles found. All studies had pregnancy as an exclusion criterion
12 minutes	Medline. Searched using MeSH terms 'influenza vaccination AND pregnancy', limited to English language papers dealing with humans	50 papers found and reviewed on screen
Total 37 minutes		

Decision needed

How would you advise her? Stop here, commit yourself to an answer before reading on. To vote in our survey, click here.

Doctor's literature search

To obtain evidence of the pros and cons of influenza vaccination in late pregnancy an electronic search was performed (Table 2). Surprisingly, no authoritative guidelines were found, nor was Level I evidence available for this simple, widespread procedure. The papers found by the Medline search were evaluated on-screen as follows:

- the titles were reviewed and the papers were judged as relevant, possibly relevant or not relevant
- the abstracts, if present, of the papers judged by their titles to be relevant or possibly relevant, were reviewed and judged as possibly providing relevant information or not
- the abstracts that remained after this selection process were judged as helping to make a decision or providing no help at all.

This approach yielded 50 papers. A review of their titles suggested 11 were relevant and 22 possibly relevant. Of these 33 papers, five abstracts appeared able to inform the decision, but only three provided possibly useful information.

The first paper describes a study in which 189 women who were immunised just before or during pregnancy were compared with a control group of 517 women. There was no association between immunisation and maternal, perinatal or infant complications or outcomes. No teratogenicity was seen. This small sample lacks the statistical power to detect even relatively frequent events, thus it provides only weak evidence. The unstructured abstract does not allow readers to judge whether this was a randomised trial, nor even whether the women received the immunisation inadvertently or deliberately. If the vaccine was given deliberately an institutional ethics review board presumably approved the practice, which would suggest the practice was thought to be safe, but this is by no means clear.

The second paper describes the influenza vaccine for 1978–79. It states that pregnant women do not appear to have any special risk from influenza vaccination; physicians evaluating them should use the same criteria applied to other persons. The third paper's abstract provides the same advice. These two papers appear to be quoting the same primary source, but the basis for their advice is not clear.

This search took 37 minutes via a high-speed university internet access portal. Searchers who do not have reliable

high-speed internet access would be expected to take longer, as might inexperienced searchers. The search yielded little evidence upon which to base a decision of whether or not to give influenza immunisation.

Librarian's literature search

An experienced medical librarian was told of the case and independently performed an electronic search of Medline and the Cumulated Index of Nursing and Allied Health Literature (CINAHL). Her search strategy is shown in Figure 2. She also sought information in the Cochrane Collaboration and AustHealth databases.

The results of the librarian's search were evaluated using the same method as for the doctor's literature search. The titles of the 45 articles found suggested that nine articles were relevant and 30 possibly relevant. Of these, 22 had abstracts, but only five appeared able to inform the decision. Three of these papers provided directly useful information while the rest provided indirect evidence.

The strongest recommendation to use influenza vaccination in pregnancy contains no information with which to judge the basis for this advice. At best this could be Level IV evidence, at worst uninformed opinion.

Another paper describing a study that aimed to test whether maternal immunisation could improve passive antibody protection in young infants reported that women in the last trimester of pregnancy were given trivalent inactivated influenza virus vaccine. Similar evidence is provided by another paper reporting a study of 448 eligible pregnant women who were offered the influenza vaccine at routine prenatal visits. These papers infer Level IV evidence, but the validity of the studies cannot be adequately judged.

Supporting evidence comes from another paper that discusses possible approaches to a flu pandemic. In the abstract the authors state 'Pregnant women should probably be vaccinated'. This is Level IV evidence at best.

The final article of the five selected reports a study of hospitalisations and deaths from selected acute cardiac or respiratory conditions in pregnant women during influenza seasons. In a nested case-control study, 4369 women enrolled in a Medicaid program with a first study event during an influenza season were compared with 21 845 controls. In comparison with postpartum women, the odds ratios associated with study events increased from 1.44 (95% confidence interval (CI) 0.97–2.15) for women at 14–20 weeks gestation to 4.67 (95% CI 3.42–6.39) for those at 37–42 weeks. Women in their third trimester without other identified risk factors for influenza morbidity had an event rate of 21.7 per 10 000 women-months during an influenza season. Approximately half of this morbidity, 10.5 (95% CI 6.7–14.3) events per 10 000 women-months, was attributable to influenza. Influenza-attributable risks in comparable non-pregnant and postpartum women were 1.91 (95% CI 1.51–2.31) and 1.16 (95% CI 0.09–2.42) per 10 000 women-months, respectively. The data suggest that, out of every 10 000 women in their third trimester without other identified risk factors who experience an average influenza season of 2.5 months, 25 will be hospitalised with influenza-related morbidity. This is not an article about treatment, but does describe the magnitude of the influenza problem in pregnant women.

Fig. 2

Experienced medical librarian's search strategy

Ovid – Medline <January 2000 to September 2000>

File Edit Search Limit View Tools Database Options Window Help

1	Influenza vaccine/	203
2	exp pregnancy complications/	4591
3	influenza/pc	170
4	exp pregnancy/	9905
5	3 and (2 or 4)	4
6	1 and (2 or 4)	4
7	5 or 6	5
8	exp fetal development/	2106
9	(1 or 3) and 8	0
10	7 or 9	5

Total time 35 minutes

The left-hand column shows the search number. The middle column shows the search terms used. These are all **Me**dical **S**ubject **H**eading (MeSH) terms, or Boolean combinations of these terms. The command 'exp' is an abbreviation for explode, which is an instruction to gather all relevant index terms that relate to the parent term. The abbreviation 'pc' stands for prevention and control. The right column shows the number of articles that match each search strategy, which can then be retrieved for viewing.

Note: the shown results are for the months January to September 2000. These searches were repeated for other years.

Comment

The paucity of information yielded by the electronic searches is disappointing. The lack of authoritative, up to date, immunisation guidelines was surprising. None of the possibly relevant papers could be accessed in full-text format. The limited evidence that was found needs to be interpreted with caution. Ideally, when assessing individual studies one should obtain the full texts of the papers to critically appraise their methods so that one can judge the validity of the studies and the applicability of the results to one's patients. At present only a few journals (such as *Australian Prescriber*) allow electronic access to their full text without prior subscription. In most instances clinicians are unable to access the papers they need to appraise.

The electronic searches conducted independently by the doctor and by the experienced medical librarian found different information. Each search took approximately 35 minutes. If critical appraisal of the full text of the articles had been possible, it would have added even more time to the process required for the practice of evidence-based medicine.

Conclusion

The road to evidence-based medicine is long, and we are but part way along it. Nonetheless, in the same way that modern transport has shrunk physical distances, it seems likely that information technology will continue to make accessible health-related information that previously was not accessible.

What are practitioners to do? To stretch the analogy further still, intrepid explorers will continue to take paths into the unknown and will through their trailblazing make information more accessible to the less adventurous. The intrepid explorers may be members of the Cochrane Collaboration or members of special societies or other organisations that take it upon themselves to produce evidence-based practice guidelines. Some individual clinicians who make the extraordinary effort of seeking out the best available evidence when they need it might also be among these explorers. Economic and other pressures dictate that not everyone can be an explorer. For the moment, in many areas there is no evidence and if there is, many doctors do not have the skills or time to find and appraise it.

