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CONTENTS

Expensive new drugs—do we really need them?

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Key words: Fiji, Pharmaceutical Benefits Scheme.

(Aust Prescr 2004;27:136–7)

It is an article of faith in modern medicine that we need new drugs to treat most disorders. This belief has important implications. It underpins the patent system, which assumes that investment in the development of new drugs is so important that the principles of the free market should be abrogated to reward pharmaceutical companies with a legally enforced period of protection from competition. The Australian Pharmaceutical Benefits Scheme (PBS) is also based on the belief that all Australians should have access to new drugs.

No one would deny the impact that drugs introduced over 20 years ago had when they were new. Penicillin (and other antibiotics), beta blockers, H_2 antagonists, and non-steroidal anti-inflammatory drugs are examples of drugs that markedly altered clinical practice and are still widely used. However, it is harder to think of drugs introduced over the last 20 years that have had a similar impact[1] – antiretroviral drugs are perhaps one example – so has the time come to question our faith in new drugs?

In this issue…

In April 2000 *Australian Prescriber* published an editorial expressing concern about the risk of thrombosis with COX-2 inhibitors. Ric Day and Garry Graham explain why the vascular effects of COX-2 inhibitors ultimately led to the sudden worldwide withdrawal of rofecoxib in October 2004.

This recall will not greatly affect developing countries where access to new drugs is limited. Rob Moulds says his experience in Fiji shows that most patients can be managed without expensive new drugs, while Judith Whitworth argues that there is an obvious need to continue drug development.

The controversy about old and new drugs rages in psychiatry. Nick Keks and Vaughan Carr debate whether the atypical antipsychotics are significantly better than the older typical drugs.

There are new analgesics, but Stephan Schug and Philip Dodd tell us that new approaches to perioperative analgesia have improved pain relief for surgical patients.

One way of looking at the question is to ask what the practice of medicine would be like if the drugs developed over the last two decades had never been introduced. The experience of treating patients in a developing country (in my case, Fiji), where most new drugs are not freely available, can bring a special perspective to the question.

Fiji has a health budget that, per capita, is less than 10% of the Australian health budget, so it cannot possibly afford a system like the PBS. Instead, Fiji has adapted the World Health Organization's model list of essential medicines[2] for local circumstances. Drugs on Fiji's essential drugs list are available free from government health centres and hospitals. Drugs not on the list must be obtained from a private pharmacy and the patient must pay the full price. The essential drugs list contains one or two representatives from most drug groups: for instance, two beta blockers (atenolol and propranolol), one ACE inhibitor (enalapril), one H_2 antagonist (ranitidine), and most of the old (and cheap) antibiotics, for example penicillin, amoxycillin and gentamicin.

Almost all the drugs on the list were introduced over 20 years ago and their patents have expired. This enables the central government pharmacy to purchase supplies at the lowest price available – often from generic manufacturers in India or Malaysia.

The diseases we treat are remarkably similar to those seen in Australia. Diabetes, hypertension, asthma and smoking-induced respiratory disorders are common. Infections are also common, but are usually caused by pathogens such as *Streptococcus pneumoniae* and *Staphylococcus aureus* rather than exotic tropical organisms.

So, do we find ourselves seriously handicapped in Fiji by lack of access to new drugs? The short answer is no. We can treat most conditions perfectly adequately with the older drugs available on the essential drugs list. We perhaps have to be more adept than doctors in developed countries at using the drugs we do have rather than simply switching the patient to a new drug. For instance, we may have to explore a wider range of doses than are commonly used in Australia. However, we are seldom seriously concerned by not being able to prescribe COX-2 inhibitors, angiotensin receptor antagonists, long-acting $beta_2$ agonists or new antiplatelet agents.

There are definite exceptions to this generalisation. Lack of a 'statin', for instance, penalises patients with cardiovascular

disease, and most patients with AIDS do not yet have access to antiretroviral drugs. Some patients whose 'gastric' conditions are not controlled with ranitidine can suffer from lack of access to a proton pump inhibitor. Perhaps our patients with diabetes might have better control with new oral hypoglycaemic drugs, although our woefully poor control of diabetes is mainly caused by socio-economic factors rather than lack of access to new drugs.

My experience in Fiji suggests that, over the last 20 years, the article of faith that we need new drugs has largely not been fulfilled. So much so that I suggest we should seriously question our belief that these new drugs are essential rather than blindly continue to support it. If we reject this faith it follows that patent protection, and subsidisation by the taxpayer, should be much harder to obtain.

Patent protection assumes that innovation requires reward to ensure continuing investment. However, the faith that we must ensure that new drugs continue to be developed has meant that patent protection is given for even trivial developments. If we reject the faith, then patent protection should only be given to real innovation.

The PBS came into being when most new drugs, such as penicillin, were truly life-saving, but unaffordable to most people. However, even when many new drugs were not life-saving, listing on the PBS continued because of the faith that we need new drugs. Listing now requires a new drug to be cost-effective in comparison to other drugs subsidised by the PBS, but many of the drugs currently available have themselves never been proven to be cost-effective. So if we reject the faith, then cost-effectiveness in comparison to current drugs should not be sufficient to justify public subsidy. Perhaps we should go back to the original criterion that a drug should be truly life-saving to justify subsidisation.

Restricting patent protection to real innovation, and restricting subsidies to truly life-saving drugs is almost certainly too powerful a pill for any government (or the medical profession) to swallow. However, is it not better to admit the true situation rather than adhere blindly to an outmoded article of faith?

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Conflict of interest: none declared

The need for new drugs: a response

Judith A. Whitworth, Director, John Curtin School of Medical Research, Australian National University, Canberra

Key words: patents, research.

(Aust Prescr 2004;27:137–8)

In 1899 Charles Duell, Commissioner for the US Patent Office, urged President McKinley to abolish his office, because 'Everything that can be invented has been invented'. At that time life expectancy was over 20 years less than it is now and infant mortality was about 15-fold higher than today. It is hard to imagine that these gains would have been made without invention.

Sir Macfarlane Burnet, one of Australia's greatest ever scientific minds, wrote in his 'atypical autobiography' in 1968, 'No one can deny that medical research has provided, by any criterion, immeasurably important benefits during 'my' fifty years … But at the risk of being proved wrong in an embarrassingly short space of years, I do not think there will be practically applicable laboratory discoveries about cancer, autoimmune disease or the degenerative conditions associated with ageing and natural death, nor in regard to schizophrenia, the other acute psychoses, and the degenerative mental changes of old age. … from the point of view of health and medical care, all that 99 per cent of the world's people would ask for, if they were articulate, is for the full implementation for their benefit of what medical science had provided by 1955.'[1]

There is a resonance here with the views expressed by Professor Moulds.[2] The World Health Organization's (WHO) model list of essential medicines has indeed contributed significantly to global medical care. In a recent article on emerging drugs in management of hypertension I wrote, 'Hypertension is a major global health problem … it is likely that, in the short term, emerging drugs will play second fiddle to more targeted use of existing drugs and that the emphasis in emerging drugs will be on modification of existing classes, proven to be of benefit in outcome studies.'[3]

Our views are less congruent in other areas. Even if one excludes 'statins' and antiretroviral drugs, it is difficult to argue we have not seen important advances in the last couple of decades. Examples include protease inhibitors, hepatitis vaccines, erythropoietin, ondansetron and kinase inhibitors. It is true the list is not as long as one would wish, but given the global and national burdens of disease, this is a strong

argument we need more, not fewer, new drugs.

Perhaps this relative paucity reflects the limitations of our old methods for drug discovery. However, the relative paucity of solutions demands new solutions and new technologies, not a retreat.

During the last 20 years new indications have emerged for older drugs, for example ACE inhibitors in acute myocardial infarction and (with indapamide) in prevention of secondary stroke, aldosterone antagonists and beta blockers to reduce mortality in heart failure, and the use of antibiotics to treat peptic ulcer. When a drug is first developed its ultimate indications (and degree of innovation) may not be recognised. At the same time, we have seen, frighteningly rapidly, the emergence of antibacterial, antimalarial and antiviral drug resistance, making some old drugs progressively less effective.

The need for new drugs is obvious – for old and new infections, as well as for the chronic diseases mentioned by Burnet – and there is enormous potential for the development of new drugs. According to the WHO Report on Genomics and World Health:

> It has been estimated that successful drug therapy currently is directed at fewer than 500 targets. Considering that the human genome contains some 30 000 genes, it is possible that its study could lead to at least 3000 to 5000 potential new targets for therapy. Currently, predominant candidates include G protein-coupled receptor families and other receptors and related molecules, a wide range of enzymes including proteases, kinases and phosphatases, hormones, growth factors, chemokines, soluble receptors and related molecules, and many others. Exactly the same principles are being applied to the search for agents to interfere with key biochemical pathways in pathogens, based on information which is being obtained from the pathogen genome project.[4]

Just as discoveries in the old disciplines of chemistry and biochemistry in the early 20th century took many years to translate into new drugs, so it will take time to learn how to realise the potential of the new discipline of genomics. But learn we must.

If a potential drug discovery/innovation/invention is not patented, it will never find its way into practice. With new drugs said to cost around $1 billion to bring to market, investment will only be made if patent protection is assured. If the degree of 'real innovation' must be predetermined, based on previous experience, valuable therapies may be lost. Whatever our differences of emphasis, the ultimate goal is the same: effective, accessible, affordable medicines for all.

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Conflict of interest: none declared

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.

Quality use of medicines – prescribing for manufacturers or patients?

Editor, – I refer to the editorial 'Quality use of generic medicines' (Aust Prescr 2004;27:80–1).

Confusion resulting from the availability of multi-sourced brands of medications is predictable within our rapidly changing prescribing and dispensing environments.

For decades, prescribing by manufacturers' brand names was manageable when most medications were available as a single brand. It should also be noted that brand names are required for all products as part of Therapeutic Goods Administration (TGA) regulatory requirements.

Australia has a growing generics segment. This is synonymous with growing numbers of brands of the same medications and it is time for current prescribing practices to be reviewed to determine better ways to manage multi-sourced brands.

An Australian Pharmaceutical Advisory Council (APAC) subcommittee has concluded that Australia should move towards increased use of active ingredient names. In the UK, this has served to educate the public and health professionals to identify medications, primarily, by their international (approved) active ingredient names and not by local, brand names.

As per the authors' comments, increased prominence of active ingredient names is being recommended by various health committees to assist patients and professionals.

An APAC subcommittee will shortly deliver a report on the management of these issues. This report will address concerns about confusion related to over-reliance by all stakeholders on brand names. The process has begun to make some simple but essential improvements to the management of all medications by speaking and writing more in the language of medicine and less in the language of marketing.

