CONTENTS

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EDITORIAL

The National Prescribing Service and *Australian Prescriber*

Stephen Phillips, General Practitioner, Maroochydore, and Chairman, National Prescribing Service Ltd.

Index words: drug information.

(Aust Prescr 2002;25:26–7)

This year sees the operations of *Australian Prescriber* enter a new era. Change is a challenging concept in any context, but can be construed to be particularly so when the focus of that change is a drug review journal, acknowledged both within Australia and internationally as one of the leading independent publications concerned with critical review and the Quality Use of Medicines (QUM). *Australian Prescriber* has been a significant component of the evolution of Australia's QUM movement over the past quarter-century.

As the National Prescribing Service assumes proprietorship of this bulletin, it is timely to outline the history of the change, and to give some insight into what the future may bring. It is also important to address the concerns, about the vitality of *Australian Prescriber* under the new management, which were aired in the previous issue.[1]

In this issue...

With *Australian Prescriber* now ensconced in its new home, Stephen Phillips, the chairman of the National Prescribing Service, gives us a glimpse of the future role of the journal within that organisation. *Australian Prescriber* will continue to talk about new drugs. In addition to the brief comments starting on page 44, this issue also contains a review of the new formulations of insulin.

Interferons are relatively new treatments for multiple sclerosis. While Richard Macdonnell and his colleagues explain the role of these new drugs, a patient tells us what it is like to be on the receiving end of these injections.

Other advances mean that elderly patients should no longer be denied surgical treatment purely because of their age. This can create a dilemma for anaesthetists and so Geoff Cutfield discusses some of the issues to consider when an elderly patient requires an anaesthetic.

There can also be dilemmas in the diagnosis of infertility, but Robert Norman reminds us that history, examination and a few simple investigations can help find the cause in many cases.

The National Prescribing Service is a product of the increasing momentum of QUM activities in Australia. Formed in 1998, the National Prescribing Service has as its mission 'to create an awareness, culture and environment that supports quality prescribing in Australia', and its primary goal is 'to improve health outcomes for all Australians through Quality Use of Medicines' – use that is judicious, safe, effective and cost-effective. The National Prescribing Service is a public company and as such, maintains total operational independence (from the Government, the pharmaceutical industry and others). This is essential if the vision of being 'the most trusted source of independent information about medicines in Australia' is to be realised.

Australia's National Medicines Policy is built on the concept of partnerships, and delivery of its objectives (of which QUM is one) cannot be achieved without the appropriate engagement of all potential contributors to the therapeutic relationship – prescribers, dispensers, consumers, regulators and producers of medicines. Another critical ingredient is the guaranteed independent evidence-based derivation of information about medicines. These themes were prominent in the report of the review of *Australian Prescriber* undertaken by Dr Andrew Herxheimer in 1997, under the auspices of the Pharmaceutical Health and Rational use of Medicines (PHARM) Committee. They are also major pillars in the philosophy of the National Prescribing Service.

There is significant congruence between the objectives of the National Prescribing Service and *Australian Prescriber*. The journal carries the formal endorsement of the National Prescribing Service as a valuable academic and pharmaceutical decision-support resource. There is a history of effective bilateral collaboration at many levels since the inception of the National Prescribing Service. The assumption by the National Prescribing Service of responsibility for publishing *Australian Prescriber* as from January 2002 can be seen as a logical integration. It could add significant value to the sum effect of QUM educational activities in Australia.

The decision to outsource production of *Australian Prescriber* was made by the Commonwealth Department of Health and Ageing. This editorial will not examine the dynamics of that decision, but it is important to point out that at all times in its deliberations on this matter, the National Prescribing Service Board's primary concern was to guard not only the survival of

Australian Prescriber, but also its national and international stature. It has always been our understanding that the outsourcing of *Australian Prescriber* had as its main driver, the isolation of the journal from the dynamics of the Government's annual budget cycle. In this context, tenure with the National Prescribing Service brings with it a minimum four-year guarantee of operational stability.

Another central concern in our negotiations with the Department of Health and Ageing has been to see sufficient funding allocated to *Australian Prescriber* to allow continued production of the journal along with the full roll-out of National Prescribing Service programs, without either impinging on the capacity of the other. The National Prescribing Service was able to convince the Department of the importance of these goals and has secured the funding needed to achieve them.

Two other factors were crucial to maintain the authority of *Australian Prescriber* in the transition to private ownership: continuity of expertise and editorial independence. The National Prescribing Service has been able to recruit key members of *Australian Prescriber* staff which in itself is a measure of their professional commitment to this public health enterprise. Our relationship with the Executive Editorial Board of *Australian Prescriber* has always been mutually productive, and an absolute commitment to its continued editorial authority has been given by the National Prescribing Service Board. The National Prescribing Service has several policies and procedures which effectively deal with the potential conflicts of interest which may arise when multi-stakeholder activities are undertaken, and I am confident these will serve us well in our management of *Australian Prescriber*.

What of the future? Business as usual in respect of the core functioning of *Australian Prescriber*. However, evolution is essential for enhanced effectiveness. We will, in consultation with the new Editorial Executive Committee of *Australian Prescriber*, professional, consumer and other stakeholders, focus on issues including greater integration of QUM messages, better penetration of target constituencies, and more efficient and interactive methods of distribution.

In this new phase of *Australian Prescriber* operations, a sense of insecurity is understandable, caution is required and scrutiny will be welcomed. The National Prescribing Service looks forward however to bringing the power of this venture to the pursuit of QUM in Australia.

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1. Executive Editorial Board. Changes at *Australian Prescriber*. Aust Prescr 2002;25:2.

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.

Over-the-counter medicines in children

Editor, – Some of us have had serious reservations about the advisability and efficacy of over-the-counter medications in children for some time (Aust Prescr 2001;24:149-51). As stated in the article, there are few reliable sources of information. I thought your readers may be interested in some others.

There is an article showing the striking absence of efficacy data for cough and cold medicines in children, and the many non-scientific factors contributing to the frequency of their use.[1] I was interested to learn that healthy children, who have not had a respiratory tract infection within the past month, cough 1-34 times per day.[2]

Another article on antipyretic therapy states that neither the detrimental effects of fever nor the salutary effects of antipyretic therapy have been confirmed experimentally. Furthermore, carefully controlled efficacy studies have never quantified the degree to which antipyretic therapy enhances the comfort of patients with fever.[3]

Even the old dependable gripe water for the treatment of colic is a sham! It now seems that its soothing effect derives from its sweet taste, which can be duplicated with sugar solutions.[4]

Ben Basger

Pharmacist

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Screening for thalassaemia

Editor, – The article 'Screening for thalassaemia' (Aust Prescr 2001;24:120-3) provided an excellent and concise overview of the thalassaemias and haemoglobinopathies in Australia.

A major point arises in relation to initial testing and how to identify a suspected carrier. While the thalassaemias and haemoglobinopathies are more prevalent in particular ethnic groups and geographical areas, the mutations causing these conditions can be found in virtually every country because of genetic drift and ethnic melding over the centuries.

Australia has a particularly heterogeneous population with an increasingly diverse pattern of these conditions. A positive family history is clearly an indication for testing, but this detects only a limited number of carriers. Clinical experience at our hospital shows that testing on the basis of name, place of birth or religion is unreliable for

detecting carriers. Furthermore, reliance on red blood cell indices (MCH and MCV) as a screening process is inadequate. Haemoglobin electrophoresis is essential for the diagnosis of β thalassaemia minor and the haemoglobin variants of clinical significance, the latter being seen with increasing frequency due to recent immigration from Asia, Africa and the Middle East.

Comprehensive testing is advisable to provide optimal detection of couples at risk of having children with severe thalassaemia, so that they can be offered genetic counselling and prenatal diagnosis if appropriate. This means that, at the very least, all antenatal patients should be tested by full blood examination and haemoglobin electrophoresis (or HPLC), plus ferritin in the presence of microcytosis, as early in pregnancy as possible. Ideally, testing should occur in primary care before conception. Partner testing can then be pursued in accordance with the recommendations in the article.

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Coeliac disease

Editor, – Recently you published articles on irritable bowel syndrome (Aust Prescr 2001;24:68-71) and oesophageal reflux (Aust Prescr 2001;24:110-2). Over the years, these diagnoses have been made by three gastroenterologists as a consequence of my epigastric reflux and colonic pains. A fourth endoscopy has now found evidence of coeliac disease in a duodenal biopsy. Since going on a gluten-free diet I am gaining weight. (Over the years, despite having a healthy appetite, I was close to being almost anorexic in appearance and my mental and physical energy was below average.) Now the pains have disappeared and I am feeling and reacting in a more appropriate way. (Even my tennis has improved!)

I write to tell your readers that coeliac disease is the 'great imitator'. It was late in life (I am 80) that it was discovered. As a student I suggested to a general practitioner that I had a malabsorption syndrome but this was discounted. (Lesson: listen to the patient.) A pathologist tells me that the physiology of the whole gastrointestinal tract is disturbed in coeliac disease. Pains, dysfunction, aphthous ulcers and bowel disturbances are the result. I now hear of increasing numbers of patients like myself being diagnosed late in life, after their symptoms had been diagnosed as something else. One wonders how many patients have had surgery and/or medications when the correct management should have been a small bowel biopsy[1] followed by a gluten-free diet.

Bill Woods
Radiologist
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Book review

Abnormal laboratory results.
R. Dunstan, editor. Sydney: McGraw-Hill; 2001.
216 pages. Price $32.95 + $6.60 postage.
20% discount for *Australian Prescriber* readers.