Postscript

The doctor contacted an expert by e-mail for advice, and received the following reply.

'In previous years the flu vaccine has not been recommended for pregnant women. This year, the NHMRC has recommended it for all pregnant women. The reason for the change was the result of a case where a pregnant woman got influenza and actually ended up dying from it; the vaccine would have prevented her death. There is no evidence that the vaccine does any harm to the mother or the baby.' (Personal communication, Associate Professor Philip Hegarty, Faculty of Health and Behavioural Sciences, Deakin University, 2000)

The Consumer Medicine Information 2001 now recommends influenza vaccination for pregnant women who are in an at-risk group.

E-mail: p.darzins@nari.unimelb.edu.au

REFERENCE

1. National Health and Medical Research Council. A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra: Commonwealth of Australia; 1999. http://www.health.gov.au/hfs/nhmrc/publications/pdf/cp30.pdf

For detailed results of the searches described in this article, click here.

Self-test questions

The following statements are either true or false (answers on page 131)

5. The Medline database contains the full text of all the journals it includes.
6. The highest level of evidence, according to the National Health and Medical Research Council, is a randomised-controlled trial.

Your questions to the PBAC

Availability of methylphenidate

What is the Pharmaceutical Benefits Advisory Committee's justification for not including methylphenidate on the Pharmaceutical Benefits Scheme for attention deficit hyperactivity disorder, while allowing dexamphetamine?

G. Shakkal
By e-mail

PBAC response:

The Pharmaceutical Benefits Advisory Committee (PBAC) has considered whether methylphenidate 10 mg tablet should be recommended for listing for the treatment of attention deficit hyperactivity disorder. Data submitted by the manufacturer indicated that although this drug may be superior to dexamphetamine in some patients, the reverse is true in others, i.e. there is no difference in overall effectiveness between the two drugs. As a consequence, the PBAC recommended that methylphenidate be listed at a price equivalent to that currently applying to the listing of dexamphetamine. However, implementation of a recommendation depends on the negotiation, between the Government and the manufacturer, of a mutually acceptable price for the product. In the case of methylphenidate the negotiations have not been successful.

The *National Health Act 1953* under which the PBAC operates does not provide for merit appeals against the recommendations of the Committee. Rather, the applicant may address the issues by re-submission to the PBAC. A re-submission may include new data, new circumstances, new argument and new approaches to provide a basis for any change in the Committee's earlier decision.

ABNORMAL LABORATORY RESULTS

Screening for thalassaemia

D.K. Bowden, Associate Professor, Thalassaemia Service, Monash Medical Centre, Melbourne

SYNOPSIS

The thalassaemias are the commonest single gene disorders in the world's population and are a common cause of hereditary anaemia. They should be suspected in any individual who has reduced red blood cell indices. A full blood examination and haemoglobin electrophoresis are the tests which should be used first to investigate a suspected carrier of a thalassaemia gene. Iron deficiency can confuse the interpretation of test results, so iron studies are also often required. DNA analysis may be needed to detect the carrier state, particularly in carriers of α-thalassaemia.

Index words: haemoglobinopathies, iron deficiency.

(Aust Prescr 2001;24:120–3)

Introduction

Functioning haemoglobin (Hb) molecules are tetramers made up of two pairs of globin chains, which bind oxygen at the iron porphyrin site attached to each chain. The different types of Hb are characterised by their globin chains, which in adults may be α, β, δ or γ. Normal adult Hb is made up of approximately 97.0% HbA ($\alpha_2\beta_2$), 2.5% of the minor adult Hb, HbA_2 ($\alpha_2\delta_2$) and less than 0.8% HbF ($\alpha_2\gamma_2$).

The thalassaemia syndromes are a heterogeneous collection of genetic disorders characterised by a reduced rate of production of one or more of the globin chains of haemoglobin. The α-globin genes are located in the α-cluster on chromosome 16 and are paired (αα/αα) whereas the single β-globin gene is found in the β cluster on chromosome 11. The thalassaemia syndromes are usually caused by point mutations or deletions in, or close to, these globin genes which reduce or abolish expression of the affected gene. The type of thalassaemia is named according to which gene is affected. Hence reduced production of α-chains is called α-thalassaemia and reduced production of β-chains is called β-thalassaemia. The resulting imbalanced globin chain production gives rise to the phenotype of thalassaemia, while the severity depends on which genes are affected and which mutation or combination of mutations is inherited.

A large number of thalassaemia mutations are now known and can all be characterised by DNA analysis. In a carrier these mutations may be silent or may result in the typical haematological phenotype characterised by red blood cell hypochromia and/or microcytosis. The inheritance of a β-thalassaemia mutation from each parent usually causes the severe disease called β-thalassaemia major.

The genetics of α-thalassaemia are more complex as one, two, three or all four genes may be affected. For example HbH disease is usually caused by the deletion of three α-globin genes (--/-α) as a result of the inheritance of a single gene deletion mutation (-α/) from one parent and a two-gene deletion mutation (--/) from the other parent.

Other mutations cause the important, clinically significant structural Hb variants, such as Hb S, C, D, E, O and Lepore. Certain combinations of these mutations may cause severe disease as outlined in Table 1.

Testing in Australia

Australia's population is ethnically diverse and there have always been a significant number of carriers of β-thalassaemia mutations. If both parents are carriers there is a 1 in 4 chance in each pregnancy of them having a child with β-thalassaemia major.

Recent immigration to Australia, especially from South-East Asia, has introduced large populations of people from areas where α-thalassaemia is common. It has now become important in screening programs, particularly antenatal testing, to detect the carrier state for both α- and β-thalassaemia, in addition to the Hb variants which in the homozygous form, or in combination with β-thalassaemia, may cause severe disease.

The laboratory diagnosis of the thalassaemia carrier state is therefore of increasing importance both for antenatal diagnosis and for clinical management. Thalassaemias are common in Australia and are a significant public health problem. In Melbourne approximately 10% of women in their first pregnancy required DNA studies to adequately characterise their carrier state and to provide sufficient information to estimate the risk that their children would have severe disease (Table 1).

Table 1

Examples of the severe disease risk states identified in recent years in Melbourne's population

β-globin mutations	Homozygous β-thalassaemia
	Hb E/ β-thalassaemia
	Hb Lepore/ β-thalassaemia
	Sickle cell disease
	HbS/β-thalassaemia
	HbS/HbC disease
	HbS/HbD disease
α-globin mutations	HbH disease (usually mild but occasionally severe)
	HbH hydrops syndrome (rare)
	Hb Bart's hydrops syndrome

Indications for testing

An accurate diagnosis may be needed to:

- explain haematological abnormality, such as reduced mean cell volume (MCV), mean cell haemoglobin (MCH), or anaemia
- confirm a diagnosis of the severe disorders such as sickle cell disease, or β-thalassaemia major
- characterise the mutation underlying a thalassaemia carrier state, particularly for α-thalassaemia where the molecular basis can only be determined and clarified by analysis of DNA
- test for silent mutations which might have clinical significance if inherited with a mutation from the other parent, for example silent α- or β-thalassaemia or coexistent α-thalassaemia in a β-thalassaemia or HbE carrier
- provide accurate genetic counselling to individuals and prospective parents
- identify serious disorders in the fetus and hence provide the additional option to couples of termination of pregnancy
- identify haemoglobins such as HbS preoperatively
- fully characterise a variant haemoglobin.