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Thiazolidinediones

Editor, – The article 'Thiazolidinediones – mechanisms of action' (Aust Prescr 2004;27:67–70), states that 'hepatotoxicity does not seem to be associated with the other two compounds (pioglitazone, rosiglitazone)'. Although admittedly this may be referring to the rare but fatal cases of hepatotoxicity associated with troglitazone, it does seem somewhat at odds with the ADRAC Bulletin. This reported on 16 cases of hepatic adverse reactions including elevated liver function tests, jaundice, hepatitis and hepatocellular damage. Although it does add the rider that 'liver enzyme levels may be elevated with diabetes or obesity'.[1]

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Reference

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Dr J.R. Greenfield and Professor D.J. Chisholm, the authors of the article, comment:

In contrast to troglitazone, which was withdrawn because of rare but fatal liver failure, placebo-controlled trials show that the risk of liver function abnormalities (reversible elevations of alanine transferase greater than three times the upper limit of normal) in patients treated with pioglitazone or rosiglitazone is 0.2–0.3% and not different from placebo-treated patients.[1] While rare case reports of hepatocellular injury and hepatic failure have been described in patients treated with these newer drugs[2], whether liver dysfunction can be definitively attributed to the thiazolidinedione has been challenged.[3] As Mr Grubb acknowledges, liver function may be abnormal in patients with diabetes and/or obesity, particularly due to non-alcoholic fatty liver disease. Furthermore, liver function may actually improve following treatment with these drugs, due to a reduction in hepatic lipid content.[4] As stated in our article, and the accompanying paper (Aust Prescr 2004;27:70–4), and by the Adverse Drug Reactions Advisory Committee, pharmacovigilance with periodic tests of liver function is recommended, despite the safety of pioglitazone and rosiglitazone.

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Warfarin: balancing the benefits and harms

Editor, – As an eye surgeon I was surprised to read that warfarin was contraindicated when eye surgery was contemplated (Aust Prescr 2004;27:88–92). Given that cataract surgery is one of the most common elective surgical procedures performed in this country and most patients are aged over 65, this advice was somewhat at odds with accepted practice. A number of papers have looked at this issue and a study from New Zealand suggested that there was no greater risk of adverse events in patients undergoing surgery being maintained on warfarin, provided their INR was between 2.0 and 2.5.[1]

T. Hodson
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Reference

1. Morris A, Elder MJ. Warfarin therapy and cataract surgery. Clin Experiment Ophthalmol 2000;28:419-22.

Dr M. Borosak, Ms S. Choo and Professor A. Street, the authors of the article, comment:

The contraindications to warfarin indicated in the article were obtained primarily from the product information. The relevant paragraph indicates that any circumstance where the 'hazard of haemorrhage might be greater than the potential clinical benefit of anticoagulation' may constitute a contraindication. It goes on to say that examples of these circumstances **may** be haemorrhagic tendencies and blood dyscrasias, recent or contemplated surgery of the central nervous system, the eye or traumatic surgery resulting in large open surfaces. The

risk:benefit analysis is the key to the decision making related to what is considered a contraindication.

This view is also supported by a study of the management of anticoagulation before and after elective surgery, which presented figures pertaining to such a risk:benefit analysis. The absolute risk of thromboembolism associated with a few days of perioperative subtherapeutic anticoagulation is generally very low while the risk of bleeding if anticoagulated may be relatively high.[1]

The study quoted by Dr Hodson describes a retrospective review of 28 cataract patients being treated with warfarin (outcomes were available for 23 eyes) who had INRs ranging from 1.0 to 2.4 (median 1.5). There were four haemorrhages, all of which were visually not significant, and there were no thromboembolic phenomena. The conclusion was that with modern techniques cataract extraction can safely and effectively be performed in patients taking warfarin who have an INR of approximately 2.0.

It is our opinion that in all perioperative circumstances the patient's individual risk factors for thrombosis and haemorrhage should be considered before a decision is made to maintain warfarin therapy and the INR level above 2.0.

Reference

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Antibiotic prescribing

Editor, – In the article 'Antibiotic prescribing: how can emergence of antibiotic resistance be delayed?' (Aust Prescr 2004;27:39–42) I note the emphasis on using these drugs for the shortest time possible. Is it time to change our advice to patients to 'make sure you complete the course, even if you feel better after a few days'?

The reason for this advice appears to be twofold. Firstly, the infection will recur if incompletely treated. Secondly, the emergence of resistance is facilitated by shorter courses of antibiotics, presumably because relatively resistant strains of the pathogenic bacteria may still be viable at the end of such a course. However, is complete eradication of the pathogen desirable or necessary in the clinical world of bacterial tonsillitis, severe otitis media, bacterial sinusitis, bacterial gastroenteritis, urinary tract infection, impetigo and chest infection? Do we actually have any evidence relating duration of antibiotic courses, emergence of resistant pathogens, and clinical 'cure' in these conditions?

Nancy Sturman
General practitioner
Indooroopilly, Qld

Dr J. Ferguson, the author of the article, comments:

The situation is complex and varies according to the infected site. With infections such as otitis media, when antibiotics are used, the counsel is now to use 'short and sharp' – an adequate dose to eradicate the pneumococcus and short duration to avoid extended selective pressure. Generally, the longer the course, the greater the selective pressure. This is facilitated by the number of bacteria present – an undrained abscess with pseudomonas will see quick emergence of resistance whereas a patient with streptococcal endocarditis will not have resistance emerge despite several weeks of therapy (the bacterial count is much lower and the intrinsic character of the organism less liable to mutational or other resistance acquisition).

Insulin glargine

Editor, – I would like to draw your attention to the review of insulin glargine (Aust Prescr 2004;27:50–1), particularly the statement that insulin glargine is not suitable for use in patients with type 2 diabetes.

Insulin glargine has an indication for use in type 2 patients in its approved product information. The use of insulin glargine in this patient group continues to be supported by a large body of clinical trial evidence, as well as postmarketing experience in many countries where it has been used in clinical trials or commercially available for almost five years.

The review, which referred to guidelines prepared by the National Institute for Clinical Excellence (NICE) in the UK, has omitted the important qualifying information which NICE made to its general advice on the use of insulin glargine. These guidelines in fact specify quite distinct groups of patients in which insulin glargine should be considered, which taken together account for a significant proportion of all patients with type 2 diabetes.[1]

In addition, the claim that 'long-term effectiveness of insulin glargine is currently unknown' is, we believe, out of date. There are several published studies involving insulin glargine lasting up to 52 weeks in duration. There is no evidence to date that the effectiveness of insulin glargine diminishes with time.

James Robertson
Senior Medical Advisor
Aventis Pharma
Lane Cove, NSW

Reference

1. National Institute for Clinical Excellence. Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine. London: NICE; 2002. http://www.nice.org.uk/pdf/53_Insulin_analogues_full_guidance.pdf [cited 2004 Nov 8]

Editorial comment:

The *Australian Prescriber* comment accurately reflected the conclusion of the National Institute for Clinical Excellence (NICE) that insulin glargine 'is not recommended for routine

use for people with type 2 diabetes who require insulin therapy'. The NICE recommended that insulin glargine should only be considered, in type 2 diabetes, for patients:

- who require assistance from a carer or healthcare professional to administer their insulin injections
- whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes
- who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs.

Medicines Australia Code of Conduct: breaches

Medicines Australia (formerly the Australian Pharmaceutical Manufacturers Association) has a code of conduct to guide the promotion of prescription drugs in Australia.[1,2] The annual report of the Code of Conduct Committee for 2004 is now available on the Medicines Australia web site.[3] Since the previous summary in *Australian Prescriber*[4] the Code of Conduct Committee has resolved 17 complaints. In nine cases there was at least one breach of the Code (Table 1).

Only three complaints were made by healthcare professionals. Most of the complaints were made by companies about their rivals' promotional materials. These promotional materials have to be withdrawn if they are in breach of the Code, however by the time a complaint is resolved the advertising campaigns may have concluded.

There seems to be a growing concern about the promotion of prescription medicines to the general public. Several complaints involved the connection between companies' products and the information on web sites about related topics. There was also a complaint about a television advertisement, but this was not upheld. More details about the complaints can be found in the annual report.[3]

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3. Medicines Australia. Code of Conduct Annual Report 2004. Canberra: Medicines Australia; 2004. http://www.medicinesaustralia.com.au [cited 2004 Nov 8]
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Table 1

Breaches of the Code of Conduct January – June 2004

Company	Drug involved in complaint		Sanction imposed by Code of Conduct Committee
	Brand name	Generic name	
AstraZeneca	Nexium	esomeprazole	withdrawal of promotional material $10 000 fine
Eli Lilly	Cialis web site	tadalafil	withdrawal of reference to prescription-only drug
GlaxoSmithKline	Seretide	fluticasone/salmeterol	withdrawal of promotional material $5000 fine
Merck Sharp & Dohme	starter packs supplied to a member of the public		$30 000 fine
Novo Nordisk	NovoSeven	eptacog alfa	withdrawal of promotional material corrective letter to specialists $20 000 fine
Pfizer	Viagra web site	sildenafil	withdrawal of reference to prescription-only drug
Sanofi-Synthelabo	Panadeine Forte	paracetamol/codeine	withdrawal of promotional material $10 000 fine
Schering Plough	Caelyx	doxorubicin	withdrawal of promotional material corrective letter to specialists $10 000 fine
Schering Plough	Pegatron media release	peginterferon alfa-2b	withdrawal of promotional material corrective letter to specialists $30 000 fine

The vascular effects of COX-2 selective inhibitors

Richard O. Day, Professor of Clinical Pharmacology, Department of Physiology and Pharmacology, School of Medical Sciences, University of New South Wales, and Director of Clinical Pharmacology and Toxicology, St Vincent's Hospital; and Garry G. Graham, Honorary Visiting Professor, Department of Physiology and Pharmacology, School of Medical Sciences, University of New South Wales, and Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney

Summary

Drugs, such as celecoxib and rofecoxib, which selectively inhibit the COX-2 enzyme, are as efficacious as other non-steroidal anti-inflammatory drugs, but reduce the risk of serious gastrointestinal bleeding and ulceration. However, the improved tolerance of the COX-2 selective inhibitors may come at the cost of an increased risk of thrombosis in patients with ischaemic heart disease if they are not also taking aspirin. Like the older non-steroidal anti-inflammatory drugs, the COX-2 selective inhibitors can also increase blood pressure, induce or worsen cardiac failure and impair kidney function to the point of renal failure. In a recent unpublished trial, on the use of rofecoxib to prevent colon cancer, the risk of myocardial infarction and stroke after 18 months of treatment was high enough to prompt the removal of rofecoxib from the market. If another COX-2 selective drug is prescribed for patients at risk of thrombosis it should be used at the lowest effective dose and for short periods wherever possible. Prophylaxis with low-dose aspirin or other anti-thrombotic treatment should be continued.