Daniel L. Worthley, Medical Resident, Royal Adelaide Hospital, Adelaide

'Abnormal laboratory results' is an established series in *Australian Prescriber*. It provides medical practitioners with current information on the role and implications of commonly ordered tests. These invaluable articles have now been re-evaluated and skilfully edited into a concise compilation.

This conveniently sized manual addresses a deceptively broad range of laboratory tests. Topics include routinely ordered assays such as thyroid function and electrolytes as well as more specialised investigations for hepatitis B and C viruses, autoimmune diseases, and Helicobacter pylori. In addition, the first three chapters provide sound advice about general interpretation of abnormal laboratory results, giving perspective to the notion of 'normality'.

With regard to the relative merit of the articles I shall keep my opinions brief, as all have been previously scrutinized by a far greater arbiter, namely the *Australian Prescriber* readership. This pre-publication validation is a great strength of this compilation, and should reassure potential purchasers.

Some limitations include repetition of information, particularly in the chapters 'Plasma creatinine' and 'Creatinine clearance and the assessment of renal function'. I also found the synopsis, included at the start of many chapters, of little value. Some articles briefly outline therapy, under the heading 'What action is needed if the result is abnormal?' Given the limited space, this is achieved with varying success. For example, in the chapter about potassium there is no reference to the use of intravenous calcium salts, for cardio-protection, or to glucose and insulin therapy for hyperkalaemia. These minor issues are, perhaps, inherent to the book's construction.

This compilation is an excellent guide to understanding the increasingly complicated array of laboratory tests. It is readily digestible yet sufficiently detailed to prove useful to medical students, hospital clinicians, and general practitioners.

Insulins in 2002

Pat Phillips, Senior Director, Department of Endocrinology, Queen Elizabeth Hospital, Woodville, South Australia

SYNOPSIS

The new soluble long-acting insulin analogues have a longer and more consistent action than the traditional crystalline preparations. The new short-acting analogues provide a quick onset, sharp peak and quicker offset than neutral insulin. They can be given immediately before eating. Compared to human insulin, they may control postprandial hyperglycaemia better and result in less hypoglycaemia between meals. The hypoglycaemic potency of short-acting analogues is similar to neutral insulin but when changing from one to the other, insulin doses should be reduced to minimise the risk of hypoglycaemia.

Index words: metformin, diabetes.

(Aust Prescr 2002;25:29–31)

Introduction

Our knowledge and use of insulin has been continuously evolving since its discovery in 1921 (Table 1). The short delay between the discovery of insulin and its commercial production and distribution was amazing (nothing like the decade or so it would take now). In the 1930s there was the drive to produce long-acting preparations. After that not much happened until the 1970s when insulin preparations were purified and U100 (100 U/mL) became standard.

In the 1980s, human insulin was produced by recombinant DNA technology. This technology was then used to synthesise insulin analogues. Insulin delivery devices improved and patients began to have choices other than syringes (e.g. pen injectors, insulin pumps).

Over the last 10 years the pharmaceutical industry has prepared various insulin analogues (short- and long-acting) and tested new ways and new routes for insulin delivery. In 2002 we have insulin preparations that have the potential to reduce the frequency and amplitude of blood glucose swings and hypoglycaemia. This will allow patients to achieve better overall glycaemic control.

Table 1

Insulin – the continuing evolution

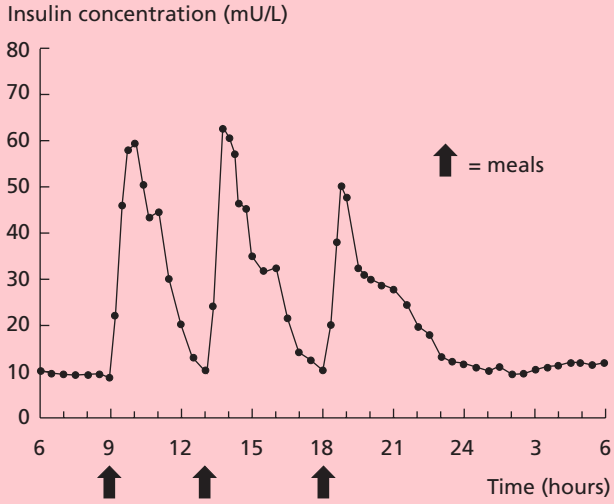
1921	Discovery
1920s	Production
1930s	Long-acting protamine/insulin zinc suspension
1970s	Mono component insulin
	Unit 100
1980s	Human insulin
	Insulin pens
1990s	Insulin analogues
2000s	Insulin smorgasbord

Can insulin treatment mimic nature?

An ideal regimen for insulin would reproduce normal pancreatic secretion (Fig. 1). There would be a basal output of 0.5–1 unit per hour (reducing during the night and increasing in the early morning) with mealtime surges (boluses) of 5–10 units to cover the ingestion of nutrients. The insulin would be delivered into the portal circulation and thus have extra effects on liver metabolism. Insulin delivery would be instantly responsive to the ambient blood glucose. The traditional crystalline* preparations and neutral human insulin cannot mimic nature.

Fig. 1

A normal 24 hour profile of insulin secretion[1]



Insulins before the analogues – intrinsically inadequate

Available preparations were delivered systemically and with variable absorption both between (e.g. abdomen versus leg) and within sites. Even the longest-acting human insulin (ultralente) often did not cover the full 24 hours and insulin injected in the evening peaked during the night and was 'running out' in the morning. The action of short-acting neutral insulin did not match nutrient input. It was slow to start (e.g. 45 minutes), did not peak until two hours after injection and was still there after 5–6 hours. Even when patients did inject 30–40 minutes before eating (as recommended but rarely practised) the concentration profile was still too blunt. Despite these apparent pharmacokinetic shortcomings the older insulins were and still are satisfactory for some patients.

* Insulin crystals are formed when protamine and/or zinc are added (neutral protamine Hagedorn (NPH), or insulin zinc suspension (IZS)). The crystals slowly dissolve and release insulin over a prolonged period.

Insulin after the analogues – better but still not ideal

The profiles of the new basal and bolus analogues allow patients to match pancreatic insulin secretion more closely than they could with the older insulins. However, the lack of portal delivery, night-time dip, morning surge and response to ambient blood glucose are still problems.

'Basal' insulins

The absorption profile of new basal insulin preparations is longer, flatter and more reproducible than previous long-acting preparations (IZS, NPH). Two types of basal insulin analogues are being studied in Australian clinical trials but they are not yet generally available.

Insoluble insulins (e.g. insulin glargine)

Changing the amino acid composition of insulin changes its solubility in subcutaneous tissues. The insulin analogue is soluble in acidic solution (in the vial) but insoluble at body pH. After injection crystals form and the insulin is then absorbed slowly.

Insulin fatty acid complex (e.g. Detemir)

When a fatty acid is attached to the insulin molecule the complex binds to albumin in the subcutaneous space and in the plasma. The insulin gradually dissociates from albumin and is then able to diffuse from the subcutaneous space into the blood stream to later gain access to the tissue insulin receptors.

'Bolus' insulins

Before moving from the subcutaneous tissues to the blood stream insulin monomers must dissociate from the hexamers present in neutral insulin preparations. This dissociation slows and prolongs the absorption profile. The amino acid compositions of the 'bolus' analogues make it easier for insulin molecules to dissociate in the subcutaneous tissue. Absorption is quicker and less prolonged. Lispro insulin achieves these effects because the positions of lysine and proline in the B chain (Lys B28 Pro B29) are switched. In insulin aspart, aspartic acid is added to the B chain (Asp B28). Both these analogues are available on the Pharmaceutical Benefits Scheme.

Insulin delivery – now patients have a choice

In 1921 patients injected large volumes of impure insulin with reusable glass syringes and large gauge needles (that they re-sharpened periodically). Often there was inflammation at injection sites and insulin antibodies modified the pharmacokinetic profile. In 2002 patients use subsidised pen injectors or disposable syringes with fine needles which make injection less painful. Patients can also use an insulin pump that delivers insulin subcutaneously at rates that can be varied to closely match the normal profile of insulin secretion (including night-time dip, morning surge and mealtime boluses).

In clinical research programs, insulin pumps have been implanted to deliver insulin into the peritoneal cavity (and thus into the portal circulation). Infusion rates are controlled by radio and insulin reservoirs are filled intermittently through a special port.

Clinical trials of oral, nasal and inhaled insulin are continuing and several pharmaceutical companies have developed new formulations and delivery devices.

Starting insulin in type 2 diabetes – sooner rather than later

The United Kingdom Prospective Diabetes Study[2] showed that type 2 diabetes is a progressive disease and that patients require increasing doses and numbers of oral hypoglycaemic drugs. Many patients eventually require insulin. However, patients and doctors are often reluctant to start it and between them they can put off the decision for years. The recommended target HbA1c is less than 7% with an 'action limit' of 8% but many patients have higher values for long periods of time. In general the higher the concentrations of blood glucose and HbA1c the greater the benefit of reducing them and the less the 'cost' of inconvenience, stress and hypoglycaemia.[3] Once the decision to start insulin is made, both patient and doctor are almost invariably surprised how easy it is and both feel much better (the patient physically and the doctor professionally).[4] Moreover patients appreciate reducing the numbers and costs of their tablets.

Insulin schedules – one size does not fit all

Weight gain and hypoglycaemia are problems when starting treatment irrespective of whether a new or old formulation of insulin is used. Recent trials have compared different regimens for starting insulin in patients with type 2 diabetes.[5] Bedtime intermediate insulin and twice-daily metformin (and stopping other oral hypoglycaemic drugs) was associated with the best glycaemic control and least weight gain and hypoglycaemia. In patients already taking metformin, an evening dose of NPH insulin, to control night-time and fasting blood glucose, with daytime doses of metformin might be a suitable starting schedule. This schedule reduces insulin resistance and weight gain in those patients, often obese, who are particularly insulin resistant and prone to weight gain with insulin therapy.