α-thalassaemia

Each individual normally inherits two pairs of functioning α-globin genes. These are designated as αα/αα. Mutations in this gene cluster causing α-thalassaemia most commonly delete one of the α-globin genes (-α/αα). Point mutations (α^T) within one of the genes may also inactivate the gene. This usually causes a phenotype with a mild carrier state ($\alpha^T\alpha/\alpha\alpha$) equivalent to having single gene deletion mutation. Rarely a point mutation in one globin gene may reduce expression of both genes resulting in a more severe phenotype equivalent to the two gene deletion carrier. Single gene deletion mutations are found in most populations, but only occur naturally at high frequencies in areas of the world where malaria is or was endemic. The common deletional mutations can have slightly different effects on the patient's red blood cells (Table 2).

In South-East Asia up to 10% of the population are carriers of the more severe two gene deletion mutation (--/αα). These two gene deletion mutations are also found sporadically in other populations, including the Mediterranean region.

Table 2

Examples of mean values of mean cell volume (MCV) and mean cell haemoglobin (MCH) in adults according to α-thalassaemia genotype*

Genotype	*MCV(fl)*	*MCH(pg)*
αα/αα (normal)	89±5	29±2
-α/αα	84±6	27±2
--/αα, or -α/-α	75±4	23±2

* These figures are a guide only to illustrate typical values and are age and sex dependent. Precise values are given in the references cited.[1,5]

The mutations of the α-globin genes may be inherited in any combination. The more severe clinical conditions arising from the inheritance of more than one α-thalassaemia mutation include HbH disease (--/-α), Hb Bart's hydrops syndrome (--/--) and the rare HbH hydrops syndrome ($\alpha^T\alpha/\alpha^T\alpha$). HbH disease varies in severity, but is commonly a moderately severe chronic haemolytic anaemia associated with Hb in the 80–100 g/L range, with periodic exacerbations of anaemia because of infection or other oxidant stress.

Hb Bart's hydrops syndrome

This is a serious and significant clinical condition. It not only leads to the death of the baby, but may also adversely affect the health of the mother during pregnancy. In unsupervised pregnancies there is up to a 50% maternal mortality with a high incidence of hypertension and haemorrhage.[1] Affected babies usually die at delivery. These at-risk pregnancies should be recognised as early as possible and termination of affected pregnancies is advised on medical grounds.

β-thalassaemia

Each individual inherits, from each parent, a single β-globin gene located in the β-globin cluster on chromosome 11. The β-thalassaemia carrier state has been known for many decades. There are often typical hypochromic microcytic red blood cell changes. Hb electrophoresis reveals the diagnostic elevation of the minor adult HbA_2 ($\alpha_2\delta_2$).

Screening is not always straightforward. Some of the mutations are now known to have a less severe effect on gene expression.[2] Although they are capable of causing severe disease in homozygotes, the indices in carriers may be borderline or normal and the HbA_2 may be minimally elevated or even in the normal range.

In most populations where β-thalassaemia is present there is also a significant incidence of α-thalassaemia. Individuals therefore commonly inherit both α-thalassaemia and β-thalassaemia, an interaction which is usually benign and leads to a milder phenotype. The α-thalassaemia carrier state is masked in this setting and ultimately can only be excluded by DNA analysis. In our experience the HbA_2 level usually remains elevated in those who are carriers of both α- and β-thalassaemia.

Structural haemoglobin variants and thalassaemia

Many haemoglobin variants of clinical significance are known. For example, the substitution of one particular amino acid in the β-globin chain produces the HbS associated with the sickle cell disorders. In Australia we encounter only a small number of variants capable of causing severe disease in the homozygote or in compound heterozygotes. These include Hb E, S, C, D, O and Lepore which are all readily identified by Hb electrophoresis. It is common for there to be no other haematological change and hence the variants will be overlooked unless Hb electrophoresis is carried out.[3] HbE behaves as a mild β-thalassaemia mutation and is common in

South-East Asia where more than 50% of the population are carriers in some areas.

Some of these variants, in combination with the β-thalassaemia gene, may cause severe disease. HbE/β-thalassaemia is common in South-East Asia and varies clinically from a mild condition to the more common severe disease equivalent to β-thalassaemia major. β-thalassaemia combined with HbS or HbC usually results in sickle cell disease although the phenotype may vary considerably from mild to severe disease depending on which combination of mutations is inherited.

Laboratory diagnosis

The thalassaemias and structurally abnormal haemoglobins are common in Australia so accurate laboratory diagnosis is of growing importance. This is because of the increasing expectation of prospective parents to be offered antenatal diagnosis if there is an identifiable risk of them having a child with severe disease. There is also a need to characterise carrier states to provide an explanation of abnormal haematology, or to help clarify an otherwise confusing clinical picture, such as the coexistence of α-thalassaemia and iron deficiency anaemia.

Appropriate genetic counselling requires the detection and adequate characterisation of thalassaemia carrier states and the Hb variants. Local policies and practices on screening vary considerably.

Initial testing

The Melbourne working party on thalassaemia and haemoglobinopathies currently recommends that all suspected carriers have a full blood examination and Hb electrophoresis. Reduced red blood cell indices (MCV and MCH) are typical of the majority of carriers of β-thalassaemia, δβ-thalassaemia* and two gene deletion α-thalassaemia. Significant reticulocytosis is likely to be found in anyone with a chronic haemolytic anaemia such as in the HbS disorders and HbH disease. If the indices are reduced iron studies should be carried out to exclude iron deficiency or to identify it as a coexisting condition.

Electrophoresis is recommended as the majority of variant haemoglobins can only be detected by Hb electrophoresis and the indices are often normal in the carrier. High-performance liquid chromatography will identify variant haemoglobins, and also quantitate the HbA_2 level. Specialised laboratories may go on to carry out other tests on Hb variants in order to characterise them more fully, before deciding whether DNA analysis is required.

β-thalassaemia

Nearly all β-thalassaemia carriers have elevated concentrations of HbA_2, and reduced indices. The accurate quantitation of HbA_2 is of particular importance and concern. The upper limit of normal for HbA_2 is 3.5% of the total Hb. Any value above this should be regarded as diagnostic of the β-thalassaemia carrier state, irrespective of the indices on the blood test. All but a few individuals, who are further studied by DNA analysis, will have a known mutation.

There are some clinically important β-thalassaemia mutations in which the indices may be normal, and the HbA_2 may also be normal, minimally elevated or borderline. Other mutations may also confuse the diagnosis of the carrier state. The HbA_2 level may be halved by the coexistence of a δ-gene mutation. These are uncommon but well known in some populations. Iron deficiency may lower a borderline HbA_2 into the normal range.[4]

Some of the less common mutations may have an entirely normal phenotype or normal indices with a mildly elevated HbA_2 level, in the 3.5–4.0% range. This is further complicated by the possibility of an individual having inherited both α- and β-thalassaemia in the carrier states where there may be an amelioration of haematological abnormality. In these situations, the MCV and MCH are variable and may be normal, or near normal. In our experience, however, the elevated HbA_2 is usually not changed by the coexistence of α-thalassaemia.