Key words: celecoxib, lumiracoxib, rofecoxib, thrombosis.

(Aust Prescr 2004;27:142–5)

Introduction

The COX-2 selective inhibitors, such as rofecoxib and celecoxib, were introduced to decrease the gastrointestinal morbidity and mortality associated with older non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit both the COX-1 and the COX-2 enzymes. However, confusion still surrounds the role of COX-2 selective inhibitors because of an increased risk of myocardial infarction and other thrombotic events.

This risk first emerged in the VIGOR study which involved over 8000 patients. Although the absolute risk was low, there was a significantly higher rate of myocardial infarction with rofecoxib (18 cases) than naproxen (3 cases). However, the dose of rofecoxib (50 mg/day) was twice the dose recommended to treat rheumatoid arthritis while naproxen was given at the appropriate anti-inflammatory dose (1000 mg/day). Further, this trial was conducted in patients with rheumatoid arthritis, an inflammatory disorder that is associated independently with increased risk of thrombosis, particularly myocardial infarction. In retrospect, about half the patients who had infarctions during the trial should have been taking low-dose aspirin as prophylaxis. However, the trial did not allow patients to take aspirin.[1]

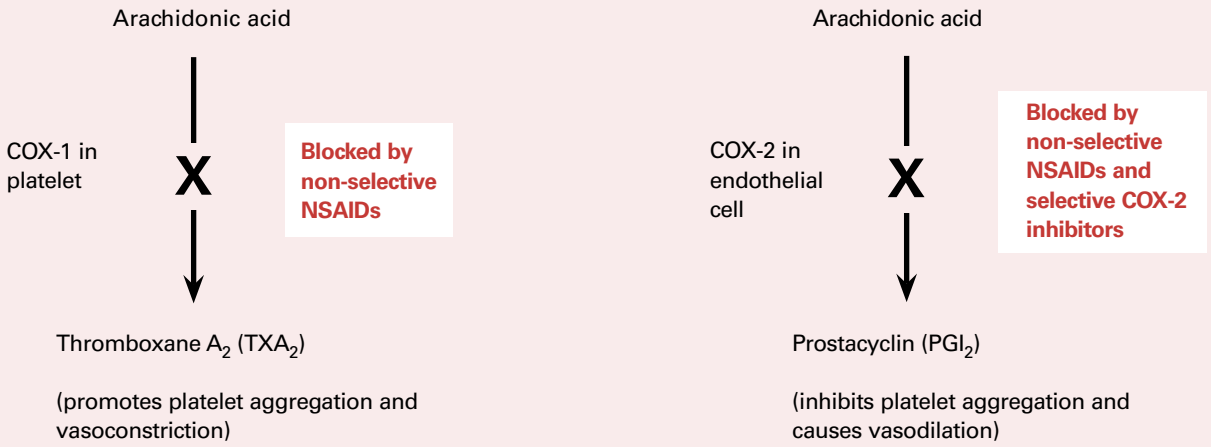
There have been a large number of claims and counter-claims about the risk of myocardial infarction with the COX-2 selective inhibitors, particularly rofecoxib. These were based on retrospective analyses, other controlled studies in osteoarthritis and rheumatoid arthritis, epidemiological studies, meta-analyses of published and unpublished studies and a recent large controlled trial of lumiracoxib in over 18 000 patients.[2,3] Most importantly, a recent unpublished trial on the use of rofecoxib to prevent colon cancer (the APPROVe study) found that treatment with rofecoxib was associated with a risk of myocardial infarction and stroke which became apparent after 18 months' treatment. The manufacturer has removed rofecoxib from the market because of this risk. Does the same risk apply to celecoxib, the other widely used COX-2 selective inhibitor presently available in Australia? Was this a class effect of COX-2 selective inhibitors and did increasing selectivity for COX-2 inhibition increase the risk? Did the underlying disease influence the findings? More importantly, should prescribers avoid COX-2 selective inhibitors in patients with vascular disease or a known risk of myocardial infarction?[4]

Mechanisms of action

The analgesic and anti-inflammatory actions of NSAIDs including COX-2 selective inhibitors are due to their effective inhibition of prostaglandin synthesis catalysed by the COX-2 isoenzyme (Fig. 1). This isoenzyme is massively up-regulated in inflammatory states such as rheumatoid arthritis, so inhibiting it reduces inflammation.

Fig. 1

Mechanisms of action of non-steroidal anti-inflammatory drugs



Aspirin and the non-selective NSAIDs inhibit COX-1 and COX-2 isoenzymes (Fig. 1). The COX-1 isoenzyme is involved in the synthesis of prostaglandins. These prostaglandins protect the gastric mucosa from ulceration and participate in platelet aggregation via the prostaglandin derivative, thromboxane A_2. Inhibition of COX-1 has been strongly implicated in the gastric ulceration and bleeding induced by the non-selective NSAIDs.

In platelets, inhibition of COX-1 leads to inhibition of thromboxane A_2 synthesis. This very effectively inhibits platelet aggregation. Low-dose aspirin irreversibly inhibits platelet aggregation via this mechanism and is therefore widely employed as prophylaxis against thrombotic cardiovascular disease. At therapeutic doses, COX-2 selective inhibitors have little effect on the COX-1 enzyme, so they do not inhibit platelet aggregation.

Thrombosis

As COX-2 selective inhibitors do not inhibit thromboxane A_2 synthesis they could be predicted to increase the risk of thrombosis. Thromboxane A_2 is not only a stimulus for platelet aggregation but also a powerful vasoconstrictor (Fig. 1). Its effects are opposed by prostacyclin, a vasodilator prostaglandin and inhibitor of platelet aggregation. Prostacyclin is produced largely by COX-2, especially in vascular tissues and probably more so in diseased vessels. COX-2 inhibition without COX-1 inhibition will therefore preserve the synthesis of the vasoconstrictive thromboxane A_2 and inhibit production of the vasodilator prostacyclin, tipping the balance toward vasoconstriction and thrombosis. Adding to this COX-2 induced imbalance, recent evidence shows that prostacyclin feeds back negatively on the synthesis of thromboxane A_2, so when prostacyclin synthesis is reduced by COX-2 selective inhibitors it leads to greater production of the prothrombotic thromboxane A_2.

Advantages of COX-2 inhibitors

COX-2 selective inhibitors were developed to reduce the risk of gastrointestinal ulceration caused by non-selective NSAIDs. By selectively inhibiting COX-2 they reduced the risk of upper gastrointestinal bleeding associated with other NSAIDs. In studies of rofecoxib and lumiracoxib, the absolute risk of serious upper gastrointestinal ulceration and bleeding is reduced by 50–60% or more compared to other NSAIDS.[1,2]

In the VIGOR study it was concluded that only 41 patients would need to be treated with rofecoxib rather than naproxen to avert one upper gastrointestinal event in a one-year period.[1] This figure was calculated from all patients in the trial and the number should be even smaller in patients who are at risk of upper gastrointestinal adverse reactions. This risk increases in patients with a history of peptic ulcer or bleeding, those taking anticoagulants and possibly patients taking oral glucocorticosteroids. If these patients require treatment with anti-inflammatory drugs, they should probably be prescribed COX-2 selective inhibitors rather than non-selective NSAIDs.[5]

The bleeding tendency associated with NSAIDs and aspirin is not seen with COX-2 selective inhibitors. They or paracetamol should be used in patients taking anticoagulants or if post-surgical bleeding is likely and a mild analgesic is indicated.

COX-2 selective drugs have no efficacy advantage

As non-selective NSAIDs inhibit both COX-1 and COX-2 there was no reason to expect that COX-2 selective inhibitors would have greater efficacy because they only inhibited the isoenzyme responsible for inflammation. Unfortunately, consumers and some prescribers were under the false impression that these medicines would be more effective as well as safer. This is part

of the reason for the gross overuse of celecoxib and rofecoxib outside the criteria of the Australian Pharmaceutical Benefits Scheme.[6] There is no evidence of increased efficacy of COX-2 selective inhibitors compared to conventional NSAIDs.

Adverse effects on renal function

Conventional NSAIDs are known to impair renal function, sometimes to the point of renal failure. This effect is observed particularly when the drugs are used perioperatively in older and sicker patients and in patients with already impaired renal function. In these situations maintenance of renal perfusion and function relies on renal prostaglandin synthesis. The possibility that COX-2 selective inhibitors might not manifest this adverse reaction has unfortunately not turned out to be the case. The risks for renal impairment are similar to those of other NSAIDs and increase with the dose of COX-2 selective inhibitor. We now know that maintenance of renal function is dependent on prostaglandins generated via the COX-2 isoenzyme.

Recommendations for prescribing

Prescribers should first consider 'non-drug options' in the management of common musculoskeletal problems such as soft tissue conditions, osteoarthritis, mechanical spinal pain problems, and inflammatory arthritis such as rheumatoid arthritis and gout. These options, including weight loss, physical therapy, and leg alignment correction via orthotics, are effective and evidence-based, but are unfortunately overlooked by prescribers. The next consideration should be whether paracetamol or an NSAID is a reasonable first pharmacotherapeutic option. Paracetamol is still recommended as first line for the bulk of musculoskeletal conditions because it is effective and relatively safe. NSAIDs including COX-2 selective inhibitors are not disease-modifying drugs, but are more appropriate if the condition is primarily inflammatory.

The more inflammatory the condition, the more reasonable prescribing an NSAID becomes. Whatever the condition being treated, the lower the dose and the shorter the exposure to these drugs, the lower the risk is for upper gastrointestinal bleeding and ulceration. Optimally, the patient can match the intake of drug with their own need for analgesia, thereby reducing unnecessary exposure. Should the patient have an increased risk of upper gastrointestinal ulceration and bleeding then prescribing expensive COX-2 selective drugs can be justified as they become cost-effective in this situation. However, this needs to be tempered with concern for adverse effects – those known to be associated with all NSAIDs and those that might be peculiar to COX-2 selective inhibitors.

If NSAIDs, including COX-2 selective inhibitors, are prescribed for patients with renal impairment, cardiac failure or hypertension, each patient should be monitored closely.[7,8] This should include eliciting symptoms and signs of heart failure, measuring weight and blood pressure and monitoring plasma creatinine and electrolytes soon after starting the drug (for example 2–4 weeks) and at regular reasonable intervals depending on the individual case.