A similar trial has not been done with the other class of drugs which increases insulin sensitivity (thiazolidinediones, e.g. rosiglitazone) but they may be suitable in some patients starting insulin. However, the 'glitazones' may be associated with increased fluid accumulation which can cause problems in patients with cardiac failure.

Combining insulin secretagogues (sulfonylureas – long-acting, glitinides – short-acting) with insulin is less appealing theoretically since one could use more long- or short-acting insulin as needed rather than add a further medication. However, they may have advantages in selected patients (for example, a glitinide may be helpful if postprandial hyperglycaemia is a problem). Similarly acarbose could theoretically be used with insulin for patients where postprandial hyperglycaemia was a problem.

As a rough guide, patients require a total daily insulin dose of half to one unit for each kilogram of their ideal weight.[†]

[†] As an approximation,

ideal healthy weight (kg) = height (cm) – 100

For example, in a 178 cm man the healthy weight is 78 kg. His total daily dose at 0.5 units/kg would be 39 units (26 units in the morning and 13 units in the evening).

Generally daytime requirements are two-thirds and night-time requirements one-third of the total. If daytime oral hypoglycaemic agents (e.g. metformin) are used, the night-time dose might be used without the morning dose. If short-acting insulin is required, the 'two-thirds, one-third' rule is useful as a starting point (two-thirds long-, one-third short-acting insulin).[6]

The bolus analogues give an insulin profile which is closer to the normal secretion pattern. They have better control of postprandial hyperglycaemia and less risk of hypoglycaemia between meals than injections of regular human insulin. Moreover, the new analogues can be given immediately before a meal rather than 30–45 minutes beforehand as recommended for neutral human insulin.

Occasionally the quick 'on and off' of the analogues proves a disadvantage. Patients must eat after the injection since the insulin peaks rapidly and occasionally they 'run out' before the next dose and their blood glucose increases. Some patients prefer the slower onset and offset of the older bolus preparations. Similarly, in some patients the shorter, more peaked profile of the older basal preparations might be preferred (for example where a morning injection of a new basal analogue results in hyperglycaemia during the middle of the day).

In theory, the overall potency of the quick-acting analogues is similar to regular neutral insulin, but in practice, effects in individual patients will vary. As usual when changing insulin it is wise to use smaller doses to start with to reduce the risk of unexpected hypoglycaemia.

The analogues can be mixed with long-acting insulins of the same brand if the insulins are injected immediately after mixing. One pre-mix is available (75% of long-acting insulin‡ and 25% of lispro).

Pre-mixes – panacea or problem?

The most commonly used insulin preparation in Australia is a pre-mixed insulin (NPH and neutral) using a pen injector. This is convenient for the patient – 'dial and shoot' – and the doctor does not have to make a choice between the 10 long-acting and 10 short-acting insulin preparations.

However, there can be problems with fixed combinations. They have limited flexibility as changing the dose changes both long- and short-acting components. Patients often use a fixed dose which may suit their requirements on one day, but cause blood glucose swings on another when their activity or eating schedule changes. Moreover the daytime NPH puts them at risk of hypoglycaemia and requires them to eat in the middle of the day. Patients may find it easier to achieve targets for glycaemic control when they can adjust their insulin regimen to their lifestyle, rather than fitting their lifestyle to their insulin.

‡ NPL, insulin lispro protamine suspension (equivalent to NPH where human neutral insulin has been replaced by lispro).

ACKNOWLEDGEMENTS

I am grateful to Dr George Phillipov for his assistance in preparing the figure and Dr John Miller, Novo Nordisk Laboratories, for information about their new analogues.

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FURTHER READING

See resources on the following web site:

www.diabetes.org.au/

Dr Phillips has received education and/or research grants from Aventis, Eli Lilly and Novo Nordisk, has been involved with clinical studies for Novo Nordisk and is involved with a clinical study for Aventis.

Self-test questions

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

1. The amino acid structure of insulin glargine enables the insulin to be rapidly released into the circulation.
2. Patients taking insulin should usually inject two-thirds of their total dose during the day and one-third at night.

Australian Prescriber wallchart

Copies of the wallchart 'Medical management of severe anaphylactoid and anaphylactic reactions' which was published with Vol. 24 No. 5 of 2001, are available for surgeries, clinics, hospitals and consulting rooms while stocks last.

To order copies contact the Australian Prescriber Mailing Service (see inside back cover for details).

Treatment of multiple sclerosis with newer immune-modulating drugs

Isabella Taylor, Department of Neurology, Austin and Repatriation Medical Centre; Richard Macdonell, Department of Neurology, Austin and Repatriation Medical Centre, and Department of Medicine, University of Melbourne; and Jennifer Coleman, Registered Nurse, Melbourne

SYNOPSIS

Multiple sclerosis can be a severely disabling disease. Recently introduced immunomodulatory drugs (interferon beta or glatiramer acetate) should be considered for the treatment of patients in the earlier stages of the disease, if they have a relapsing-remitting course. These therapies have replaced older immunosuppressants such as methotrexate, at this stage of the disease. On average, immunomodulatory drugs reduce relapse rates by about 30% and retard the progression of disability by about 12–18 months. Whilst these benefits are relatively modest, they offer for the first time a means to alter the natural history of the disease. Several studies suggest that the positive effects of these drugs on the rate of progression of disability and relapse frequency are maintained over time. They all need to be given by frequent injections, and regular monitoring of their adverse effects is a necessary part of management. Immunomodulatory drugs have been used in multiple sclerosis patients intensively for at least 10 years without any apparent long-term adverse effects.

Index words: interferon beta, glatiramer acetate.

(Aust Prescr 2002;25:32–5)

Introduction

Multiple sclerosis is a chronic inflammatory, demyelinating disease of the central nervous system and is the commonest cause of neurological disability in young adults. In most patients it initially follows a relapsing-remitting course and in the early stages there is often complete recovery between attacks. With time, there is less recovery and finally most patients enter a secondary progressive phase. About 10% of patients have a primary progressive course with deterioration from the outset without relapses and remissions.

Multiple sclerosis should be managed with education and counselling as well as medications. Acute attacks can be treated with intravenous methylprednisolone. This shortens the duration of symptoms associated with a relapse, although it probably does not alter the ultimate recovery following an attack.[1]

New immune-modulating therapies (drugs which adjust the activity of the immune response to a desired level), interferon beta-1b (Betaferon), interferon beta-1a (Avonex and Rebif) and glatiramer acetate are now available. These drugs are of value in the relapsing-remitting phase of the disease[2,3,4,5] and appear to alter the natural history of multiple sclerosis. They have not been compared with other treatments, such as methotrexate.

Rationale for therapy with immunomodulatory drugs

The rate and extent of axonal loss during the relapsing-remitting phase of the disease is thought to determine when a patient enters the secondary progressive phase. Beyond a certain threshold, further axonal loss leads to more rapid disablement.[6] In double-blind, placebo-controlled trials, immunomodulatory drugs have reduced the frequency of relapses and the volume of the lesions seen with MRI. We hope that this will also reduce the rate of axonal loss over time and hence delay entry into the secondary progressive phase. While this concept is difficult to prove *in vivo*, one placebo-controlled study of interferon beta-1a (Avonex) found a reduction in the rate of brain atrophy, used as a marker of axonal loss, in the second year of treatment.[7] A number of studies have also shown treatment has a positive effect on the rate of disability progression in patients in the early phases of multiple sclerosis (Table 1).[3,4,5]

There have been two placebo-controlled studies of interferon beta (1a or 1b) in secondary progressive multiple sclerosis.[8,9] The first study showed a positive effect on delaying progression. (Proportion of patients with confirmed progression over three years: 49.7% placebo versus 38.9% for interferon beta-1b, $p < 0.005$).[8] The second study found no difference between interferon beta-1a (Rebif) and placebo on the progression of disability over three years.[9] One explanation for this discrepancy may be that some of the patients in the initial study were still in the relapsing-remitting phase rather than a secondary progressive phase because they had a higher relapse rate than expected.

The evidence of efficacy of immunomodulatory drugs in the secondary progressive phase of multiple sclerosis is therefore not established.

Subsidy of immunomodulatory therapy

Treatment costs more than $1000 per month. The Pharmaceutical Benefits Scheme subsidises immunomodulatory drugs for the treatment of patients with relapsing-remitting multiple sclerosis who:

- have had two attacks in the preceding two years with partial or complete recovery

Table 1

A comparison of the results of pivotal double-blind controlled trials of immunomodulatory drugs in the treatment of patients in the relapsing-remitting phase of multiple sclerosis

	Interferon beta-1a (Rebif)[4]		*Interferon beta-1a (Avonex)*[3]		*Interferon beta-1b (Betaferon)*[2]		*Glatiramer acetate*[5,16]	
	Placebo	44 microgram interferon beta-1a three times weekly	Placebo	30 microgram (6 million units) interferon beta -1a weekly	Placebo	0.25 mg (8 million units) interferon beta -1b (alternate days)	Placebo	20 mg glatiramer acetate (daily)
Mean relapse rate after 12 months	1.08	0.87	NR		1.43	0.97	1.02	0.81
Mean relapse rate after 24 months	2.56	1.73**	0.90	0.61**	1.27	0.84***	1.68	1.19**
Probability of sustained disability progression by >1 on EDSS† scale (sustained at two years)	48%	24%*	33.3%	21.1%*	NA		28.8%	20.8%*
Mean change in MRI lesion load (over 12 months) compared with baseline MRI scans performed at trial entry	10.9% (area)	–3.8%*** (area)	–3.3% (volume)	–13.1%* (volume)	12.2% (area)	–1.1% *** (area)	4.7 mL (volume)	3.0 mL** (volume)