α-thalassaemia

The identification of an α-thalassaemia carrier is more complex and relies ultimately on DNA analysis to complete the testing and identify the mutation. Two gene deletion α-thalassaemia (--/αα), and homozygous single gene deletion α-thalassaemia (-α/-α) have a similar phenotype and typically show a moderate reduction in the MCV and MCH (Table 2).[1] Abnormality is more likely in the MCH rather than the MCV. This has been known for many years, however there seems to be a reluctance for laboratories to screen using the MCH as the primary critical reference value.[2,3] Two gene deletion α-thalassaemia is most common in South-East Asia, but also occurs sporadically in other parts of the world. It should always be considered in anyone with suggestive indices, although DNA analysis is required for characterisation.

The majority of individuals with single gene deletion α-thalassaemia have entirely normal haematology.[1] In this situation, the carrier state can only be identified by DNA analysis. Therefore haematologically normal partners of an individual with a two gene deletion α-thalassaemia require DNA analysis to determine whether or not there is a risk of them having a child with HbH disease (Table 3).

Iron deficiency

Iron deficiency is common in adult women in Australia. In 1997 up to 40% of women attending their first antenatal appointment in Melbourne were iron deficient. This is not a universal figure, and is probably disproportionately high for the general population, however, it is a serious potential complicating factor when testing for a thalassaemia carrier state. Both iron deficiency and a thalassaemia carrier state may result in a low MCV and MCH. Erythrocytosis is more likely to be caused by thalassaemia, but it is not a diagnostic finding.

In pregnant women with a low MCV and MCH Hb electrophoresis should be carried out routinely, irrespective

* In δβ-thalassaemia the production of δ chains and β chains is impaired.

Table 3

Tests to be performed in the partner of a carrier to determine the risk of having a child with severe disease

Disorder found in one partner	*Test to be carried out in other partner to exclude severe disease risk in a child*
β-thalassaemia carrier	FBE, Hb electrophoresis, to exclude β-thalassaemia and δβ-thalassaemia carrier state, and Hb S, E, O, D, C and Lepore
Carrier of Hb Lepore, δβ-thalassaemia, Hb S, C, D, E or O	as for β-thalassaemia carrier
Two gene deletion α-thalassaemia (--/αα)	FBE, Hb electrophoresis, HbH inclusion prep, DNA analysis (to exclude risk of having a child with HbH disease or Bart's hydrops syndrome)
Single gene deletion α-thalassaemia (-α/αα or -α/-α)	as for two gene deletion α-thalassaemia to identify risk of having a child with HbH disease

FBE = full blood examination

of iron status. If possible the father should be tested. If a non-iron deficient partner has evidence of a thalassaemia carrier state or other haemoglobinopathy, then the woman should have full testing, including DNA analysis to adequately define the risk of them having a child with severe disease (Table 3).

Summary

The identification of carriers of thalassaemia and other clinically significant haemoglobinopathies is a two-stage process. Initially evidence for the carrier state is sought by carrying out a full blood examination and Hb electrophoresis. Iron deficiency can be excluded as a complicating factor by iron studies in individuals who show a haematological abnormality consistent with this diagnosis. In this relatively simple way evidence for all but single gene deletion α-thalassaemia (and most non-deletional point mutations) will usually be obtained. Further studies including DNA analysis can then be carried out for final clarification of the carrier state. In this way it is usually possible to identify all but a few mutations and to provide informative counselling for individuals and couples.

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REFERENCES

1. Higgs DR. alpha-Thalassaemia. Ballieres Best Pract Res Clin Haematol 1993;6:117-50.
2. The laboratory diagnosis of haemoglobinopathies. Br J Haematol 1998;101:783-92.
3. Hendy JG, Monagle PT, Bowden DK. Antenatal screening and prenatal diagnosis of thalassaemia. Med J Aust 1999;170:623-4.
4. Wasi P, Disthasongchan P, Na-Nakorn S. The effect of iron deficiency on the levels of haemoglobins A2 and E. J Lab Clin Med 1968;71:85-91.
5. Williams TN, Maitland K, Ganczakowski M, Peto TE, Clegg JB, Weatherall DJ, et al. Red blood cell phenotypes in the alpha + thalassaemias from early childhood to maturity. Br J Haematol 1996;95:266-72.

Self-test questions

The following statements are either true or false (answers on page 131)

7. Thalassaemia and iron deficiency can cause microcytosis of red blood cells.
8. Babies who carry mutations for both α-thalassaemia and β-thalassaemia usually die at birth.

Gardener's corner

Australians are increasingly using complementary medicines. *Australian Prescriber* will therefore be commenting occasionally on some of these medicines. This is not an endorsement of their effectiveness, but an attempt to provide health professionals with some information about the products their patients may be taking.

Agnus castus fruit

The fruits of the chaste tree (*Vitex agnus castus*) have historically been used as a remedy for gynaecological problems. While the active ingredient is uncertain, the fruits contain flavonoids and iridoids. Although the mechanism of action is unknown the active ingredient is thought to modulate the secretion of prolactin. It may also bind to opioid receptors.

A recent placebo-controlled trial studied an extract (Ze440) of agnus castus fruit in 170 women with premenstrual syndrome.[1] After three months, women who took the extract reported a greater reduction in symptoms than the women taking a placebo did. There were significant reductions in anger, irritability, headache, and breast fullness.

The fruit is not known to have serious adverse effects and none emerged in this trial. It is not known if there are any significant drug interactions with the extract.

Although significantly more women responded to the extract only 52% had an improvement of more than 50% in their symptoms. (24% of the women taking a placebo had a greater than 50% improvement.) The trial did not investigate if these benefits were maintained after the end of the study. Other formulations cannot be assumed to have the same efficacy as the extract used in this trial.

REFERENCE

1. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. Br Med J 2001;322:134-7.

Treatment of urticaria

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SYNOPSIS

Urticaria and angioedema can be caused by allergic and non-allergic mechanisms. While acute urticaria usually resolves quickly, chronic urticaria can persist for years. Management begins with a classification of the type of urticaria. Extensive investigations are usually unnecessary. Treatment includes avoiding the factors which provoke the reaction. When this is not possible, antihistamines remain the treatment of choice. A non-sedating antihistamine is preferred. More severe cases may require corticosteroids or immunosuppressant drugs.

Index words: anaphylaxis, angioedema, antihistamines.

(Aust Prescr 2001;24:124–6)

Introduction

Urticaria is a common condition affecting approximately 25% of the population at some time. It has many causes. Urticaria is unpredictable and results in a great deal of distress because of the intense pruritis, and the interference it causes to sleep and daily life. The fundamental step in managing a patient with urticaria is to try and classify the nature of the condition. This will determine which, if any, investigations are necessary. Antihistamines remain the mainstay of treatment, but in some cases other strategies are necessary.

In approximately 50% of patients, urticaria and angioedema coexist, while 40% experience urticaria alone and 10% will have isolated angioedema. The hallmark of urticaria is transient (less than 24 hours duration) pruritic wheals. Angioedema is a deep dermal, subcutaneous or submucosal oedema resulting in swelling which generally lasts 24 hours and sometimes longer.

Urticaria/angioedema is generally classified as acute (lasting up to six weeks) and chronic (lasting longer than six weeks). Urticaria may also occur intermittently, where lesions appear for days or weeks with symptom-free intervals lasting weeks or months.