Concomitant medicines including anticoagulants, prednisone, diuretics, beta blockers, ACE inhibitors and other antihypertensive drugs can have serious interactions with NSAIDs, including COX-2 selective inhibitors. Appropriate monitoring is needed if a decision is made to prescribe interacting drugs.[5]

Patients at risk of thrombosis

Individuals with a history of myocardial infarct, angina, coronary artery stents or known risk factors such as hypertension, hyperlipidaemia, smoking, diabetes or obesity are at risk of arterial thrombosis. Uncontrolled inflammation itself, as found in conditions such as rheumatoid arthritis, is an important independent risk factor for accelerated cardiovascular disease. If the patient is also elderly then the risk is further increased.

These patients are often prescribed low-dose aspirin or other platelet inhibitory therapy. The CLASS study suggested that the gastrointestinal safety advantage of celecoxib over a conventional NSAID is lost when low-dose aspirin is taken concomitantly.[9] This was again noted in the large study of lumiracoxib.[2] Other data have suggested that the gastrointestinal safety of a COX-2 selective inhibitor together with low-dose aspirin is greater than a combination of a non-selective NSAID with aspirin[10], but this view is much less likely to be correct in the light of the lumiracoxib data.[2] However, low-dose aspirin should not be stopped if COX-2 selective inhibitors or other NSAIDs (despite their platelet inhibitory actions) are prescribed.

Unknowns

It may be that the greatest risk of inducing a myocardial infarction is in a patient with undiagnosed coronary vascular disease. Before COX-2 selective inhibitors became available, this patient may have been prescribed another NSAID. This would have had an aspirin-like antiplatelet effect and, if anything, might have been expected to reduce the risk of infarction. If the patient is instead commenced on a COX-2 selective inhibitor the balance swings towards a prothrombotic state that theoretically might result in an infarction. This theoretical point is supported by the results of the VIGOR study and the termination of the APPROVe study because of an excess risk of myocardial infarction and stroke in patients taking rofecoxib for 18 months.

The APPROVe study was a three-year randomised controlled trial to see if rofecoxib 25 mg/day could suppress the recurrence of colonic polyps. Among the 2600 patients enrolled, 45 taking rofecoxib and 25 taking placebo suffered confirmed, serious adverse thrombotic events. This difference was only apparent

after 18 months. The relative risk is about 2.0, but the extent to which this risk of myocardial infarction or stroke has been proven is currently unclear because of the absence of detailed published information.

In vitro studies indicate that celecoxib is somewhat less COX-2 selective than rofecoxib and may therefore be safer in patients at risk of thrombosis. There has not been as strong a signal for thrombotic risk with celecoxib[11,12], but further studies are clearly required as placebo-controlled trials of the size and duration of APPROVe are not yet available.

Until more data are available, the COX-2 selective inhibitors should only be used in low doses and for short periods. Low-dose aspirin or other anti-thrombotic treatment should be continued in patients at risk of thrombosis.

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Professor Day is a member of advisory committees on COX-2 inhibitors for Merck Sharp & Dohme (Aust) Pty Ltd which markets rofecoxib and etoricoxib, and previously for Pfizer Pty Ltd which markets celecoxib. He is a member of a general advisory committee of GlaxoSmithKline which markets paracetamol.

GlaxoSmithKline have supported research projects of Professor Graham on paracetamol.

Self-test questions

The following statements are either true or false (answers on page 165)

1. Patients taking low-dose aspirin, for the prevention of heart disease, should stop their aspirin if they are prescribed a COX-2 selective inhibitor.
2. The efficacy of COX-2 selective inhibitors is significantly greater than the efficacy of other non-steroidal anti-inflammatory drugs.

Are atypical antipsychotics advantageous? – the case for

Nicholas A. Keks, Professor and Director of Psychiatry, Box Hill Hospital, Eastern Health, and Monash University, Melbourne

Summary

Atypical antipsychotics are a diverse group of drugs. Their widespread use has significantly improved the treatment of schizophrenia. Most patients no longer experience extrapyramidal adverse effects from drugs, including the often irreversible tardive dyskinesia. However, serious adverse reactions can occur with atypical antipsychotics. While atypical antipsychotics have modest efficacy advantages over typical antipsychotics, the efficacy varies between drugs and from patient to patient. Many patients still do not respond adequately to drug treatment of their psychosis. Despite their cost, the atypical antipsychotic drugs are preferred because of their better adverse effect profile and efficacy advantages in some patients.

Key words: schizophrenia, adverse effects.

(Aust Prescr 2004;27:146–9)

Introduction

Antipsychotics were originally called 'neuroleptics' (from the Latin, to grasp the neuron) because extrapyramidal adverse effects were thought to be essential for their therapeutic efficacy. Typical antipsychotics, such as chlorpromazine, improved the outcome by about 50% compared to the pre-neuroleptic era. Many patients who had previously been institutionalised were enabled to live in the community.

There were significant problems with neuroleptic treatment because many patients experienced extrapyramidal adverse effects (Table 1). These included tardive dyskinesia, a disfiguring, stigmatising and often irreversible problem. The prevalence of tardive dyskinesia was estimated to be approximately 20% of patients, but it significantly affected more than 39% of those on long-term treatment with depot neuroleptics.[1] Clearly, there was a need for drugs which were better tolerated than the typical antipsychotics.

Characteristics of atypical antipsychotic drugs

The term 'atypical' refers primarily to the low propensity of an antipsychotic to induce extrapyramidal adverse effects, compared to typical antipsychotics. Clozapine, which was developed in the 1960s, was the first drug to be recognised as atypical, although thioridazine (which is no longer widely used due to its association with QT_c prolongation) also had moderate atypical characteristics. As clozapine was associated with serious toxicity, similar antipsychotics (serotonin-dopamine antagonists) were developed and risperidone, olanzapine and quetiapine became available. Despite some similar characteristics, these drugs are clinically quite different from each other in their adverse effect profiles (Table 2). Key associations are hyperprolactinaemia with risperidone, weight gain with olanzapine and sedation with quetiapine.

Amisulpride, a benzamide, comes from a different direction in atypical antipsychotic development. It is a highly selective dopamine D2 receptor blocker, unrelated to the serotonin-dopamine antagonists. Its main adverse effect is hyperprolactinaemia. More recently aripiprazole, the first partial dopamine agonist to prove to be an effective atypical antipsychotic, has become available. Its adverse effects are primarily nausea and insomnia.

Extrapyramidal adverse effects

The key characteristic of atypical antipsychotics is that the drugs effectively treat psychoses at doses which do not induce extrapyramidal adverse effects. In contrast, the typical drugs tend to cause extrapyramidal adverse effects at the doses which are effective for psychotic symptoms. Extrapyramidal

Table 1

Extrapyramidal adverse effects

Dystonias – oculogyric crisis – torticollis – opisthotonus – laryngeal dystonia	Terrifying, occur soon after starting drug. (Laryngeal dystonia can be life-threatening.)
Parkinsonism	Occurs in days to weeks after starting drug. Primarily rigidity; may worsen negative symptoms and depression.
Akathisia	Restless legs; tormenting and associated with suicide. An emotional sense of agitation or restlessness even in the absence of motor movements.
Tardive dyskinesia	Repetitive involuntary movements, especially seen around mouth and tongue, but can affect any part of body. Often irreversible.

Table 2

Relative frequency of common adverse effects of antipsychotics at usual therapeutic doses

Note: this is the frequency of occurrence of adverse effects, not the intensity with which they occur

Drug	Usual daily oral dose range (mg)	Sedation	Postural hypotension	Anticholinergic	Extrapyramidal	Weight gain
Atypical drugs						
amisulpride	400-1000 (acute psychosis) 100-300 (negative symptoms)	+	+	0	++ *	+
aripiprazole	10-30	++	+	0	+	+
clozapine	200-600	+++	+++	+++	+	+++
olanzapine	5-20	+++	+	++	+	+++
quetiapine	300-750	+++	++	+	+ *	++
risperidone	2-6	++ (initially)	+++ (initially)	0	++	++
ziprasidone	80-160	++	+	+	+	+
Typical drugs						
chlorpromazine	75-500	+++	+++	+++	++	+++
droperidol	5-10 (intramuscular) †	++	+	+	+++	+
fluphenazine	5-20	+	+	+	+++	+++
haloperidol	1-7.5	+	+	+	+++	++
pericyazine	15-75	+++	++	+++	+	++
pimozide	2-12 ‡	++	+	+	+++	+
thioridazine	300-600	+++	+++	+++	+	+++
trifluoperazine	5-20	+	++	+	+++	++
zuclopenthixol acetate	50-150 (intramuscular) §	+++	+	++	+++	++
zuclopenthixol dihydrochloride	10-75	+++	+	++	+++	++

Approximate frequencies of adverse effects:

0 (<2%) = negligible or absent; + (>2%) infrequent; ++ (>10%) = moderately frequent; +++ (>30%) = frequent

* rarely a problem at usual therapeutic doses

† doses >5 mg should not be given without immediate access to ECG monitoring and resuscitation facilities

‡ use doses >12 mg only under specialist supervision

§ single dose, not to be repeated for 2 to 3 days

Table reprinted with permission from Table 8.6, Therapeutic Guidelines: Psychotropic. Version 5. Melbourne: Therapeutic Guidelines Limited; 2003.

adverse effects still occur with risperidone, olanzapine and amisulpride if the dose is increased beyond the therapeutic range. Clozapine and quetiapine rarely cause extrapyramidal adverse effects at any dose, unless the patient has Parkinson's disease. Aripiprazole causes extrapyramidal adverse effects at a comparable rate to placebo, although a small proportion of patients may experience akathisia.

Meta-analyses confirm that atypical antipsychotics cause fewer extrapyramidal adverse effects than typical drugs, particularly haloperidol.[2] It has been strongly suggested that this advantage disappears for risperidone, olanzapine and amisulpride if low doses of typical antipsychotics are used in comparison.[3] However, even at low doses typical drugs will cause extrapyramidal adverse effects in a proportion of patients, while for practical purposes clozapine and quetiapine do not cause extrapyramidal adverse effects.

In clinical practice extrapyramidal adverse effects are now seen infrequently. The contrast with the past, when many patients were affected by Parkinsonism and tardive dyskinesia, is striking in settings such as psychiatric inpatient units where it is now hard to find a case for teaching purposes. Tardive dyskinesia is now seen mainly in patients on long-term therapy with depot formulations of typical antipsychotics.

Other adverse effects

All typical antipsychotics, risperidone, amisulpride and to a small extent olanzapine, cause hyperprolactinaemia. Consequences include amenorrhoea, sexual dysfunction, galactorrhoea and gynaecomastia. In contrast, clozapine, quetiapine and aripiprazole do not elevate serum prolactin concentrations.