NA Not assessed NR Not reported *** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$ † Expanded disability status score

Table 2

Currently available newer immunomodulators for the treatment of multiple sclerosis in Australia

Drug	*Route*	*Dose*	*Adverse effects*
Interferon beta-1a (Rebif)	Subcutaneous (single-dose pre-filled syringe) Auto-injector available	44 microgram three times a week (e.g. Monday, Wednesday, Friday)	Injection site reactions occur with subcutaneous injections in 100% of patients, severe with skin ulceration in 10%
Interferon beta-1a (Avonex)	Intramuscular (reconstituted) Not suitable for auto-injector	30 microgram (6 million units) weekly	No reactions with intramuscular injections Flu-like symptom complex (fever, chills, malaise, myalgia, sweating) after injections: up to 76%
Interferon beta-1b (Betaferon)	Subcutaneous (reconstituted) Auto-injector available	0.25 mg (8 million units) on alternate days	Elevated liver enzymes, alteration in blood count, hypersensitivity reactions, neutralising antibodies Depression, may aggravate spasticity
Glatiramer acetate	Subcutaneous (reconstituted) Auto-injector available	20 mg daily	Injection site reactions in 100%. Severe with skin ulceration: rare Immediate post-injection reaction (10%) occurs straight after injection and consists of transient flushing, chest tightness, dyspnoea, palpitations

- remain ambulant
- have their diagnosis confirmed by MRI of the brain or spinal cord.

These criteria mirror those used for patient selection in most of the clinical trials. Patients who have progression of disability despite treatment are not eligible for repeat prescription of subsidised drugs.

Interferon beta

Interferon beta is a normal constituent of the human immune system. It is produced by immunologically active cells in response to inflammation or infection and seems to dampen inflammatory reactions by directly inhibiting the proliferation, migration and activation of immune cells through various mechanisms.[10] The Avonex and Rebif preparations have an identical protein structure to the human molecule while Betaferon differs by one amino acid. These preparations are produced in large quantities by genetically modified bacteria or cells (*E. coli* or hamster ovary). The contraindications and adverse reactions of all the beta interferons are similar. They are reasonably well tolerated, but patients should be educated regarding potential adverse effects (Table 2).

Contraindications

Interferons are contraindicated in women who are trying to conceive and during pregnancy (category D) and lactation.

They should be ceased three months before planned conception, but may be resumed immediately after delivery or when breastfeeding stops. If a woman taking interferon becomes pregnant, termination of pregnancy is not advised; the potential risks (as shown by animal models) to the fetus should be discussed with the patient. These risks appear to be low and a number of successful pregnancies have occurred in such a situation.

Beta interferons are contraindicated in decompensated hepatic disease and in patients with refractory epilepsy.[11] The use of interferon beta preparations in patients with a history of **severe** depression and/or suicidal ideation is also contraindicated. They should be used with caution in patients with anaemia, thrombocytopenia or monoclonal gammopathies.

Adverse reactions

The commonest adverse reaction is a flu-like symptom complex.[11] Symptoms commence 2–6 hours after injection and resolve within 24 hours. They can be managed by taking paracetamol or ibuprofen just before the injection and again four hours afterwards. Evening injections are advised so patients sleep through their symptoms. This reaction is usually only a significant problem for the first 3–6 months after starting therapy.

Injection site reactions commonly occur 24–48 hours after subcutaneous (not intramuscular) injection, but rarely progress to skin necrosis. To minimise these reactions education about aseptic injection technique and rotating injection sites is essential. The injections are usually given in the lower abdomen, buttocks or anterior thighs.

Halving the dose of the first few injections may reduce the severity of flu-like symptoms and injection site reactions. Ensuring the solution is not cold (i.e. at body temperature) or applying ice to the injection site before injection will minimise discomfort. Subcutaneous injections are better tolerated if given with an automated self-injecting device.

Depression can occur but beta interferons may be given to patients with depression if it is being treated. Prophylactic antidepressants are not indicated in those with a past history of depression. These patients should be informed that symptoms of depression might be aggravated by beta interferon treatment, particularly if the drug is injected more than once a week. This association is a weak one but patients with a history of depression should be closely monitored.[11]

Serious hypersensitivity reactions (bronchospasm, anaphylaxis) may occur infrequently. Betaferon and Rebif may exacerbate spasticity in some patients.

At the recommended doses, lymphopenia, neutropenia, thrombocytopenia, anaemia and elevated concentrations of liver enzymes can occur, particularly in the early phase of treatment.[11] As these adverse reactions are related to dose frequency, they are less likely to occur with weekly injections. Antimicrosomal antibodies may also be detected, but this rarely leads to clinically evident thyroid disease. Low calcium and high uric acid concentrations also appear to be associated with interferon beta-1b.

Neutralising antibodies develop in up to one third of patients. They are more frequent with the subcutaneously administered beta interferons. Further research is required to determine the clinical significance of these antibodies which may spontaneously lower in titre even if treatment continues. Testing for antibodies is not available in Australia.

Recommended monitoring

Regularly review the patient's injection technique and injection sites. Check liver function and the full blood count before starting therapy, then every three months. Monitor renal function if it is impaired.

Most mild laboratory abnormalities do not require treatment to be stopped. In the clinical trials of interferon beta-1b, treatment was stopped if hepatic transaminase concentrations exceeded ten times the upper limit of normal, or if bilirubin concentrations exceeded five times the upper limit of normal. In all instances, liver enzymes returned to normal on cessation of the drug and patients had no ill effects. If the drug is ceased, because of liver enzyme abnormalities, it may be resumed at 25% of the original dose and slowly increased with regular monitoring.[11]

Glatiramer acetate

Glatiramer acetate is a mixture of synthetic polypeptides designed to simulate myelin basic protein, a putative target antigen in multiple sclerosis. It interferes with MHC class II antigen binding on antigen presenting cells and induces antigen specific T suppressor cells.[12] Glatiramer acetate, in addition to being a first-line therapy, should also be considered in those who do not respond to or who do not tolerate interferon beta because of adverse effects. Monitoring of liver function and full blood count is not required.

Contraindications

Apart from hypersensitivity, there are no absolute contraindications to glatiramer acetate. It is not recommended when pregnancy is planned, during pregnancy (category B1) and lactation.

Adverse events

Occasionally a reaction occurs **immediately** after injection consisting of transient flushing, chest tightness, dyspnoea and palpitations. These self-limiting reactions tend to be isolated events which are unpredictable and infrequent.[5]

Injection site reactions commonly occur 24–48 hours after subcutaneous injection. To reduce these events the patients can take similar measures to those advised for beta interferon.

Comparing the preparations

In a recent unrandomised study over the first 18 months of therapy, frequent (daily or three times a week) subcutaneous injections (interferon beta-1a and -1b or glatiramer acetate) were more effective than weekly doses of intramuscular interferon beta-1a in reducing relapse frequency. There are no data to show if this finding affects the rate at which long-term disability develops.[13]

Betaferon, Avonex and glatiramer have to be reconstituted before injection. This can be difficult for patients with poor

dexterity, who may prefer Rebif which comes in a prepacked syringe.

Autoinjectors are available for subcutaneous injection of Betaferon, Rebif and glatiramer, but not Avonex as this requires an intramuscular injection and more detailed instructions.

Glatiramer is given as a daily injection, Avonex is a weekly injection, Rebif is injected three times a week and Betaferon is given every other day. The frequency of injections influences the incidence of flu-like adverse effects to the interferon beta preparations.

A higher dose of Avonex (60 microgram) has been compared to the currently available (30 microgram) dose. Both doses were equally effective in reducing disability progression, suggesting that the 30 microgram dose is around the dose ceiling for Avonex.[14]

There is a dose effect for subcutaneously administered beta interferon. Higher doses have a greater effect on relapse frequency and MRI lesion load.[15]

There is a comparative study of beta interferons and glatiramer acetate currently underway in the USA. This aims to compare the effectiveness of Avonex against glatiramer acetate. There are no data from this trial available as yet.

Large-scale double-blind placebo-controlled trials involving previously used treatments such as methotrexate and azathioprine have not been performed. It is therefore difficult to compare their efficacy with that of the new immunomodulating drugs. The newer drugs also have a different pattern of adverse effects from the older drugs.

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Conflict of interest: none declared

Self-test questions

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

3. Interferon beta significantly slows the deterioration of patients with progressive multiple sclerosis.
4. Patients whose disability increases while they are taking interferon beta should have their dose increased.

Multiple sclerosis: a patient's perspective

Laurel C. is a 48-year-old mother of two teenaged children. She has been taking an immunomodulating drug for five years.

AP: *When did you find out you had multiple sclerosis?*

LC: I woke up one morning in 1997 with numbness and tingling in my left foot. Over the next week, this spread to the whole left side of my body. I lost balance and was dragging my leg and bumping into things. My general practitioner organised an urgent appointment with a neurologist. An MRI scan showed I had multiple sclerosis.

Looking back I had probably had attacks before. In 1992 I developed Bell's palsy and I remember other

times when I had tingling in my hands and feet. I had also lined the pockets of naturopaths trying to find a remedy for my fatigue.

AP: *How did you react to the diagnosis?*

LC: There was a mixture of shock and relief. While there was relief that somebody knew what was wrong with me, I was horrified because my aunt had been disabled by multiple sclerosis and died at a young age.

AP: *What treatment did you have?*

LC: I was given cortisone tablets. The attack lasted three months and then I started on interferon injections. I was told these may help slow the progression of the multiple sclerosis.