Chronic urticaria is relatively common, occurring in 0.1% of the population, with 20% still having problems 10 years after its onset. Pruritus is invariably distressing, usually at its worst in the evening and during the night. Chronic urticaria causes a major impairment to the individual's quality of life and its impact on the patient should never be underestimated.

Aetiology

The final common pathway in the induction of urticaria/angioedema involves local increase in the permeability of capillaries and small venules triggered by mediators released as a consequence of mast cell degranulation. This degranulation may result from immunological or non-immunological triggers.

IgE-mediated reactions are the commonest causes of acute urticaria and are generally severe, with a dramatic onset. Other manifestations of anaphylaxis may be evident. Symptoms will occur within minutes to a few hours of exposure to an allergen. Acute reactions are most commonly experienced in childhood. Foods such as nuts, eggs, milk and seafood account for many of these reactions. Reactions to insect stings also fall into this category. Some patients react to a physical stimulus, for example cold or vibration.

Any drug is capable of producing an acute allergic reaction manifested by acute urticaria but antibiotics, particularly penicillin, remain the commonest cause of an acute urticarial drug reaction. Non-steroidal anti-inflammatory drugs including aspirin are other common drugs causing acute urticaria/angioedema. Although the reaction is indistinguishable from an IgE-mediated reaction, the mechanism is considered to be related to inhibition of cyclo-oxygenase. Aspirin and related compounds are also common non-specific provokers of chronic urticaria/angioedema and should be avoided by all patients with the condition. ACE inhibitors are associated with provocation of angioedema and should not be prescribed to patients with urticaria/angioedema.

Infection may play a role in some cases of urticaria as is seen commonly in children with viral infections, during prodromal stages of hepatitis B and with Epstein Barr virus infection. Intercurrent viral infections commonly exacerbate chronic urticaria.

Most urticaria occurring on a daily basis will not have an IgE-mediated mechanism. There is no increased frequency of atopy in chronic urticaria – systemic involvement is minimal although patients will often complain of excessive fatigue.

Diagnosis of chronic urticaria

The evaluation of a patient with prolonged symptoms begins with an attempt to classify the type of chronic urticaria.

Patients should be differentiated into those whose lesions occur spontaneously and those with symptoms caused by physical factors. If a patient suffers primarily from a physical urticaria there is usually no need for further investigation beyond any challenge necessary to confirm the diagnosis. Many patients who have physical urticaria are subjected to costly tests and unnecessary dietary examinations which never influence the management of their long-term condition.

The physical urticarias[1] are characterised by whealing and itching following the appropriate physical stimulus. It is

common to observe patients with more than one type of physical urticaria. Dermographism, literally 'writing on the skin', may occur as an isolated finding. Individuals present with traumatically induced urticaria. This condition is present in approximately 5% of the population.

Cholinergic urticaria is a commonly seen physical urticaria, predominantly found in teenagers and young adults. It probably occurs at some time during the lives of 15% of the population. Characteristically, it appears as very small, intensely itchy wheals, over the neck, arms, thighs and trunk in response to increased body heat. Activation of the cholinergic sympathetic innervation of the sweat glands is a likely mechanism.

Most commonly, the wheals of physical urticaria come on soon after the appropriate stimulus and are usually transitory. Delayed pressure urticaria is the exception to this. In this condition, there is a delay of two or more hours between the stimulus and the appearance of the lesions, which are often painful as well as itchy. They can last more than 24 hours.

Once the physical urticarias are excluded, some of the remaining cases of chronic urticaria may be the result of food/food chemical intolerance. As the mechanisms for this intolerance are not understood, there are no *in vitro* or *in vivo* tests which aid diagnosis. An elimination diet, followed by blinded, placebo-controlled challenges, is the appropriate investigation. Any elimination diet should be monitored carefully and not continued for long periods of time.

In the remaining patients, an underlying cause is usually not found. Recently, it has become clear that 25–50% of patients with chronic urticaria have an autoimmune problem. Certain autoantibodies have been identified and these are responsible for the repeated release of histamine from activated mast cells.

Urticarial vasculitis

This is a differential diagnosis of chronic urticaria. Historically, patients have their lesions for longer than 24 hours and these often fade leaving a bruise or an area of pigmentation. A skin biopsy, preferably of a recent lesion, is necessary to confirm the diagnosis. Once confirmed, patients require investigation to exclude an underlying cause such as hepatitis B and C, systemic lupus erythematosis, paraproteinaemia and inflammatory bowel disease. Urticarial vasculitis is usually non-responsive to antihistamines and often requires corticosteroids to bring the condition under control. A second immunomodulatory agent is frequently required to minimise long-term exposure to steroids.

Management

Treatment begins with an attempt at classifying the nature of the patient's urticaria.

Management of the patient with a physical urticaria begins with an explanation of how the physical factor(s) provoke the reaction. No laboratory investigations are necessary. Avoidance measures can be very effective in limiting the number of episodes. Antihistamines may have a useful role in some cases although they are typically ineffective in patients with delayed pressure urticaria.

Those patients who have suffered an acute, severe episode, usually with other features of an acute allergic reaction, require careful assessment, including skin testing with appropriate allergens. Most cases of urticaria and angioedema of less than six weeks duration will settle with symptomatic measures and rarely require investigation.

In patients with chronic urticaria, an explanation of the condition and its tendency to be a long-lived problem is essential if they are to come to terms with a very distressing situation and learn to manage it. Reassurance that the problem is not a sign of cancer or any other severe disease is important. Extensive laboratory investigation is unnecessary and rarely yields useful results, but appropriate investigation should follow any clues from a careful history and physical examination.

Patients with chronic urticaria and angioedema require counselling about the avoidance of non-specific aggravating factors such as overheating, overexertion, alcohol excess, and the use of aspirin and related compounds. Simple measures such as tepid showers, oatmeal baths and ice packs can give some temporary relief.

Antihistamines

The cornerstone of pharmacological management is the use of H_1 antagonists. All patients with frequent symptoms should use an antihistamine every day in an attempt to achieve complete suppression of wheals. This is more effective than taking a drug 'as needed' when symptoms become severe. For regular use, the newer, non-sedating antihistamines have distinct advantages over the older drugs in their superior safety profile and in particular, their relative lack of sedation. There are few data to suggest that one drug in this class is superior to another, although patients usually express a preference for a particular product. When night-time pruritis is severe and interrupts sleep, a sedative antihistamine may be useful before bedtime, but the patient must be warned about early morning drowsiness. In severe cases, some practitioners advocate a non-sedating antihistamine in the morning and a sedating one at night.

Doxepin

In troublesome cases, doxepin is certainly worth a trial.[2] Doxepin is a tricyclic antidepressant, which possesses both H_1 and H_2 antagonist properties. Its sedative action may be beneficial when sleep disturbance is troublesome. The mild anxiolytic effects may also be an advantage if the patient has a lot of psychological distress. A dosage of 25–50 mg at night is usually effective.

Cimetidine

In many patients, H_1 antagonists do not adequately control symptoms. Following the discovery that the blood vessels of the skin contain H_2 receptors in addition to H_1 receptors, a number of trials have studied the effect of adding an H_2 antagonist to an H_1 antagonist in the management of chronic urticaria. While the early studies were inconclusive, a number of studies have found a benefit from adding cimetidine.[3] This strategy is worth a trial for a few weeks in patients not well controlled with H_1 antagonists alone.