Table 3

Symptoms of schizophrenia

Positive	- delusions - hallucinations - thought disorder	Symptoms which are more responsive to antipsychotic medication than negative symptoms.
Negative	- flat affect - poverty of thought - amotivation - social withdrawal	Develop with progression of illness, cause disability, persistence signifies onset of chronic illness.
Cognitive	- distractibility - impaired working memory - impaired executive function	Dysfunction tends to occur in association with negative symptoms.
Mood	- mania - depression	Mood disorder often occurs in schizophrenia. Anxiety can occur at any stage of illness.

Atypical antipsychotics can cause other serious adverse effects (as can typical antipsychotics). Clozapine is associated with agranulocytosis, myocarditis/cardiomyopathy and convulsions. Due to its toxicity, only specialists can prescribe clozapine and close monitoring is required. Clozapine and olanzapine are particularly prone to cause weight gain and may be associated with increased risk of diabetes mellitus and hyperlipidaemias.[4,5] Periodic physical evaluation of patients with schizophrenia and related psychoses is therefore an increasingly important part of management, especially in general practice.

Efficacy of atypical versus typical antipsychotics

The symptoms of psychosis can be divided into a number of treatment-relevant dimensions (Table 3). Clozapine, amisulpride, risperidone and olanzapine have consistently established superiority over typical drugs for the treatment of positive symptoms.[6] The effects are modest and may not be seen in some patients. However, the symptom benefits many patients obtain are frequently translated into significant improvements in functioning and quality of life. All atypical antipsychotics reduce negative symptoms and clozapine, risperidone, olanzapine and amisulpride have established superiority over typical drugs.[2] It is possible that the benefits for negative symptoms occur at least partly through the reduction in extrapyramidal adverse effects. Atypical antipsychotics are also more beneficial than conventional drugs for cognitive dysfunction.

Long-term treatment

The treatment of schizophrenia and related psychoses is often lifelong. A vital dimension of therapeutic efficacy is therefore relapse prevention over long periods of time. Studies of adequate duration in relapse prevention have not been carried out. The major exception is a double-blind study which compared risperidone and haloperidol at usual clinical doses for over two years. Risperidone was associated with lower rates of relapse, and fewer extrapyramidal adverse effects, including tardive dyskinesia.[7] An editorial accompanying these results declared that evidence now supported the use of risperidone over haloperidol in relapse prevention. It is not certain whether the results of this study can be generalised to other atypical antipsychotics; similar trials are needed for the other drugs.[8]

Mood disorders

Interestingly, all atypical antipsychotics have a greater antidepressant efficacy than typical drugs and may be beneficial as adjunctive therapy to antidepressants in some patients. Olanzapine has demonstrated efficacy as monotherapy in mania, risperidone has been effective in combination with a mood stabiliser, and clozapine can be helpful in treatment-resistant mania. Evidence has emerged about the efficacy of quetiapine and aripiprazole in mania and quetiapine in depression. In contrast, the effectiveness of typical antipsychotics in mood disorders can be regarded as partial, at best.

Effectiveness

In community settings, treatment with clozapine has consistently shown superiority over typical drugs in areas such as suicidal behaviour, cognition and aggression. Among authoritative clinical guidelines for the management of schizophrenia, there is uniform agreement that patients who have not responded to other treatments should receive a trial of clozapine.

Evidence for other atypical antipsychotics is less consistent. A recent study comparing long-term treatment with olanzapine versus haloperidol plus benztropine demonstrated only minor benefits for olanzapine, with no differences on many outcome measures despite much higher cost.[9]

Promising developments

A long-acting injectable formulation of risperidone is now available. This is comparable in efficacy to oral risperidone, and may cause fewer and less severe extrapyramidal adverse effects.

Olanzapine is also available in a short-acting injectable formulation. This is being used primarily for management of acutely disturbed patients. Its safety profile is superior to that of intramuscular droperidol and haloperidol.

Aripiprazole differs from all previous typical and atypical drugs, which are dopamine antagonists. Partial dopamine agonism may theoretically assist both hyper- and hypo-dopaminergic dysfunction in different brain areas. Aripiprazole has shown efficacy and a favourable adverse effect profile in studies in schizophrenia.

Conclusion

Atypical antipsychotics are a heterogenous group of drugs and generalisations about the group are only sometimes justifiable. A number of atypical antipsychotics have superior efficacy with respect to typical drugs in positive, negative, cognitive and mood symptoms. All atypical antipsychotics are associated with a lower risk of extrapyramidal adverse effects, a characteristic of major significance to patient outcomes. In addition, several atypical antipsychotics do not cause the hyperprolactinaemia associated with all typical compounds. The benefits of reduced extrapyramidal adverse effects justify the cost of prescribing atypical instead of typical antipsychotics.

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Professor Keks has received research funding from, or has been a consultant to, all pharmaceutical companies marketing atypical antipsychotic drugs in Australia.

Are atypical antipsychotics advantageous? – the case against

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Summary

Conventional antipsychotic drugs are just as effective as atypical antipsychotics. Some of the atypical drugs appear to have an efficacy advantage, but it is small and of marginal clinical significance. The apparent better tolerability of the atypical antipsychotics in terms of extrapyramidal symptoms is variable and dose-dependent. It needs to be balanced against the problems of weight gain and metabolic adverse effects that are likely to contribute to long-term morbidity and mortality. Atypical antipsychotics are far more expensive than conventional drugs. Whatever modest benefits some of them may appear to have are outweighed by their high costs.

Key words: cost-effectiveness, schizophrenia.

(Aust Prescr 2004;27:149–51)

Introduction

There is a tendency for Australian doctors to prescribe newer and more expensive drugs. In psychiatry this is reflected in the dramatic increase in prescriptions for so-called 'atypical' antipsychotic drugs in preference to 'conventional' or 'typical' antipsychotics. Atypical antipsychotics account for over two-thirds of all antipsychotic drug prescriptions, and in 2003 the most commonly prescribed atypical antipsychotics (olanzapine, risperidone and quetiapine) accounted for a million prescriptions at a cost to government of $197 million. However, do these drugs offer significant clinical advantages that make them good value for money?

What is an atypical antipsychotic?

All currently available antipsychotic drugs competitively block dopamine D2 receptors. This is the basis of their antipsychotic efficacy, but it is also the mechanism by which they induce extrapyramidal adverse effects and increase prolactin concentrations.

Atypical antipsychotics are defined by an absence or marked reduction of extrapyramidal effects and prolactin elevation. These characteristics are probably due to a lower affinity for D2 receptors, compared to most typical antipsychotics.

However, using these defining criteria, there is no clear boundary between typical and atypical drugs. All antipsychotics have the potential to produce extrapyramidal adverse effects in a dose-dependent manner and most increase prolactin. The other pharmacological properties of the typical and atypical drugs also overlap, for example, their capacities to block various monoamine and acetylcholine receptors and produce other adverse effects. Neither group is homogenous with respect to its adverse effect profile.

Clinical trials of comparative efficacy

Studies comparing typical and atypical antipsychotics usually show equal efficacy or, at most, modest therapeutic superiority for the atypical drug. There is usually an advantage for atypical antipsychotics with respect to extrapyramidal adverse effects. However, the randomised controlled trials, from which such results are derived, need to be interpreted with caution.

Selection of comparator

The choice and dose of the comparator (typical) drug is one that usually gives the atypical drug the best chance of appearing in a favourable light. In particular, the dose of the comparator is frequently higher than would be required for optimal therapeutic blockade of D2 receptors. This can have a number of effects:

- the rate and severity of adverse effects produced by the typical drug are greater than for the atypical drug
- secondary negative symptoms and cognitive impairment are likely to be greater with the typical than with the atypical drug.

Under these conditions the high rate of dropout from trials, which is often as much as 50–60% over six weeks or so, is not likely to be random. This can further bias results in favour of the atypical drug.

Selection of patients and outcomes

Controlled trials usually measure only symptoms, adverse effects and relapse/remission indicators. They fail to provide a broader perspective using more comprehensive measures such as social and occupational function, quality of life, and health utility indices that would make cost-effectiveness analyses easier to undertake. The nature of randomised clinical trials is such that large numbers of potentially eligible patients are excluded for various reasons such as inability to give consent, and comorbid substance abuse. These and other factors contribute to selection bias. Likewise, patients having their first episode of psychosis are rarely explicitly identified and studied in phase II or III clinical trials. Schizophrenia is not a homogenous disease and different patients may respond differently to the same drug, but this is not knowable in advance and thus clinical trials cannot yet be designed to take this into account.

Duration of trials

Most therapeutic trials are brief (about 6–8 weeks) and there is a relative paucity of long duration trials (six months to one year or more). This is not just a function of the difficulties in retaining participants in clinical trials, but relates to industry's imperative to demonstrate efficacy and satisfy the requirements of regulatory agencies. Given that schizophrenia, the primary indication for atypical antipsychotics, is a chronic or relapsing condition, long-term study data are especially important. The absence of these data leaves large gaps in our knowledge about long-term efficacy and safety.

Sponsorship

To these methodological shortcomings and sources of bias in comparative efficacy studies should be added the bias inherent in clinical trials sponsored by the pharmaceutical industry. Although this bias has not been directly addressed in schizophrenia, there is evidence to suggest that trials sponsored by pharmaceutical companies are 3–4 times more likely than non-industry sponsored trials to report results in favour of the company's product.[1,2]

Comparative effectiveness

A number of meta-analyses have been published comparing the efficacy of typical and atypical antipsychotics. One much criticised systematic review reported that there was no clear evidence that atypical drugs were more effective or better tolerated.[3] Another found a 'modest' advantage for atypical antipsychotics in relapse prevention.[4] A further study reported that, while the atypical antipsychotics aripiprazole, quetiapine and ziprasidone had no greater efficacy than typical drugs, there was a statistically significant but small advantage (effect size 0.21–0.29) for amisulpride, olanzapine and risperidone.[5] The same study reported a moderate advantage (effect size 0.49) for clozapine relative to typical drugs. This study highlights the fact that, in terms of efficacy, the atypical drugs are clearly heterogeneous.

While clozapine has generally been regarded as effective for treatment-resistant schizophrenia, another recent meta-analysis did not find it had a substantial advantage.[6] The meta-analysis noted that where a greater advantage was found for clozapine it was associated with short duration studies, financial support from a drug company and higher baseline symptom score. However, there is evidence that clozapine can be effective in reducing suicidal ideation and improving negative symptoms.