AP: *How did you find the treatment?*

LC: I have a phobia about needles. Having to inject myself was one of my greatest fears. I could not even watch the video which showed you how to inject. I would sit for half an hour before I could insert the needle.

Although I now inject myself every other day I still need to call on my internal strength to do it.

AP: *Were there any adverse reactions?*

LC: At first the side effects were horrendous. I wondered what I was doing to myself. There was redness, swelling and tenderness at the injection site. I often would wake up at 2.00 a.m., after an injection, with severe pain in my legs. I would be shaking and felt like I had a bad dose of the flu. Sometimes I had to stay in bed all day to recover.

After about a month the side effects reduced. They are less of a problem now, so I would encourage other people to persevere with their treatment as the initial severe side effects should not be long-term.

AP: *Have you used any complementary therapies?*

LC: I have tried them all, including high doses of intravenous vitamins. While some therapists say they can cure you, none of the therapies worked for me. I did find a mixture of Chinese medicine and massage improved my general well-being.

Changing my lifestyle has also helped. I exercise and have a good diet. High stress levels have an adverse effect on my condition, so I made the decision to retire from full-time work three years ago.

AP: *Has the treatment worked?*

LC: I have constant tingling, numbness and aches, but I do not let them restrict me. I am able to play golf and I have not had a serious attack since 1997. I see my neurologist once or twice a year and have a check of my blood tests. I would like to have another MRI to see if things have improved.

AP: *Is there anything you would like to say to doctors treating other patients with multiple sclerosis?*

LC: General practitioners are only going to have a couple of patients with multiple sclerosis, so they cannot be expected to know everything about the disease. They should encourage patients to have a positive attitude to the illness, and to maybe re-evaluate their lifestyle.

When you have multiple sclerosis you have to be prepared to take control and help yourself. General practitioners, therefore, need to be aware that most of their patients will be trying alternative therapies.

Patient support organisations

MS Australia

There are MS Societies in all States of Australia. These State Societies provide information and education for people with MS, families, carers and health professionals as well as the general community. They promote awareness of MS, and raise funds for research and service provision. They also provide support services such as the Immunotherapy Support Programs whereby MS Society nurses give information regarding the immune-modulating drugs, teach self-injection techniques, and offer ongoing support and advice in the management of any side effects.

MS Australia represents the national interests of people with MS, promotes and funds research and produces the quarterly magazine 'MS Life'.

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Grapefruit juice interactions

Prepared by Janet McNeece, Senior Pharmacist, Medicines Information Centre, Royal Adelaide Hospital, Adelaide

Questions about the interaction of drugs with grapefruit juice have increased. I have therefore collated available data to produce a table which may help when assessing the significance and clinical relevance of an interaction. The full table is available with this article on the *Australian Prescriber* web site (www.australianprescriber.com).

The CYP3A4 enzyme system is found in the liver and in enterocytes. Some drugs are therefore metabolised as they are absorbed by the enterocytes. Drugs can also be pumped back into the intestinal lumen by a P-glycoprotein (Pgp) transporter. Pgp and CYP3A4 may therefore act in tandem as a barrier to drugs getting from the gut to the systemic circulation. Inhibition of either or both systems can increase the bioavailability of a drug.[1] Grapefruit juice appears to selectively inhibit CYP3A4 in the small intestine. However, the interactions are not simple competition for substrate metabolism, grapefruit juice acts by selective post-translational downregulation of enzyme expression in the intestinal wall.[2,3] The inhibition can last up to 24 hours with a maximal effect when the juice is given with the drug or up to four hours before the drug.[4]

All interactions studied so far have used grapefruit juice.[5] There are no useful studies with whole grapefruit.[6] Sweet orange juice does not interact, however, Seville (or bitter) orange juice can inhibit CYP3A4 (although this does not affect cyclosporin[7]).

Of the many interactions studied only cyclosporin can be definitely said to have a clinically significant interaction. The clinical significance of increased concentrations of sirolimus and tacrolimus is less clear. Other interactions which may be clinically significant occur with amiodarone, atorvastatin, carbamazepine, felodipine and simvastatin.

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FURTHER READING

Martin J, Fay M. Cytochrome P450 interactions: are they clinically relevant? Aust Prescr 2001;24:10-2.

ABNORMAL LABORATORY RESULTS

Fertility testing

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SYNOPSIS

Hormone testing is helpful in the investigation of infertility, but excessive testing is rarely valuable. The history of infertility and examination of both partners usually enables a simple approach to testing. Tests of ovulation rely on measuring serum progesterone seven days before an expected period. Measurement of serum testosterone is sufficient to exclude ovarian or adrenal tumours as a cause of hyperandrogenism, while prolactin and thyroid stimulating hormone may be valuable in women with irregular periods. Semen analysis is essential in the infertile male.

Index words: infertility, progesterone, testosterone.

(Aust Prescr 2002;25:38–40)

Introduction

The general practitioner is usually the first person to see the 10–15% of couples who are concerned about their fertility. At some time in their lives, approximately half of these couples will seek medical advice. A third of these people will need to be referred to a specialist or assisted reproductive technology unit. In a third of infertility cases there is a female factor, in another third a male factor and in the remaining third there will be a combination of both, or no detected cause. The investigation by the general practitioner depends upon the couple's history, their ages and the findings on examination (Fig. 1). Patients who present with less than 12 months of infertility should have minimal testing unless a clear cause is found from clinical assessment. Selection of tests after this will depend on the potential cause of infertility indicated by the history and examination.

Female infertility

A detailed history of the menstrual cycle often provides a clue to problems such as anovulation or ovarian failure. A general examination should be carried out, in addition to a pelvic examination, to look for problems such as hypothyroidism or hirsutism.

Issues to consider when measuring female hormones

The concentrations of most hormones fluctuate during the menstrual cycle, and in the case of luteinising hormone (LH) and follicle stimulating hormone (FSH) there is also a minute by minute pulsatile variation. Most hormones should be measured in the first seven days of the cycle when there is little fluctuation in their concentrations, but the pulsatile release of hormones such as LH may lead to quite variable results between specimens. The measurement of hormones such as prolactin can be significantly affected by stress and medication. Progesterone and 17-hydroxyprogesterone vary substantially between the follicular and luteal phase of the cycle. In the perimenopause, the concentrations of FSH can fluctuate markedly as the ovarian sensitivity to gonadotrophins varies.

Tests for detection of ovulation

The most appropriate test for detecting ovulation is a serum progesterone concentration. This is performed approximately seven days before the predicted date of a menstrual period (day 1). The day can be calculated on the basis of a 14 day luteal phase so if the menstrual cycle is 28 days, test on day 21. Test on day 23 of a 30 day cycle, and day 25 of a 32 day cycle.

A progesterone concentration above 20–25 nmol/L confirms ovulation occurred in that cycle. Lower values mean either anovulation or inappropriate timing of the blood test. A low concentration can be checked by taking two measurements of progesterone a week apart in the next cycle or alternatively recalculating the day of testing.

Urinary dip sticks for LH are also widely used for ovulation detection, but are expensive, open to problems of interpretation and are only of value when periods are regular. Blood or urinary LH tests are of no value in general practice.