Leukotriene antagonists

The leukotrienes are important products of mast cell activation and degranulation. Inhibition of these mediators may play a useful role in the management of chronic urticaria. With the advent of the leukotriene receptor antagonists, there is the opportunity for exploring this possibility. Results of clinical trials are awaited.

Other drugs

A variety of other drugs have been tried in resistant cases. Small studies have been published regarding the use of calcium antagonists and thyroxine in those with thyroid autoimmunity. Hydroxychloroquine and dapsone have also been used in occasional cases but in general, none of these drugs has been dramatically effective and all have significant potential adverse effects.

Immunomodulatory drugs

In patients identified as having autoimmune urticaria, initial treatment is the same as for any other urticaria, commencing with an adequate trial of antihistamines. However, patients with autoimmune urticaria tend to be more severely affected and less responsive to simple drugs. When the condition is causing marked disruption, other strategies may be considered. Reports of success with plasmapheresis and immunoglobulin infusions have been published, but this treatment should be regarded as experimental. A placebo-controlled trial of cyclosporin has had impressive results.[4] None of these treatments cures the condition, but they may be preferable to prolonged steroid use.

Corticosteroids

When rapid control of urticaria is needed, a short tapering course of steroids may be used, but in any other situation their role is limited. If prednisolone is to be used, it is advisable to give a moderate starting dose, e.g. 0.5 mg/kg (20–25 mg) for a few days before tapering slowly over a 10 day period.

Invariably, prolonged use of steroids leads to numerous adverse effects and severe rebound in urticaria when withdrawal is attempted.

REFERENCES

1. Greaves M. Chronic urticaria. J Allergy Clin Immunol 2000;105:664-72.
2. Greene SL, Reed CE, Schroeter AL. Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. J Am Acad Dermatol 1985;12:669-75. (Randomised trial)
3. Bleehen SS, Thomas SE, Greaves MW, Newton J, Kennedy CT, Hindley F, et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. Br J Dermatol 1987;117:81-8. (Randomised trial)
4. Grattan CE, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. Br J Dermatol 2000;143:365-72. (Randomised trial)

Self-test questions

The following statements are either true or false (answers on page 131)

9. H_2 antagonists are ineffective in urticaria as there are no H_2 receptors in the skin.
10. Hepatitis C is a cause of urticarial vasculitis.

Facilitators file

The National Prescribing Service (NPS) has provided funds to divisions of general practice to employ facilitators. These facilitators visit general practitioners to discuss common prescribing problems. During their visits the facilitators are finding some interesting issues. *Australian Prescriber* is planning to publish some of these findings from time to time.

Combination antihypertensives

If a patient's blood pressure cannot be controlled by lifestyle changes drug treatment is needed. Therapeutic guidelines recommend starting treatment with one drug and adjusting the dose.[1] The NPS facilitators have, however, discovered that many patients are being started on fixed dose combination products.

The Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee has also found evidence that combination products are being used as first-line therapy. A review of new prescriptions for a product containing irbesartan and hydrochlorothiazide found that 17% of patients had not previously been prescribed an angiotensin receptor antagonist, an ACE inhibitor or a diuretic. Approximately 16% of patients who were prescribed a combination containing fosinopril and hydrochlorothiazide had not previously taken an ACE inhibitor, an angiotensin receptor antagonist or a diuretic.

Although some patients will need more than one drug to control their hypertension, it is best practice to start with a single product. Even some cases of severe hypertension can be managed with a single drug. Patients who do need two drugs may need doses which differ from those found in combination products. The fixed doses in these products make it difficult to titrate the dose to achieve optimum control of each patient's blood pressure.

REFERENCE

1. Writing Group for Therapeutic Guidelines: Cardiovascular. Therapeutic Guidelines: Cardiovascular. 3rd ed. Melbourne: Therapeutic Guidelines Ltd.; 1999.

Combination products – love them or loathe them?

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SYNOPSIS

The introduction of new combination products requires prescribers to decide whether or not to include these formulations in their personal formulary. Although there is little firm evidence to guide us, factors in favour of their use include better patient compliance, simplicity for prescribers, and in some cases reduced cost. Factors against their use include the inability to adjust the dose of each component separately, exposing the patient unnecessarily to more than one drug, and incompatible kinetics. Prescribers should only consider prescribing a combination product if it will facilitate treatment according to generally accepted guidelines.

Index words: compliance, cost of drugs.

(Aust Prescr 2001;24:127–9)

Introduction

Prescribers have recently been presented with an array of new combination products, such as the combination of a thiazide diuretic and an ACE inhibitor. Australia has been slow to allow the marketing of these products. They have been available for years in Europe, where physicians are confronted with a bewildering array of combinations. Indeed sometimes it seems all the different drugs for treating hypertension have been combined in as many different permutations as possible.

So what should our attitude be to these products? Should we welcome the fact that Australia has finally been dragged into the modern world of therapeutics, or should we bemoan the fact that one of the bastions of rational prescribing has finally been breached?

Combination products are not new in Australia. They are widespread, indeed almost the norm, in the 'over-the-counter' area. Combination analgesics (e.g. paracetamol with codeine) have been available for years. Special cases have also been made, and accepted, in the past for combinations such as sulfamethoxazole with trimethoprim, or amoxycillin and clavulanic acid to broaden their antimicrobial spectrum, or the combination of L-dopa plus a peripheral decarboxylase inhibitor, to decrease the peripheral adverse effects of L-dopa. However, the recent approval of a large number of combination products seems to signal that the Australian Drug Evaluation Committee and the Therapeutic Goods Administration have relaxed their opposition to these formulations.

Pros and cons

The main arguments for and against combination products are summarised in Table 1. Unfortunately, the clarity of the arguments is not always accompanied by equal clarity of evidence. Each argument needs to be looked at critically rather than simply accepted.

Compliance

It seems intuitively obvious that patients are more likely to take one tablet than two or more tablets. However, the evidence for this assertion involves extrapolation from old compliance studies showing that there is in general an inverse relationship between compliance and the frequency and complexity of medication regimens.[1,2] This extrapolation may be invalid at the lowest end of the complexity range when going from two tablets daily to one tablet daily. The extrapolation also might not hold when patients are taking many drugs and only a small change is made to the complexity of their regimen.

Simplicity of prescribing

In general, it is more convenient to prescribe a combination product than it is to prescribe the individual components separately. However, there is no evidence that the simpler it is to prescribe a drug, the more likely it is to be done well. In fact experience suggests the opposite. 'Simple' prescribing can all too easily slip into 'lazy' prescribing. For example, in hospitals there has long been concern that compound analgesics (such as paracetamol and dextropropoxyphene) are overprescribed when the compound formulation is easier to prescribe than the individual components.

Cost

The cost of drugs is an important factor. It is an argument for using a combination product which costs less than the sum of its components. However, prices are fickle and go up and down, so cost should not be used as the basis for long-term prescribing policies. Patient co-payments are less for a single combination item than for two separate items.