In relation to cognitive function, it seems likely that atypical drugs do not have significant advantages when compared to low therapeutic doses of a typical antipsychotic.[7] Even with respect to extrapyramidal adverse effects atypical antipsychotics appear to have no advantages over low-potency antipsychotics such as chlorpromazine.[8]

It seems reasonable to conclude that:

- atypical antipsychotics are not all the same and should not be regarded as a homogenous class in terms of efficacy and adverse effects
- if there are any efficacy advantages for some atypical antipsychotics, they are small, with the possible exception of clozapine
- there is as yet no consistently demonstrated advantage for atypical antipsychotics in terms of negative symptoms or cognitive function
- there is a tolerability advantage for atypical antipsychotics as far as extrapyramidal adverse effects are concerned, but this is dose-dependent and most antipsychotics, if given at sufficiently high doses, will cause these adverse effects in a substantial proportion of patients.

While tardive dyskinesia is less likely to occur with atypical drugs, weight gain, obesity, hyperlipidaemia, impaired glucose tolerance and diabetes mellitus have been associated with atypical antipsychotics, most notably clozapine, olanzapine and, to a lesser extent, quetiapine. In some cases there may therefore have to be a trade-off between the short-term tolerability of atypical drugs and the potential long-term morbidity or mortality due to metabolic and cardiovascular diseases.

Cost-effectiveness of atypical antipsychotics

If there is a small efficacy advantage for at least some atypical antipsychotics (excluding clozapine as a special case with particular indications), is this advantage worth the large additional cost? For example, if the average cost of haloperidol is about 2 cents per day and that of olanzapine $11 per day, does olanzapine confer an additional benefit commensurate with its greater cost? Few adequately designed independent studies have tried to address these questions.

One randomised controlled trial of 12 months used a comprehensive set of outcome measures in comparing olanzapine and haloperidol (with prophylactic benztropine). It found no advantages for olanzapine in compliance, symptoms, extrapyramidal symptoms or overall quality of life. A small benefit for olanzapine in improving cognition and reducing akathisia had to be balanced against weight gain and vastly greater costs of the order of US$3–9000 per year.[9]

An Australian cost-modelling study has also looked at the issues. It reported that the relatively modest health benefits of risperidone and olanzapine were associated with an unfavourable cost-effectiveness profile compared to typical antipsychotics, unless the typical drugs caused moderate to severe adverse effects.[10]

Conclusion

Are atypical antipsychotics advantageous? The short answer is perhaps sometimes, but not much. Atypical antipsychotics are not a homogenous class. There may be an efficacy advantage for some of these drugs, but this is small, of marginal clinical significance, and vastly outweighed by their very high cost. Insufficient attention is being paid to their weight gain and metabolic adverse effects, with attendant implications for long-term morbidity and mortality, in favour of emphasising short-term tolerability advantages.

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Professor Carr is Director of Hunter Mental Health.

Perioperative analgesia

Stephan A. Schug and Philip Dodd, Department of Anaesthesia and Pain Medicine, Royal Perth Hospital and University of Western Australia, Perth

Summary

Dedicated pain services in many hospitals have improved postoperative pain management and increased the safety and efficacy of analgesia. Modern techniques follow concepts of pre-emptive analgesia (providing analgesia throughout the perioperative period to prevent long-term consequences), multimodal analgesia (balanced combination of analgesics with different modes of action) and perioperative rehabilitation. Newer drugs such as parecoxib, tramadol and enantiomer-specific local anaesthetics have increased the options for perioperative analgesia.

Key words: pain, surgery.

(Aust Prescr 2004;27:152–4)

Introduction

The concept of an anaesthetics-based pain service to provide postoperative analgesia on surgical wards was first suggested over 15 years ago. This concept has provided a useful framework for the improvement of postoperative pain management, has gained widespread acceptance all over the world and has permitted safe and effective advancement of analgesic techniques. There is good evidence that a regular assessment of a patient's pain by use of verbal or numerical rating or visual analogue scales increases the awareness of pain as a problem and results in more appropriate treatment of pain. This has led to the suggestion that pain should be assessed as the 'fifth vital sign'.

Treatment concepts

The approach to managing the patient's pain should begin before the operation. Management may involve pre-emptive analgesia, multimodal analgesia and perioperative rehabilitation.

Pre-emptive analgesia

In the past, pre-emptive analgesia has been interpreted by many as meaning that applying an analgesic technique before the incision results in better pain control after the operation than applying the same technique after the incision. This concept has been repeatedly shown to be valid in animal experiments, however studies in humans were never as convincing. A recent meta-analysis came to the conclusion that there is little experimental support for a pre-emptive analgesic effect in clinical settings.[1]

In many studies more severe or prolonged acute pain in the postoperative period as well as postsurgical complications, commonly leading to increased nociception, were significant predictors for the development of chronic pain.[2] It might therefore be much more logical and fruitful to expand the concept of pre-emptive analgesia. This has been done by assessing what benefits extending the balanced, multimodal analgesia approach, from the preoperative period to well into the postoperative period, may have on long-term consequences of trauma, surgery and acute pain. Effective and aggressive management of acute pain could help to prevent the development of chronic pain states.

Multimodal analgesia

Balanced or multimodal analgesia involves the selective use of specific drugs in combination. The concept relies on using multiple analgesic drugs with different modes of action (for example non-opioid combined with opioid) or via different routes of administration (for example local anaesthetic block combined with a systemic analgesic). There is now good evidence that this approach improves analgesia due to additive or synergistic effects. This permits the doses of the individual drugs to be reduced thereby reducing the incidence and severity of adverse effects.[3] Multimodal analgesia can be used for day cases as well as for inpatient surgery.[4]

Perioperative rehabilitation

Beside the pharmacological options for improving pain relief, future efforts need to focus on better organisational structures, enabling a more integrated multidisciplinary approach to patient care with a greater involvement of nurses and surgeons.

Nurses will have an increasing role in co-ordinating postoperative analgesia. Surgeons also need to be involved intensely in the postoperative management of patients if our future goal is to use the modalities of balanced analgesia, integrated into a new overall concept of postoperative rehabilitation, to reduce morbidity and mortality and speed up recovery. Such an approach to management of the postoperative patient should include preoperative patient information and teaching, attenuation of intra- and

postoperative stress, pain relief, early and effective exercise, early enteral nutrition and possibly the use of growth factors.[5]

Drug treatment

The choice of drug treatment is influenced by the likely severity of the patient's pain. A multimodal approach can include non-opioids, opioids and local anaesthetics given by a variety of routes.

Non-opioids

Non-opioid analgesics will continue to remain important 'background' medications for perioperative pain. Paracetamol is the most universally useful medication here and should become a regular prescription for all acute pain problems irrespective of severity and cause. When combined with opioids, paracetamol improves the quality of analgesia and increases patient satisfaction.

Non-steroidal anti-inflammatory drugs (NSAIDs) should not be used routinely in all postoperative patients. Their beneficial and harmful effects need to be assessed for each patient before they are prescribed. While they are very beneficial in situations of inflammatory pain, problems related to gastrointestinal erosion and ulceration, renal toxicity, platelet dysfunction, airway constriction and poor bone healing limit their usefulness, particularly in at-risk patients. However, a recent meta-analysis suggested NSAIDs should not be withheld from patients with normal preoperative renal function.[6]

Although the COX-2 inhibitors were developed for chronic use in arthritis, there is interest in their possible role in the management of acute pain. Parecoxib, a COX-2 inhibitor for parenteral administration, offers some safety advantages over ketorolac as it has a gastrointestinal safety profile comparable to placebo and no effect on platelet function. However, the renal toxicity and propensity to precipitate heart failure is similar to that of other NSAIDs and it is only approved in Australia for single use.[7]

Opioids

Opioids continue to be the mainstay of perioperative analgesia. Overall it seems that nearly any opioid that is a full agonist at opioid receptors can be used, as long as the dose is titrated to individual needs by means of devices allowing patient-controlled analgesia or by nursing staff giving doses on demand. An early change to oral administration, again on demand, is cost-effective and facilitates continuation of analgesia after increasingly earlier discharge from hospital. Pethidine might be the only opioid that should be avoided in view of its short duration of action. It has a neurotoxic metabolite (norpethidine) and a high propensity to induce drug-seeking behaviour.

Tramadol is commonly classified as an atypical centrally-acting analgesic due to its inherent multimodal action on opioid, but also noradrenergic and serotonergic, receptors. In clinical trials it has shown analgesic efficacy comparable to morphine (in a parenteral dose ratio of 10:1 and an oral dose ratio of 5:1 due to its high bioavailability). Tramadol has a reduced incidence and severity of opioid adverse effects, particularly respiratory depression, ileus and constipation. There is limited potential for tolerance, physical dependence and addiction. Dosage regimens for optimal analgesia are still being refined, and nausea and vomiting remains as problematical as with all opioids.[8]

Local anaesthetics

From wound infiltration to sub-arachnoid injection, local anaesthetics have been widely used to alleviate pain. Single shot injections do not work long enough to provide analgesia throughout the postoperative period, but can be very effective in covering the most severe pain early on, in particular facilitating return home after day-case surgery. Continuous regional analgesia by means of infusion of local anaesthetic agents via epidural, interpleural, nerve sheath or simple wound catheters has become a routine technique in many hospitals and even in the outpatient setting. Unresolved issues with regard to these techniques are related to the choice of mode of delivery (continuous infusion versus patient-controlled infusions), choice of drug (local anaesthetics, opioids, adjuvants) and, most recently, the increased risks of epidural catheters in patients given thromboprophylactic drugs such as low-molecular weight heparin or clopidogrel.

Recently, several newer alternatives to the tried and tested local anaesthetics, lignocaine and bupivacaine, have been developed. Enantiomer-specific, long-acting amide local anaesthetics such as ropivacaine and, more recently, levobupivacaine have similar pharmacokinetics and efficacy to bupivacaine, but have a lower risk of causing serious cardiotoxicity.[9]

Adjuvants

Ketamine is well known as a 'dissociative' anaesthetic and evidence for its general use is not very robust. It is currently gaining favour as an adjunct for acute pain management in some specific circumstances due to its effects as an N-methyl-D-aspartate antagonist. It is used to treat acute pain poorly responsive to opioids including neuropathic pain, but is also used for relief of procedure-related pain. Dysphoric adverse effects are minimal with low-dose regimens or adjuvant low-dose benzodiazepines. Further research into optimal dosing, administration routes and the roles of individual isomers is required.[10]

Conclusion

A better understanding of pain physiology and the increasing diversity of approaches to eliminate pain should benefit patients and help bring to an end the less than satisfactory management

of pain in the postoperative setting. Pain is subjective, and so every patient represents a new set of circumstances for which we need to extend and adapt our knowledge of pain control. Adequate analgesia provides not only comfort and satisfaction for the patient, but aids their recovery as well. This has obvious benefits for the patient, but also has implications for the patient's short- and long-term use of healthcare facilities, and subsequent costs to society.

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Self-test questions

The following statements are either true or false (answers on page 165)

3. Regular doses of paracetamol can improve the quality of opioid analgesia.
4. COX-2 inhibitors lack the renal toxicity of other non-steroidal anti-inflammatory drugs.