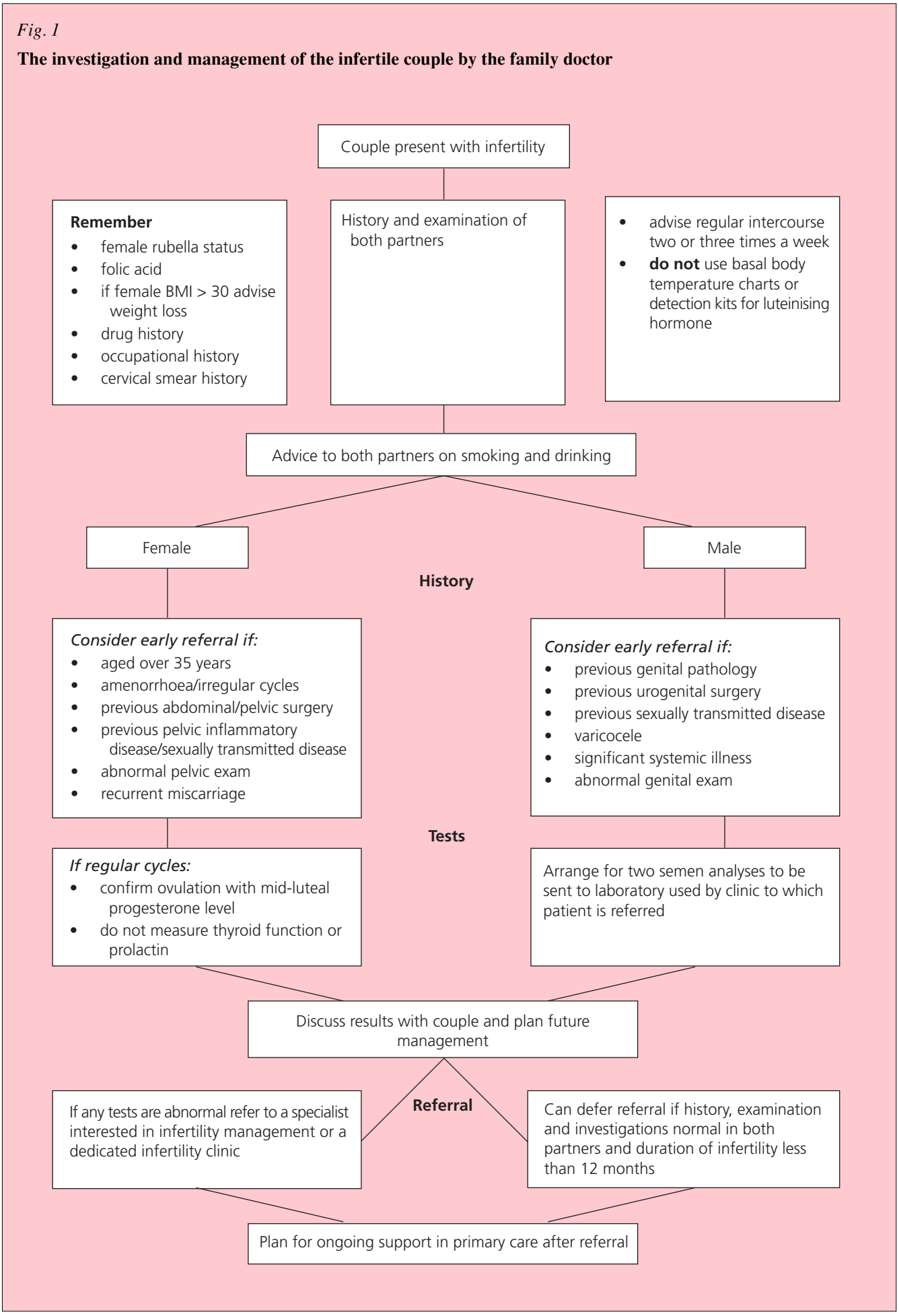
Tests for hirsutism

The commonest cause of hair growth in women with abnormal periods is polycystic ovary syndrome. The most appropriate test for hyperandrogenaemia is a serum total testosterone. This will normally be below 2 nmol/L but can vary from laboratory to laboratory and also during the menstrual cycle. Values of testosterone above 10 nmol/L are suggestive of a testosterone producing tumour of the ovary or adrenal. As testosterone is bound to sex hormone binding globulin, an estimate of free androgen can be obtained by calculating the ratio of testosterone to sex hormone binding globulin (the free androgen index). Direct measurement of free testosterone is technically flawed and a useless test.

Tests for other androgens, such as androstenedione and dehydroepiandrosterone, are of little value in general practice. The commonly used LH:FSH ratio is also of little value although a raised LH with a normal FSH is helpful in the diagnosis of polycystic ovary syndrome. Measurement of 17-hydroxyprogesterone is occasionally helpful where late

Fig. 1

The investigation and management of the infertile couple by the family doctor



onset congenital adrenal hyperplasia (an inherited condition affecting one of the enzymes in the adrenal gland) is suspected.

Many women with polycystic ovary syndrome will develop diabetes. When the syndrome is diagnosed in an overweight patient, diabetes mellitus and hypertriglyceridaemia should be excluded.

Tests for early menopause

The only test of any value where the diagnosis is uncertain is serum FSH. The concentration may be raised above 20–30 IU/L, but this test should be repeated on several occasions as the condition of ovarian failure fluctuates remarkably. There is no place for measuring oestradiol or LH in this situation.

Tests for early pregnancy

Human chorionic gonadotrophin is the best test for early pregnancy. Values over 25 U/L in the blood or urine are usually diagnostic of pregnancy. Concentrations below this are reported as equivocal or negative. If the result is equivocal it can be repeated two days later and should have at least doubled in value. While modern laboratory assays for human chorionic gonadotrophin are reliable, urinary home pregnancy tests are often less satisfactory. There is usually a 1:1 relationship between concentrations of human chorionic gonadotrophin in blood and urine. However, blood testing is more reliable and is positive 1–2 days earlier.

Tests for menstrual irregularity

Where abnormal periods are present, measurement of serum prolactin is of value. Prolactin concentrations are increased by stress, hypothyroidism, dopamine depleting drugs and microadenoma of the pituitary as well as by pregnancy and lactation. When periods are irregular, measuring thyroid stimulating hormone is important to exclude primary hypothyroidism. Routine measurement of FSH, LH and oestradiol for infertility is of little value except in early menopause. Chromosome analysis is needed in cases of primary amenorrhoea.

Male infertility

After a history and examination, semen analysis is the essential test.

Semen analysis

Infertility in a couple requires analysis of a sample of semen. A semen specimen should be produced, after three days abstinence from ejaculation, into a clean wide-topped jar and delivered to the laboratory within 20 minutes. Previous illness and some drugs (e.g. anabolic steroids, testosterone) can seriously affect the amount and motility of the sperm.

Analysis required

The volume, concentration, motility and morphology of the seminal specimen are measured. Sperm numbers should be above 20 x 10^6 per mL, their motility should be at least 50% and their morphology should be above 20% normal. Morphology is poorly assessed by most laboratories other than those routinely dealing with infertility, but it predicts the chances of fertility. Single, double or triple defects necessitate the measurement of a second specimen in a specialist laboratory and probable referral to a specialist.

Other tests

In patients with azoospermia, small testes and a high FSH, chromosome analysis may be required to exclude conditions such as Klinefelter's syndrome (XXY). Other disorders of semen analysis may require the measurement of FSH and LH to show whether the defect is in the testis (high result) or in the hypothalamus or pituitary (low result). Serum testosterone is normally well above 10 nmol/L and low values may necessitate testosterone replacement or injection of human chorionic gonadotrophin depending on the cause and desire for fertility. Occasionally, microadenomas of the pituitary can present with high prolactin values and male infertility. Sperm antibody testing is important in specialist practice but not in primary care as a routine investigation.

Conclusion

Infertility is a condition initially best dealt with by the general practitioner. After history and examination, selective testing of hormones is helpful for making the diagnosis and for decisions regarding referral. Inappropriate hormone testing is expensive and a waste of resources.

Conflict of interest: none declared

Self-test questions

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

5. Measurement of oestradiol is a valuable test in infertility and early menopause.
6. Day 21 progesterone is the best test for ovulation in a 28 day cycle.

Overseas readers

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APMA Code of Conduct

The Australian Pharmaceutical Manufacturers Association Code of Conduct[1] provides guidelines for the ethical marketing and promotion of prescription pharmaceutical products in Australia. It complements the legal requirements of the Therapeutic Goods Regulations and the Therapeutic Goods Administration.

Compliance with the Code is a condition of APMA membership, and the Association's members represent more than 90% of pharmaceutical companies. The Code, established in 1960, is regularly revised.

The Code has two arms, a complaint driven mechanism and a monitoring function. Two independent committees are responsible for these functions. The Code of Conduct Committee considers complaints to determine whether a breach of the Code has occurred, and if so, the appropriate sanction that should be imposed. The most severe sanction is expulsion from the APMA, but this has never been used.[2] Pharmaceutical companies can appeal against the decision of the Committee.

The Committee comprises representatives from industry and organisations such as the Consumers' Health Forum, a patient support organisation, the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, the Royal Australian College of General Practitioners and the Australian Medical Association.

The independent Monitoring Committee reviewed over 380 pieces of promotional material during the year for products in the systemic anti-infectives and antihypertensive therapeutic classes. Compliance with the Code of Conduct ranged from 82% to 95%. Advice regarding the outcomes of the Committee's deliberations was provided to the relevant companies to enhance their compliance with the Code.

Breaches of the Code (Table 1)

In the interests of transparency, the Code includes a requirement for regular publication of Code breaches in medical journals. This information includes the names of companies who have had complaints brought against them, a summary of the complaints and sanctions imposed.

In 2000–01 37 complaints were received. Most (22) of these were from pharmaceutical companies, but 10 were from health professionals. Four of the complaints were subsequently withdrawn, one was returned to the complainant. Three were resolved by intercompany discussions and mediation. Two complaints were not considered because they were similar to previous complaints.

Of the 27 complaints evaluated by the Committee, 17 were found to be in breach of the Code. (The results of an appeal about one complaint are not yet known.)

NOTE

The APMA Code of Conduct is available from:

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Web site: www.apma.com.au

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Table 1
Breaches of the Code of Conduct July 2000–June 2001

Company	*Breaches*	*Drug – brand name*	*Drug – generic name*	*Sanction imposed by Code of Conduct Committee*
Bayer	1	Adalat Oros	nifedipine	Advertisements not to be used again
Beiersdorf	1	Aethoxysklerol	polidocanol (laureth-9)	Withdrawal of poster
Eli Lilly	1	Zyprexa	olanzapine	Advertisements not to be used again
Glaxo Wellcome	4	Relenza	zanamivir	Advertisements not to be used again Radio and television commercials not to be used again
		Flixotide	fluticasone	Advertisement not to be used again
		Seretide	fluticasone with salmeterol	$15 000 fine
Merck Sharp and Dohme	1	Zocor	simvastatin	Corrective advertisement required
Organon	1	Livial	tibolone	Promotional mailer not to be used again
Servier	1	Coversyl Plus	perindopril with indapamide	Corrective letter required
SmithKline Beecham	2	Augmentin	amoxycillin with clavulanic acid	Promotional material not to be used again Withdrawal of materials
Solvay	4	Femoston	oestradiol with dydrogesterone	$5000 fine; withdrawal of promotional material
		Duphaston	dydrogesterone	Promotional material not to be used again
		Teveten	eprosartan	$5000 fine; promotional material not to be used again
		Promotional competition		Promotional material not to be used again

Anaesthesia and perioperative care for elderly surgical patients

Geoff Cutfield, Professor of Anaesthesia and Intensive Care, University of Newcastle, John Hunter Hospital, Newcastle, New South Wales

SYNOPSIS

Age alone is no longer a barrier to surgery. Ageing changes the body's capacity to cope with the stress of illness and surgery. The anaesthetist must assess these changes and the perioperative factors which contribute to poor outcomes. To reduce morbidity and mortality there must be adequate pain control, thromboembolic prophylaxis and correction of inadequate nutrition and hydration. In the postoperative period there is a need to be alert for sepsis and delirium. An admission to hospital also provides an opportunity to assess the patient's other health care needs.