Table 1

Arguments for and against combination products

For	*Against*
• Improved patient compliance	• The inability to adjust the doses of the individual components
• Convenience for prescribers	• Exposing the patient to more than one drug unnecessarily
• Reduced expense	• Different pharmacokinetics of the components

Dose adjustment

The inability to adjust the doses of the individual components is a strong argument against the use of combination products. It is only relevant, however, if both components are dose sensitive. A combination may be appropriate if the prescriber and patient have determined that each component is required at the dose contained in the combination. However, how often will the dose of each drug be titrated, before starting the combination?

If only one component in the combination is dose sensitive, then the overall dose can be adjusted to reflect the patient's particular dose requirement for that component, and it will not matter that the dose of the other component(s) automatically changes as well. However, no drug is totally dose insensitive, particularly for adverse effects. So the inability to adjust the individual components will always be a disadvantage.

Unnecessary risk

The issue of exposing the patient to more than one drug unnecessarily only pertains if the patient does not require one or more of the components of the compound product. Ideally this should not occur, as the patient should only be prescribed a combination product when both components are required.

In real life it is likely that an initial judgement, presumably based on the severity of the problem, will often be made that two drugs will be required. The decision to start treatment with a combination may not always be correct. Some patients may therefore be exposed to an extra drug, and thus unnecessarily run the risk of adverse effects.

Pharmacokinetics

If the time course of the clinically important effects of the components of a combination follows their individual kinetics, there will be a major problem if the components have substantially different pharmacokinetics. If the kinetics of both components are relevant to their effects, it will be impossible to have a regimen for repeated doses that does not result in either underdosing or overdosing of one of the components.

If only one component has an effect which follows its kinetics then the dose frequency can be set to better reflect the kinetics of that particular component. It will not then matter that the other component is being taken either too frequently or not frequently enough.

To use or not to use?

An important factor influencing our decision on whether or not to prescribe a particular combination product is how well it enables us to prescribe according to generally accepted therapeutic guidelines. To put this in perspective, it might be helpful to consider the example of a hypothetical compound product, e.g. bendrofluazide 5 mg plus enalapril 10 mg, for hypertension.

Both drugs are usually given once daily, so in terms of their pharmacokinetics the combination is reasonable. However the maximum dose of bendrofluazide is normally only 5 mg daily to minimise metabolic adverse effects, whereas enalapril may need dose adjustment up to 20 mg, or even 40 mg, daily. You cannot titrate the individual doses of a combination product, so from a dose adjustment point of view, this combination product is not good.

If the prescriber has already established that a particular patient requires both bendrofluazide 5 mg daily and enalapril 10 mg daily to control their blood pressure, it would obviously be reasonable to switch the patient to the combination product. Cost will presumably be the main factor influencing this decision, although compliance might also be better with the combination product. However, the consequences of missing a tablet will be greater than when the patient was taking the drugs individually and only missed one of them.

A significant problem is likely to be the temptation to prescribe the combination as first-line treatment for hypertension. Current guidelines recommend thiazide diuretics or beta blockers as first-line treatment. Although the use of an ACE inhibitor may be reasonable, combinations are not recommended as first-line treatment.

To justify the use of the combination as first-line treatment the prescriber must decide if the particular patient is going to need two drugs rather than one. No one should trust their judgement on that issue! Although there is a relation between the severity of hypertension and the number of drugs required for satisfactory control, not all patients, even those with moderately severe hypertension, will require two drugs. There is at present no evidence on how to make the judgement in individual patients as to whether or not they will eventually require two drugs rather than one drug to control their blood pressure.

A reasonable approach in all but a very severe case would be to commence treatment with bendrofluazide 2.5 mg daily alone. If the response is not ideal, then an ACE inhibitor, in this case enalapril, could be added. If this controls the hypertension the use of the combination product might then be appropriate. However if the response is very poor, or if the patient develops any adverse effects, it would be more logical to substitute another drug for the thiazide, and a beta blocker might be more consistent with guidelines than an ACE inhibitor.

If a patient is already taking bendrofluazide or enalapril, and control is unsatisfactory, the prescriber should decide, before changing to the combination product, whether or not the second drug would normally be added to, or substituted for, the first drug. If addition is reasonable, then using the combination product might be appropriate, but if substitution is indicated then the combination product would not be appropriate.

Conclusion

Combination products require us to think carefully about our prescribing. In some circumstances they might simplify, or even improve, therapy. However there is a real possibility they will tempt us into 'lazy' prescribing.

We should consider if using a combination product helps us to prescribe according to accepted guidelines. Paradoxically, an innovation which at first sight seems to simplify prescribing will perhaps make it more complex.

Conflict of interest: none declared

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REFERENCES

1. Wright EC. Non-compliance – or how many aunts has Matilda? Lancet 1993;342:909-13.
2. Greenberg RN. Overview of patient compliance with medication dosing: a literature review. Clin Ther 1984;6:592-9.

New drugs

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

Dexmedetomidine

Precedex (Abbott)

2 mL ampoules containing 100 microgram/mL

Approved indication: sedation

Australian Medicines Handbook Section 2.2

For several years it has been known that the antihypertensive drug clonidine can reduce the required dose of anaesthetic drugs. It does this by stimulating alpha$_2$ adrenoceptors. Dexmedetomidine also acts as an agonist at these receptors. This action has analgesic effects and, possibly because of an effect on the locus ceruleus, also causes sedation.

Dexmedetomidine has been approved for the sedation of intubated post-surgical patients during treatment in intensive care. It has been compared with placebo for this indication in a British study. Patients who were given dexmedetomidine required 80% less midazolam for sedation and 50% less morphine for analgesia.[1] A study comparing dexmedetomidine with propofol found that both drugs adequately sedated the patients. Those given dexmedetomidine required significantly less morphine for analgesia. Dexmedetomidine has an advantage because it causes little respiratory depression, so patients can be extubated without having to wait for their respiratory function to recover.

As dexmedetomidine is given by infusion, it must be diluted before use. A loading dose is given over 10 minutes followed by a maintenance infusion which is adjusted according to the clinical response. The infusion should not exceed 24 hours.

Dexmedetomidine has a half-life of two hours. It is almost completely metabolised with most of the metabolites being excreted in the urine. Dose reductions may be needed for patients with renal or hepatic impairment. Although cytochrome P450 2A6 is involved in the metabolism clinically significant interactions are thought to be unlikely.

Dexmedetomidine does interact with anaesthetic drugs, opioids and sedatives so it should only be used in intensive care. Patients require monitoring of their electrocardiogram, oxygen saturation and blood pressure.

Hypotension is the most common adverse reaction, occurring in 22% of patients, however some patients will become hypertensive. Dexmedetomidine can also cause bradycardia. Patients who are elderly, or who have diabetes or heart failure, have an increased risk of these adverse effects because of changes in their autonomic nervous systems. Lower doses are recommended for the elderly.

Dexmedetomidine has been approved on the evidence gathered from fewer than 600 patients. It may take more clinical experience to determine whether its benefits are outweighed by the adverse reactions.

REFERENCE

1. Venn RM, Bradshaw CJ, Spencer R, Brealey D, Caudwell E, Naughton C, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia 1999;54:1136-42.