Book review

Drugs and breastfeeding 2004 guide. Melbourne: Royal Women's Hospital; 2004. 261 pages. Price $33 including GST*

Jane Talbot, General practitioner, Kalamunda, Western Australia

As a practising general practitioner/obstetrician I am always on the lookout for up-to-date but easily accessible information for my breast-feeding mothers. With the ever increasing number of drugs on the market, it is often difficult to be totally accurate.

This spiral-bound, pocket-sized book fits the bill nicely. Apart from a comprehensive list of drugs (900 in all), which are cross referenced with the trade names (for those of us who do not uniformly use generic names), the value of this book lies in the extra advice in relationship to what may happen to the baby, which is the question the mother always asks.

This is handled by five issues: M/P (milk to plasma ratio), PK (peak time), T ½ (half-life), percentage dose to infant (sometimes) and excretion into milk for each drug – listed clearly.

For example, I have always had a problem with metronidazole which I often want to prescribe to breast-feeding women. The book tells me all that I need to know: M/P 0.4–1.8, PK 1–2 hours, T ½ 6.3–8.3 hours and in the box about excretion into milk, it reassures me that I will do the baby no harm. Nice to know!

I also like the presentation of the University of California, San Diego Medical Center algorithm at the beginning of the book (page 7), which is succinct, easy to use and in itself worthy of remembering, or reflecting upon when prescribing drugs for a breast-feeding mother.

I would recommend this book to all those professionals the authors have targeted – general practitioners, hospital medical officers, obstetricians, midwives and lactation consultants.

* Order form at http://www.rwh.org.au/emplibrary/pharmacy_rwh/d&bf_order_form.pdf [cited 2004 Nov 8]

Your questions to the PBAC

Analgesics for the elderly

Our practice looks after patients in a local nursing home. We occasionally see patients who have conditions that do not fit the restrictions for prescribing a drug on the Pharmaceutical Benefits Scheme (PBS). As a result of this, there are two specific problems. Firstly, we are unable to prescribe what we believe to be the best drug and so we opt for a sub-optimal treatment. Secondly, we are unable to order repeat prescriptions and so we have to see the patient more frequently just to write prescriptions. This results in additional visits and higher Medicare and prescribing costs.

An example of this difficulty is in prescribing adequate, appropriate analgesia in a form that patients can take. We feel very strongly that we are sometimes not able to provide the best possible care to our patients and this frustrates us.

Three cases illustrate this difficulty:

1. An 85-year-old demented patient with severe osteoarthritis who is not compliant with oral medication.

Fentanyl patches would be a reasonable option to control her severe pain. However, as she does not have terminal malignancy, this is not an option on the PBS.

2. An elderly bedridden patient who has multiple spinal fractures due to osteoporosis, severe osteoarthritis and requires opiates for pain control.

This patient should not have to be sent to a pain management clinic or be admitted to hospital for pain relief. However, this is what is required to satisfy the PBS as the patient does not have a terminal malignancy. The patient cannot get more than 10 days supply of controlled release morphine at a time.

3. An elderly dying demented patient who is in pain and is in need of palliative care.

Fentanyl patches might be appropriate, but again this is not allowed by the PBS as the patient does not have a terminal malignancy.

We believe the PBS restrictions should be changed so that patients in aged care facilities have easier access to opioids in order to improve their care.

Chris Boyle
Damian Welbourne
Tim Cocks
Rachel Hughes
Prabaka Subbaraju
Elizabeth Kaiko

General practitioners
Raymond Terrace Family Practice
Raymond Terrace, NSW

PBAC response:

While the Pharmaceutical Benefits Advisory Committee (PBAC) and the Government endeavour to provide affordable access to pharmaceuticals to the Australian community, the PBAC also has a responsibility that PBS-listed medicines are used in medically appropriate ways and will therefore recommend that certain restrictions apply to the prescribing of some listed pharmaceuticals, such as the opioid analgesics.

Most narcotic analgesics for non-cancer pain can be prescribed in small quantities on the PBS. Increased quantities and/or repeats can be obtained for patients with proven malignant neoplasia or chronic severe disabling pain where treatment is initiated in a hospital. The requirement for a hospital assessment before approving increased maximum quantities and/or repeats arose out of the belief that the management of severe chronic pain of non-malignant origin represents a complex problem, which is best addressed through expert evaluation of individual patients by interdisciplinary teams in hospitals.

The PBAC regularly reviews listings and has in recent years considered a number of requests to relax the restricted availability of opioid analgesics. It is therefore aware that restricting the quantities of drugs available for patients with chronic severe disabling pain not associated with proven malignant neoplasia is frustrating to prescribers. The PBAC agrees that some changes to the restrictions may be desirable, however, it is reluctant to recommend any changes without wider consultation.

The PBAC has recommended that a working group be established to examine this issue. It is planned to convene this group shortly, with the intent of reporting back to the PBAC as soon as possible.

With respect to the PBS availability of fentanyl patches in the treatment of non-malignant pain, there is added complexity. Before the patches can be recommended for listing for this purpose, the PBAC must be presented with an application that shows fentanyl is cost-effective for this indication.

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

What does TGA approval of medicines mean?

John McEwen, Principal Medical Adviser, Therapeutic Goods Administration, Canberra

Summary

The Therapeutic Goods Administration is a Commonwealth Government agency that regulates medical devices and drugs. Prescription medicines and over-the-counter medicines which meet Australian standards of quality, safety and efficacy are included on the Australian Register of Therapeutic Goods. Medicines may be registered or listed. Registered products are thoroughly evaluated and are labelled with an AUST R number. Listed products, such as complementary medicines, do not have to undergo the same assessments and are labelled with an AUST L number. They are not routinely evaluated before marketing, but are subject to a random audit after listing. Some medicines, such as those compounded for individual patients, are not regulated.

Key words: drug industry, drug regulation.

(Aust Prescr 2004;27:156–8)

Introduction

The Therapeutic Goods Administration (TGA) is a division of the Australian Department of Health and Ageing. Its principal role is as the national regulator of therapeutic goods – a collective term covering medicines, medical devices and some related products. The TGA administers the *Therapeutic Goods Act 1989*, the objects of which include 'a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods that are used in Australia, whether produced in Australia or elsewhere, or exported from Australia'. These activities are fully funded by fees charged for assessments, annual registrations and inspections.

Australian Register of Therapeutic Goods

The lawful supply of any therapeutic good in Australia requires that the product is included on the Australian Register of Therapeutic Goods (ARTG). There are two types of entry on the ARTG. Some products are 'registered' and have an AUST R number on their label. Other products are 'listed' and have an AUST L number. The TGA decides if products are suitable for listing or require registration. Manufacturers are not permitted to suggest or imply in their advertisements that inclusion in the ARTG is a recommendation or endorsement by the TGA.

AUST R products

Medicines that are registered include:

- almost all prescription medicines
- a number of products, such as vaccines, which although not classified in law as needing a prescription warrant detailed evaluation
- almost all conventional over-the-counter medicines including, for example, packs of aspirin and paracetamol tablets sold from supermarkets
- a very small number of complementary medicines where the TGA has been satisfied that specific claims of efficacy in treatment or prevention of a disease are supported by adequate evidence.

The approval of AUST R products is based on satisfactory assessments of their quality, efficacy and safety.

Prescription medicines

The Australian system for the pre-registration evaluation of new active substances, as well as such things as new routes of administration and the extensions of approved uses ('indications') of already marketed products, has evolved since it was established in 1963. Most prescription medicines in use currently have been evaluated through this system. Nowadays an application for registration of a new active substance must be supported by extensive information about the synthesis of the substance, the method of manufacture of the dose forms, studies of its pharmacology and toxicology in animals and clinical trials in humans demonstrating the efficacy and safety of the product in its proposed use. In addition, certification that manufacture has complied with Good Manufacturing Practice is obligatory.

Registration in Australia does not expire. A product remains registered unless there are grounds for cancellation or the sponsor ceases marketing. A small number of active substances, such as aspirin, were supplied in Australia long before any evaluation process was in place. Their registration is not reviewed unless a safety issue arises or a change in use is proposed.

Many of the prescription medicines used in Australia are versions of the innovator product, usually produced by other manufacturers. These generic products are subject to the same regulation of manufacture and quality standards. However, only evidence that the formulation is bioequivalent to the innovator product is required, rather than a full demonstration of

efficacy and safety.[1] Bioequivalence studies usually involve a comparative study of the product in human volunteers, but benchtop testing of dissolution may suffice for some products. Similar testing in human volunteers is required to support the claims of modified-release formulations.

Over-the-counter medicines

Nowadays, almost all active substances in non-prescription medicines first enter the market as ingredients of prescription medicines. To assess whether or not an active substance is suitable for use in a non-prescription medicine usually requires the substance to have been used for at least two years as a prescription medicine. Not all active substances make the transition from prescription to over-the-counter use. The volume of new information to support efficacy and safety is usually less, because the registration of the over-the-counter product can draw on the accumulated experience as a prescription product. New over-the-counter products are assessed by the TGA for quality, efficacy and safety. The standards for such things as quality and circumstances of manufacture are essentially the same as those of prescription medicines.

AUST L products

The group of medicines that are listed consists almost entirely of complementary medicines. These include herbal medicines, most vitamin and mineral supplements, other nutritional supplements, traditional medicines such as Ayurvedic medicines and traditional Chinese medicines, and aromatherapy oils.[2]

This category of listed products came into effect in 1991 as a means of regulating products that seemed by their nature to have a low risk of causing adverse effects. Similar requirements for manufacture, including certification of Good Manufacturing Practice, apply as to AUST R products, but they are not evaluated before inclusion in the ARTG. The principal mechanism for ensuring that these products are safe is through the requirements of the Therapeutic Goods Regulations 1990. AUST L medicines must:

- not contain substances that are prohibited imports, come from endangered species or be covered by the national regulations which control access to many substances (Standard for the Uniform Scheduling of Drugs and Poisons)
- conform with lists of permitted ingredients (minerals, vitamins, declared listable substances).

In some instances, there are additional requirements such as dose limits, specified label warnings and limits on plant parts or methods of preparation. Certain herbs are not permitted.

The initial approach to regulation of AUST L products did not require evidence to support manufacturers' claims, provided the products were not for the treatment of serious illnesses.

A concern that multiple and at times improbable claims were being made about products led to the introduction in April 1999 of a requirement that sponsors of AUST L products must hold evidence to substantiate their claims. This evidence may be called for and evaluated by the TGA, should a concern or complaint arise at any time during the life of a product. If the evidence is inadequate, the TGA may cancel the listing for the product. A random sample of approximately 20% of new listings are assessed in detail for compliance with the listing requirements.