Index words: ageing, analgesia, thromboembolism.

(Aust Prescr 2002;25:42–4)

Introduction

In Australia in recent years spending has increased to support the care of elderly patients. This movement includes surgical care and is supported by an accumulation of evidence which shows that age alone can no longer be considered an independent risk factor for a poor outcome following general surgery.[1] 'With continual improvements in both anaesthesia and surgical expertise, surgery can no longer be denied to patients solely on the basis of age'.[2] It is arguable that a patient would ever be considered unsuitable for anaesthesia, rather unsuitable for the proposed surgical procedure.

The challenge we face in this decade is refining our skills to determine with more precision where the balance is between the benefit and cost (including harm) of matching interventions to each patient's needs. At a practical level, there is much that can be done to curb costs and wastage through better management of perioperative care, to foster multidisciplinary approaches and give appropriate time and resources to the appropriate care of elderly patients.

Understanding the impact of the ageing process

Understanding the physiological, pharmacodynamic and pharmacokinetic impact of the ageing process is important (Table 1).

The effects of ageing in an individual patient are accentuated by disease. The reductions in functional reserve in each organ system represent parallel reductions in the patient's capability to maintain homeostasis in the face of surgical stress and the actions of anaesthetic drugs.

After considering the effects of ageing and assessing the impact of the particular elderly patient's burden of illness – the surgical pathology itself, and any coexisting diseases – the anaesthetist is better equipped to appraise the factors which determine the risk of a poor outcome. With such foreknowledge it should be possible to prepare a management plan which minimises the impact of such risks. This is the crux of the preoperative assessment process. It requires the anaesthetist to spend time with the patient and must not be compromised by short-sighted 'drives for efficiency'.

The scope for tailoring anaesthetic management to the patient's condition has been widened considerably recently with good data upon which to base management decisions and the addition of several important drugs to our pharmacopoeia. These drugs have less lingering hypnotic and depressant effects.

Table 1

Effect of age on physiological processes
(The data in this table were accumulated from 'average' and healthy populations)

Function	*Percentage decline from age 20-30 years to age 60-80 years*
body temperature, arterial pH	0%
total number of neurones	0.2%
resting pulse rate, height, craniocerebral index	5%
nerve conduction, haematocrit, body weight, total lung capacity	10%
albumin, maximum pulse rate, basal metabolic rate, body water, arterial oxygen tension (PaO_2)	15%
total body potassium	15–20%
diet, renal mass, FEV_1, brain weight	20%
muscle mass, intracellular water, hypoxic and hypercarbic responses	25%
tissue oxygen delivery	20–30%
vital capacity, cardiac index, cerebral blood flow, alveolar parenchyma	30%
maximum oxygen uptake, anaerobic threshold, creatinine clearance, lean body mass	35%
number of alveoli	30–40%
glomerular filtration rate	40%
hepatic blood flow	40–50%
cortical neurones, renal plasma flow, ventilatory reserve	50%
maximum breathing capacity	60%

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Optimum management of perioperative care

Alongside rigorous planning of anaesthetic management there should be optimum management of perioperative medical care by a multidisciplinary team. This team tackles those conditions which contribute to morbidity and prolonged aftercare:

- pain
- delirium
- sepsis
- deep vein thrombosis
- poor nutrition and hydration
- rehabilitation planning.

The available evidence showing the benefit of taking specific measures directed at each of these factors has been reviewed in patients with hip fracture.[3]

Adequacy of pain control

There is a complex interplay between each patient's sensitivity to pain and the effectiveness of analgesic strategies. Perioperative pain management in elderly patients is therefore never routine.

Practically none of the analgesic drugs in current use are purely pain relieving. Opioids, non-steroidal anti-inflammatory drugs and local anaesthetics have a plethora of actions and consequently a host of reported adverse effects. For this reason alone, prescribing and medication administration routines result in many elderly patients receiving inadequate analgesia. A study of analgesic delivery after hip fracture highlighted the fact that patients with dementia received one third of the equivalent analgesic medication given to patients without cognitive impairment.[4] The authors commented that quite apart from the inhumanity, such care can only worsen the progress of cognitive dysfunction.

The implications for patient care are clear. We must give time and professional effort to assessing pain control. For example, to discern whether an elderly patient's sleep disturbance and its deleterious effect on their orientation is the result of inadequate or excessive analgesia requires astute observation and continuity of supervision. These roles are increasingly the province of the acute pain services which most hospitals have developed.

Delirium

Delirium is an organic mental disorder characterised by acute onset, altered level of consciousness, fluctuating course and disturbances in orientation, memory, attention, thought and behaviour. It is associated with significant increases in functional disability, length of hospital stay, rates of admission to long-term care institutions, mortality and health care costs.

In the perioperative period, when there is a confluence of factors (for example drug effects, poor pain control, infections, unfamiliar environment and sensory deprivation) the prevalence of delirium increases to 15–50% of patients in the over-70 age group.[5] An earlier systematic review highlighted the frustration in managing delirious patients and the poor absolute risk reduction achieved by attempts at preventive strategies.[6] That review was made difficult by the small number of studies and the small numbers of patients in each one. A more recent study of 852 general medical patients shows the benefits of multicomponent therapy aimed at each of the known risk factors.[7] This approach is very likely to be equally applicable to surgical patients where the risk factors include:

- pre-admission cognitive impairment
- sleep deprivation
- immobility
- visual impairment
- hearing impairment
- dehydration.

Sedative-hypnotic and anticholinergic medications in general should not be used because of their central nervous system effects. A quiet environment and a supportive reorientation should be encouraged. This is the regular gentle and empathetic evaluation of mental state and level of comfort of the elderly patient.

Sepsis

Postoperative infection is a significant contributor to mortality and morbidity. This can be related to the operative site, to developing urinary tract or respiratory infection or to hospital-acquired sepsis at cannula sites.

Recognition of infection in elderly patients is frequently delayed. In part this may relate to the nature of the patient, but also to the altered symptoms and signs of infection in elderly patients. In comparison with younger patients, the absence of fever and the masking of other signs (e.g. tachycardia) by concurrent drug therapy mean that the diagnosis of infection is often not made until sepsis is well established.

The evidence for the benefits of antibiotic prophylaxis is convincing. There was a 44% reduction in the incidence of infection in a meta-analysis of seven studies that compared antibiotic use with placebo for elderly patients undergoing hip arthroplasty.[3] Weaker (in terms of not being generated by systematic review or randomised controlled clinical trial), but compelling evidence is available for the benefit of antibiotic prophylaxis in gynaecological[8] and urological[9] surgery.

Deep vein thrombosis prophylaxis

As there is an increased incidence of venous thrombosis and pulmonary embolism after surgery, thromboembolic prophylaxis has been endorsed by almost all recent studies of elderly surgical patients.[10] This may take many forms, from low-dose heparin (unless contraindicated, for example immediately after neurosurgery) to low molecular weight heparin and aspirin. The beneficial effect of compression stockings is indisputable.[11]

Nutrition and hydration

Both the level of hydration and the balance of nutritional requirements need attention in elderly patients. Recognising

nutritional deficits and correcting them contributes significantly to improved outcomes for older surgical patients. This has been particularly clearly shown in patients with femoral neck fractures.[12,13]

Rehabilitation planning

Early mobilisation improves patients' perceptions and orientation as well as shortening hospital stay. There are but a few clinical situations where strict bed rest needs to be enforced. Furthermore, in orthopaedic patients, the benefits of postoperative exercise and balance training in reducing falls and facilitating discharge have been substantiated in a recent systematic review.[14]

The surgical episode as an opportunity for enhancing life quality

For a significant proportion of elderly patients, a surgical procedure represents the first medical contact the patient has made for some time, if not the first ever. For others it affords the opportunity to work in liaison with the general practitioner to review and stabilise therapy for coexisting disease in a supervised environment.

The whole episode should ideally be one of holistic care, with evaluation of and provision for all the health needs of the patient. Examples of beneficial parallel interventions range from the simple, such as reviewing medication, to the more complex, such as getting hypertension under control and preventing its contribution to the progression of dementia.[15] The aim should be to enhance the quality of life where possible. In this context, the anaesthetist's role is significant and complementary.

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Conflict of interest: none declared

Self-test questions

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

7. Patients with cognitive impairment require less postoperative analgesia than other patients.
8. Older patients have fewer alveoli than younger adults.

New drugs

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

Amprenavir

Agenerase (Glaxo Wellcome)

150 mg capsules, and 240 mL bottles containing 15 mg/mL oral solution

Approved indication: HIV-1

Australian Medicines Handbook Section 5.3.5

Amprenavir is the fifth protease inhibitor to be approved for use in Australia. It can be used to treat HIV infection in combination with other antiretroviral drugs, such as zidovudine and lamivudine. By inhibiting the protease in HIV-1, amprenavir results in the production of non-infectious virions.

Patients take amprenavir twice a day. As the dose is 20 mg/kg the patients need to take several capsules. The oral solution is

less bioavailable than the capsules, so the doses are not equivalent. Although absorption is affected by food, amprenavir can be taken with or without food. The volume of distribution is large, but amprenavir does not greatly penetrate the blood brain barrier. Concentrations in cerebrospinal fluid are less than 1% of the plasma concentration.

Amprenavir is eliminated by hepatic metabolism and has a half-life of 7-11 hours. The metabolism of amprenavir involves cytochrome CYP3A4. It therefore has many potential interactions including those with other drugs used to treat HIV. Patients taking amprenavir should not be given drugs such as midazolam, triazolam, ergot derivatives and rifampicin.