Imatinib mesylate

Glivec (Novartis)

50 mg and 100 mg capsules

Approved indication: chronic myeloid leukaemia

Australian Medicines Handbook Section 14.3.9

Most patients with chronic myeloid leukaemia have a translocation of chromosomes 9 and 22. The abnormal chromosome, known as the Philadelphia chromosome, results in the production of an abnormal tyrosine kinase. This enzyme contributes to the production of malignant cells.

Imatinib aims to inhibit the abnormal tyrosine kinase. This action stops cell proliferation and can induce apoptosis of tumour cells.

The drug is well absorbed so it can be given by mouth. It has a half-life of 18 hours and is mainly cleared by metabolism. This metabolism involves cytochrome P450 3A4 so there is a potential for interactions with inhibitors of this enzyme such as grapefruit juice, erythromycin and ketoconazole. Although there have been no studies, drugs such as phenytoin, carbamazepine, dexamethasone and St John's wort may reduce the concentrations of imatinib by inducing P450 3A4. Imatinib has other potential interactions because it also inhibits P450 2D6 and 2C9.

In a pilot study 58 patients with chronic myeloid leukemia who were in blast crisis, were treated with daily doses between

300 mg and 1 g. There was a response in 14 of the 20 patients with a lymphoid blast crisis or acute lymphoblastic leukaemia. In the 38 patients with myeloid blast crisis 21 responded.[1]

Another study treated 83 patients with chronic myeloid leukaemia who had not responded to interferon alfa. All the patients who took 140 mg or more had at least a 50% fall in their white blood cell count.[2]

These early trials were followed by larger studies. In a study of 532 people with chronic myeloid leukaemia who had been unsuccessfully treated with interferon there was a complete haematological response in 88% of the patients. (Their white cell counts fell below 10 x 10^9/L.) In 15% of patients there was a confirmed cytogenetic response as bone marrow biopsy showed no cells with the Philadelphia chromosome. A study of 235 patients in the accelerated phase of the disease showed that 400 mg or 600 mg imatinib produced a complete haematological response in 28% and a confirmed complete cytogenic response in 4%. In patients with myeloid blast crisis there was a complete haematological response in 4% and a confirmed complete cytogenic response in 1%.

During clinical trials up to 68% of patients reported nausea and many vomited. Fluid retention occurred in up to 68% but could often be managed with diuretics. Regular blood counts are required as imatinib is associated with anaemia, neutropenia and thrombocytopenia. Haemorrhage occurred in 13% of the patients who failed interferon therapy and in 48% of those with a myeloid blast crisis. Particular caution is needed if the patient is also taking warfarin. One patient died of acute liver failure which could have been related to an interaction with paracetamol. High doses of paracetamol should therefore be avoided.

Most patients have been followed up for less than six months so there are no long-term safety data about imatinib. There is also a possibility that drug resistance could develop. Further research is needed as it is not yet known whether or not the improvements in laboratory results will lead to better clinical outcomes for the patients.

REFERENCES

1. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001;344:1038-42.
2. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001;344:1031-7.

Levobupivacaine hydrochloride

Chirocaine (Abbott)

10 mL ampoules containing 2.5 mg/mL, 5 mg/mL and 7.5 mg/mL

Approved indication: anaesthesia

Australian Medicines Handbook Section 2.1

Bupivacaine is an amide-type local anaesthetic. Although it blocks neurotransmission, its membrane stabilising action also affects the myocardium. This can cause fatal cardiotoxicity. As bupivacaine is widely used in surgery and obstetrics, attempts have been made to develop a safer long-acting local anaesthetic.

The bupivacaine molecule is a racemic compound. Levobupivacaine is the S-enantiomer of bupivacaine and is thought to have less cardiotoxic potential than the R-enantiomer. The pharmacokinetic parameters of levobupivacaine are similar to those of bupivacaine.

Levobupivacaine has been studied in surgical anaesthesia and for pain management. It can be used for local infiltration, epidural, intrathecal and peripheral nerve blocks. For epidural analgesia it can be given with fentanyl, morphine or clonidine. Double-blind comparisons of levobupivacaine and bupivacaine show that their anaesthetic effects are similar.

The adverse effects of the two drugs are also similar. They are influenced by how the drugs are administered, for example hypotension often occurs during epidural anaesthesia. Nausea and vomiting also occur commonly with both drugs.

To reduce adverse effects the smallest dose and concentration should be used. The 7.5 mg/mL concentration should not be used in children or in obstetrics. Like bupivacaine intravascular injection must be avoided, and levobupivacaine is contraindicated for intravenous regional anaesthesia (Bier's block) because of cardiotoxicity. It is also contraindicated as a paracervical block. Test doses with a short-acting local anaesthetic can be used before using levobupivacaine for a complete nerve block. Although animal studies suggest a benefit, it remains to be proven whether levobupivacaine has significantly less toxicity than bupivacaine.

Trastuzumab

Herceptin (Roche)

vials containing 150 mg lyophilised powder

Approved indication: breast cancer

Australian Medicines Handbook Section 14.1

In up to 30% of patients with breast cancer there is an overexpression of the HER2 gene. This oncogene codes for a receptor to epidermal growth factor. Trastuzumab is a monoclonal antibody which can block this receptor. This inhibits the growth of breast cancer cells.

Trastuzumab is a humanised murine antibody produced by recombinant technology. It is given as a slow intravenous infusion. The first loading dose is given over 90 minutes. If this is well tolerated, subsequent weekly infusions can be given over 30 minutes. These infusions are repeated until the cancer progresses.

The half-life of trastuzumab is approximately six days, but a steady state is not reached for 16-32 weeks. As trastuzumab has non-linear pharmocokinetics its clearance decreases as the dose increases. Serum concentrations are also increased if the drug is given with paclitaxel.

Trastuzumab has been studied as monotherapy for women with metastatic tumours that overexpress HER2. The 222 women in this study had failed to respond to chemotherapy, but 15% showed some response to trastuzumab.

The drug has also been used in combination with chemotherapy for metastatic breast cancer. In terms of the median time before the disease progressed, trastuzumab had significant advantages. Trastuzumab with paclitaxel delayed progression more than paclitaxel alone, and with an anthracycline and cyclophosphamide it delayed progression more than that combination alone. Overall, adding trastuzumab to chemotherapy increased the median time to disease progression by 61%.

Trastuzumab is a protein, so patients can develop hypersensitivity reactions. Serious reactions have occurred during the infusions and many other patients will experience fevers or chills. There is a risk of cardiotoxicity, and approximately 9% of patients treated with trastuzumab will develop heart failure. This risk may be increased in patients treated with anthracyclines so, for combination regimens, only the taxanes can be used with trastuzumab. Common adverse reactions include nausea, vomiting and diarrhoea.

Trastuzumab appears to improve the survival of women with metastatic breast cancer who have overexpression of the HER2 oncogene, but not all women will benefit. Only a small number (8/222) of women had a complete response to monotherapy. In that study, the median time to tumour progression was only three months. When trastuzumab is given with paclitaxel the median time to progression is seven months. Although this increases one year survival from 62% to 73%, the difference is not statistically significant.

Correction

Buprenorphine (Aust Prescr 2001;24:71)

There was an error in the gazettal notice, issued by the Therapeutic Goods Administration, regarding the strengths of buprenorphine sublingual tablets. The available strengths are 0.4 mg, 2 mg and 8 mg, not 2 mg, 4 mg and 8 mg.

Answers to self-test questions

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

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