Clinical trials show that adding amprenavir to a combination of zidovudine and lamivudine in previously untreated patients is more efficacious than the combination alone. Almost 60% of patients will have concentrations of viral RNA less than 400 copies/mL after 16 weeks of treatment. An open label extension of this study resulted in 43% of the patients being at or below the target concentration after 48 weeks.[1]

In patients who have previously had treatment, but not with a protease inhibitor, 30% will have less than 400 copies/mL after 48 weeks. If amprenavir is given to patients who have already been treated with a protease inhibitor, 34% will have less than 200 copies/mL after 24 weeks of taking the dual protease inhibitor regimen. The response rate is reduced if the patients have previously taken a non-nucleoside reverse transcriptase inhibitor.

Adverse effects are common and include nausea, vomiting and diarrhoea. Some patients will develop rashes. These usually resolve spontaneously, but the Stevens-Johnstone syndrome has been reported. Other uncommon adverse effects include lipodystrophy, hyperlipidaemia and diabetes mellitus.

The capsule formulation contains vitamin E, so patients are advised not to take supplements of vitamin E. The oral solution is not suitable for young children and pregnant women because it contains the potentially toxic propylene glycol. This formulation is also contraindicated in patients with hepatic or renal impairment.

In patients who have not previously had a protease inhibitor as part of their treatment, indinavir may be better tolerated and have greater efficacy than amprenavir. However, it is only approved for patients who have previously been treated with a protease inhibitor. HIV can become resistant to protease inhibitors, however the profile of resistance to amprenavir differs from that of other protease inhibitors. It may therefore have a role in 'salvage therapy' when resistance to other protease inhibitors has developed.

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Azelastine

AZEP (Sigma)

0.1% nasal spray

Approved indication: allergic rhinitis

Australian Medicines Handbook Section 9.4.3

When seasonal or perennial rhinitis is severe enough to require drug treatment, a topical antihistamine is an alternative to topical nasal corticosteroids. Azelastine is an H_1-receptor antagonist which has been approved for use in patients over five years old.

Patients spray a dose of azelastine into each nostril twice a day. Within 15 minutes this starts to relieve nasal symptoms induced by histamine or allergens. The effect of a dose can last for up to 12 hours. Part of each dose is absorbed. This is then extensively metabolised with most of the metabolites being excreted in the faeces. The major metabolite, desmethylazelastine, is also an H_1-receptor antagonist. It has a half-life of 56 hours so there is a potential for accumulation with twice-daily doses.

In studies of seasonal allergic rhinitis, azelastine was as effective as oral terfenadine at reducing symptoms such as rhinorrhoea, nasal irritation and sneezing. Similar results were observed in patients with perennial allergic rhinitis.

Most of the adverse effects occur in the nose. They include stinging, itching, sneezing and epistaxis. Some patients will develop an altered taste sensation and possibly nausea.

While azelastine may have a more rapid effect, it is not more effective than nasal corticosteroids. In a placebo-controlled trial budesonide had a significantly greater effect on the symptoms of perennial allergic rhinitis.[1] A short study (two weeks) found that beclomethasone produced a greater improvement in the overall symptoms of seasonal allergic rhinitis.[2]

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Gadoteridol

Prohance (Bracco)

279.3 mg/mL in 5, 10, 15 and 20 mL vials and 5, 10, 15 and 17 mL syringes

Approved indication: magnetic resonance imaging

Gadoteridol adds to the choice of contrast agents for use in magnetic resonance imaging. It is a non-ionic complex of gadolinium with a low molecular weight. Gadoteridol does not cross the blood-brain barrier, but if the barrier is damaged gadoteridol will penetrate into lesions such as tumours. It also highlights areas of increased vascularity so it has been used to improve the delimitation of lesions elsewhere in the body.

Apart from its paramagnetic effects, gadoteridol has no pharmacological activity in the body. After intravenous injection, most of the dose is excreted unchanged in the urine within 24 hours. There is little information about the effect of renal impairment on the clearance of gadoteridol. Severe renal impairment is a contraindication.

Adverse reactions are uncommon, but prescribers need to be equipped to deal with anaphylactoid reactions. The more frequent adverse effects of gadoteridol include nausea, altered taste, headache and pain at the injection site.

Gadoteridol has been available in Europe and the USA for several years. It does not appear to have any significant advantages over similar products.

Lanreotide

Somatuline LA (Ipsen)

glass vials containing 40 mg as powder (only 30 mg is available for the patient due to losses of the active ingredient during sterilisation, resuspension and administration)

Approved indication: acromegaly

Australian Medicines Handbook Section 10.6.4

Somatostatin is a peptide which inhibits the secretion of growth hormone. Synthetic analogues of somatostatin, such as octreotide and lanreotide, can therefore be used in the treatment of acromegaly which results from an excessive concentration of growth hormone.

Lanreotide is indicated for patients whose concentrations of growth hormone remain high despite surgery and/or radiotherapy. It is also indicated for patients who are refractory to treatment with a dopamine agonist.

A modified-release formulation allows lanreotide to be initially given every 14 days. After reconstitution it is injected intramuscularly. There is a rapid release, followed by a prolonged release from the microparticles in the formulation. The half-life of this formulation is approximately five days. Although the product is injected its bioavailability is 57%.

A European study involving 125 patients compared injections of 30 mg lanreotide every 10–14 days with monthly injections of 20 mg of modified-release octreotide. The growth hormone concentration was reduced significantly more by octreotide than by lanreotide and more patients reached the target concentrations.[1]

The most frequent adverse effects of lanreotide are reactions at the injection site and gastrointestinal upsets. As lanreotide may reduce gall bladder motility, patients should have an ultrasound scan before treatment and every six months during treatment.

Although more than half the patients treated with lanreotide will respond satisfactorily, some need injections more frequently than every 14 days. Lanreotide may be less effective than octreotide.

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Linezolid

Zyvox (Pharmacia)

600 mg film-coated tablets

granules for oral suspension (20 mg/mL)

infusion bags containing 600 mg/300 mL

Approved indication: specified infections

Australian Medicines Handbook Section 5.1

The oxazolidinones are a new class of antibiotic. They are likely to have a role in the treatment of infections caused by resistant organisms.

Linezolid is the first drug of the class to be approved in Australia. Its inhibition of bacterial protein synthesis makes it bacteriostatic against staphylococci and enterococci, and bactericidal against most streptococci. Linezolid can be used to treat methicillin-resistant staphylococci and vancomycin-resistant enterococci. It is not active against *Haemophilus influenzae*, *Pseudomonas aeruginoia*, *Neisseria* or *Enterobacteriaceae*. *Legionella* and *Moraxella catarrhalis* are only intermediately susceptible to linezolid.

When taken by mouth, linezolid is almost completely absorbed. It has a half-life of 5-7 hours and is mainly eliminated by metabolism. As linezolid weakly inhibits monoamine oxidase there is a potential for interactions with tyramine and sympathomimetic drugs such as pseudoephedrine.

Adverse effects are common; 70% of the patients in one study had an adverse event.[1] The most frequent problems are headache, nausea, diarrhoea and candidiasis. Liver function is commonly disturbed and some patients develop myelosuppression. The haemoglobin and platelet count should be checked in any patient who takes linezolid for more than two weeks. Patients are also at risk of pseudomembranous colitis.

Some of the trials investigating the efficacy of linezolid have not been published. One published study was a double-blind comparison with vancomycin for the treatment of 396 patients with nosocomial pneumonia. Approximately 18% of the inpatients given linezolid died compared with 25% of the vancomycin group. None of the deaths in the linezolid group were due to a lack of response. The cure rate was 53% for linezolid and 52% for vancomycin.[1]

Although linezolid has been studied in soft tissue infections and community-acquired pneumonia, as well as in nosocomial pneumonia, it is not approved for general use in these conditions. As linezolid is unlikely to have cross-resistance with other antibiotics, because of its different mechanism of action, it should be reserved for organisms which are resistant to other antibiotics. As linezolid has oral formulations it may have a practical advantage over quinupristin/dalfopristin (see 'New drugs' Aust Prescr 2000;23:65), which is approved for the intravenous treatment of resistant organisms, but the two drugs have not been compared in clinical trials.

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Meloxicam

Mobic (Boehringer Ingelheim)

7.5 mg and 15 mg tablets

Approved indication: osteoarthritis

Australian Medicines Handbook Section 15.1

The new cyclo-oxygenase inhibitors are being promoted as drugs which inhibit the COX-2 enzyme more than the COX-1 enzyme. Although meloxicam is in a different class of non-steroidal anti-inflammatory drugs, it also inhibits COX-2 more than COX-1 (see 'COX-2 inhibitors' Aust Prescr 2000;23:30-2).

Patients take meloxicam once a day. It is absorbed slowly and has a half-life of 15-20 hours. Most of the dose is metabolised and this involves cytochrome P450 2C9 and 3A4. Although CYP2C9 predominates, caution is needed if an inhibitor of CYP3A4 is prescribed concurrently with meloxicam. It is contraindicated in patients taking drugs, such as sulfamethoxazole, which inhibit CYP2C9.

In clinical trials meloxicam has been as effective as sustained-release diclofenac in relieving the symptoms of osteoarthritis. For short-term treatment, meloxicam was as effective as piroxicam.

If taken for more than six months, meloxicam is associated with gastrointestinal adverse effects in more than 20% of patients. Common problems include diarrhoea, dyspepsia and nausea. Although the overall incidence may be less than for similar drugs, there is no clear reduction in serious adverse effects such as bleeding or perforation of peptic ulcers.

Correction

Daivonex (Aust Prescr 2001;24:158)

There was a typographical error in the New Formulations section of New drugs, regarding calcipotriol scalp solution (CSL). The brand name is Daivonex, not Diavonex.

Answers to self-test questions

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

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