In 2003 an expert committee recommended that sponsors of AUST L medicines should submit summaries of the evidence they hold to support the efficacy of their products, and that the TGA should randomly audit this information.[3] Where there is evidence to support the efficacy of an AUST L medicine in a serious illness, registration (AUST R status) can be sought.

Exemptions

Medicines (except for gene therapy) that are dispensed or extemporaneously compounded for a particular person are currently exempt from TGA regulation. Some clinics and pharmacists are using this exemption as a means for supplying very large numbers of patients with medicines made in those pharmacies. On occasions, claims about special characteristics such as 'slow release product' are made. Such products are not assessed or regulated by the TGA. Similar exemptions apply to medicines individually dispensed by traditional Chinese medicine and homeopathic practitioners.[4]

> Sponsors of AUST L products must hold evidence to substantiate their claims

Some other medicines are also exempt from the requirement for inclusion in the ARTG. Perhaps the most important are homeopathic medicines. This exemption from TGA regulation has seen the marketing of such purported homeopathic products as homeopathic somatropin and homeopathic melatonin. Increased TGA regulation of homeopathic products has therefore been recommended.[3] This might be expected to focus on ensuring that such products are formulated with regard to homeopathic principles and practices and are made in compliance with the same manufacturing requirements as conventional medicines.

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Further information

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The Australian Register of Therapeutic Goods
Requests for searches and reports Phone 1800 010 624
http://www.tga.gov.au/docs/html/artg.htm [cited 2004 Nov 8]

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 165)

5. The Therapeutic Goods Administration routinely evaluates the quality, safety and efficacy of all new products listed on the Australian Register of Therapeutic Goods.
6. Complementary medicines are not regulated by the Therapeutic Goods Administration.

Book review

Pocket guide to chest X-rays. G. Briggs. Sydney: McGraw-Hill Australia; 2004. 172 pages. Price $32.95 including GST *

Lindy Viviers, Senior Resident Medical Officer, Division of Medicine, John Hunter Hospital, Newcastle, NSW

For a quick revision of the basics of chest X-ray interpretation, as well as some more advanced tips, 'Pocket guide to chest X-rays' by Greg Briggs is a useful addition to the clinician's library. The guide begins with a summary of the major radiological modalities and their indications in practice. It explains the techniques of chest radiography in easily understood prose with accompanying diagrams. This is followed by a section on radiological anatomy and a thorough description of normal chest X-rays and variants. It thus offers the reader the chance to consolidate their knowledge of 'the norm' with which to compare abnormal X-rays presented in the remainder of its pages.

The book endeavours to be a practical guide to be used as an adjunct to a physician's practice. It outlines a systematic checklist with which to approach all chest X-rays and this is probably one of its foremost strengths. The bulk of the book is a collection of actual chest X-rays that showcase the common pathologies which clinicians encounter. For a large majority of students and trainees a picture can speak a thousand words and this book offers approximately 50 X-rays of conditions seen in everyday practice. The descriptions of these are straightforward and easy to follow. A noteworthy inclusion is a list of common pitfalls in interpreting chest X-rays, at least one or two of which the honest clinician will recognise.

The appendices are also worth mentioning. One is devoted to various signs in thoracic radiology, which, while being very detailed in its descriptions, would probably be more useful if accompanied by the actual radiological pictures. Nonetheless, a number of these signs are referred to in the body of the book and it is a matter of looking them up. The second appendix is simply a quick reference list of causes and differential diagnoses commonly encountered by doctors. The last is an alphabetical list of syndromes particularly relevant to chest radiology, some of which are more recognisable than others, and would probably spur a number of us to revisit our textbooks.

This guide's main use is as a reference in the context of patient care, however the medical student would find it invaluable as a learning tool as well. On the whole this is an easy, informative read that encapsulates a rather enormous area of medicine into a concise, manageable whole.

* *Australian Prescriber* readers are offered 15% discount by McGraw-Hill Australia (phone (02) 9900 1806 or email cservice_sydney@mcgraw-hill.com and quote code BCX15).

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3. Reviewers must declare any conflicts of interest.
4. Reviewers are not paid, but may keep the review copy.
5. Book reviews may be edited.
6. Not all reviews are published.
7. No payments or commissions are accepted for these reviews from publishers.

Book review

Health care and notions of risk. R.B. Clark.

Melbourne: Therapeutic Guidelines; 2004.

72 pages. Price including GST $33; students $25.30; plus postage

Janette Donovan, Consumer Class Director, Board of the National Prescribing Service, Sydney

This book is a consumer view of medical adverse events, patient participation in healthcare decision-making, risk perception and patient safety in the Australian healthcare system. It is based on an analysis of the Australian Patient Safety survey which was a comprehensive study of Australians' attitudes to participation in health care and perceptions of safety. The book explains the likelihood and types of medical adverse events, models of consumer involvement in healthcare decision-making and the views of consumers about the safety of health services.

Medicine-related adverse events are the main category of adverse events reported, but the lack of resources and the exposure to infection were the most important consumer issues in relation to safety. Chapter 5 discusses the factors which predict adverse events. It is interesting that consumers perceived nursing homes, residential aged care, hospitals and doctors' surgeries as places where adverse events were likely to occur.

Younger people aged 18–34 years are significantly more likely to report an adverse event than the older age groups. According to the author, this may be due to younger people feeling more empowered in healthcare decision-making, but more data are needed to clarify why this is the case.

The final chapter of the book attempts to place the findings of the study within a policy context. A key finding is that the lack of resources and exposure to infection have contributed to a recent fall in confidence in relation to the safety of health care. Another finding with implications for health policy is consumers' preference for a shared decision-making model. Sharing information reduces the risk of experiencing an adverse event.

The book concludes that the value of this Australian study is that future studies may be able to focus on vulnerable groups. These include people with poor health and those who have a number of hospital admissions.

I can recommend this book to all those interested in consumer perceptions of risk, safety and quality and participation in health care. It will also be valuable to those interested in greater consumer participation in the policy, planning, delivery and evaluation of health care.

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 Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Adefovir dipivoxil

Hepsera (Gilead Sciences)

10 mg tablets

Approved indication: hepatitis B

Australian Medicines Handbook section 5.3

Although Australian children are now immunised against hepatitis B, infection still occurs in adults and is endemic in Aboriginal and Torres Strait Islander communities. Some people who are infected develop chronic hepatitis B which may lead to cirrhosis and liver failure. Patients with chronic hepatitis B can be treated with injections of interferon. Lamivudine, a nucleoside analogue, can be used as an oral treatment.

Adefovir is a nucleotide analogue of adenosine monophosphate. Cells convert adefovir to adefovir diphosphate which competes with the normal substrate of the viral DNA polymerase. The concentration of adefovir diphosphate needed to inhibit the enzyme in hepatitis B virus is lower than the concentration which inhibits human DNA polymerase. When adefovir diphosphate gets incorporated into viral DNA, it inhibits replication by preventing elongation of the nucleic acid chain.

As adefovir is not well absorbed it is given as a prodrug. Adefovir dipivoxil is taken once a day and is converted to adefovir (bioavailability 59%) by hydrolysis. Most of this adefovir is later excreted unchanged in the urine.

Patients who **do not have** detectable hepatitis B e antigen[1] (HBeAg) may have an increased risk of progressive liver damage. A multicentre study randomised 123 of these patients to take adefovir dipivoxil and 61 to take a placebo for 48 weeks. Concentrations of viral DNA reduced significantly in 51% of the adefovir group but not in any of the patients given a placebo. Although 33% of the placebo group had improved liver histology, this was significantly less than the 64% who improved with adefovir dipivoxil.[2]

Another study of 515 patients who **did have** detectable HBeAg produced similar results. While viral DNA concentrations were not reduced by placebo, they were undetectable in 39% of patients taking adefovir dipivoxil 30 mg and in 21% of those taking 10 mg. Liver biopsies after 48 weeks of treatment showed improvement in 59% (30 mg) and 53% (10 mg) of the adefovir group and 25% of the placebo group.[3] As adverse effects are more frequent at higher doses the recommended daily dose of adefovir dipivoxil is 10 mg.

In the clinical trials adverse events occurred with a similar frequency in patients taking adefovir dipivoxil or placebo. Common adverse events include asthenia, headache, abdominal pain and diarrhoea. Adefovir dipivoxil can be prescribed for patients with hepatic impairment, but the dose requires adjustment in patients with renal impairment. Nephrotoxicity may occur during long-term therapy so renal function should be monitored particularly if the patient takes other treatments, such as non-steroidal anti-inflammatory drugs, which affect the kidney.

The effectiveness of lamivudine in chronic hepatitis B is reduced because the virus becomes resistant to the drug. So far, the virus has not developed significant resistance to adefovir. A small study in patients with HIV infection who also had lamivudine-resistant hepatitis B found that adefovir dipivoxil significantly reduced the concentrations of viral DNA.[4]

The available drugs for hepatitis B have not yet been compared directly so it is difficult to know which will produce the best outcomes for patients. While liver histology improved in the patients who responded to adefovir dipivoxil, we do not know if this will reduce the long-term complications of chronic hepatitis B. The optimum duration of treatment is uncertain, and up to 25% of patients will develop an exacerbation of their hepatitis after they stop taking adefovir dipivoxil.

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Anakinra

Kineret (Amgen)

100 mg/0.67 mL in pre-filled syringes

Approved indication: rheumatoid arthritis

Australian Medicines Handbook section 15.2.2

The current treatment of rheumatoid arthritis involves the early use of disease-modifying antirheumatic drugs (DMARDs).[1] If these drugs are not effective a biological agent may be considered. These agents are aimed at the pro-inflammatory cytokines which are involved in the pathogenesis of rheumatoid arthritis.

The structure of anakinra differs by only one amino acid from the structure of the naturally occurring human interleukin-1 receptor antagonist. This difference is to enable genetically engineered *Escherichia coli to* produce anakinra.

Anakinra antagonises interleukin 1α and 1β at the interleukin-1 type 1 receptor. As these interleukins are inflammatory mediators, competition for their receptor may prevent joint damage.

Patients have to subcutaneously inject anakinra every day. The maximum plasma concentration is reached in 3–7 hours. Anakinra is probably cleared by the kidneys and has a half-life of 4–6 hours.

In a clinical trial involving 472 patients, anakinra was compared to injections of a placebo. After 24 weeks the rheumatoid arthritis was less active in patients randomised to receive anakinra. They had fewer swollen joints, less pain and a shorter duration of morning stiffness.[2] This trial was extended for a year with patients from the placebo group being switched to treatment with anakinra. A total of 218 patients completed the extension. Efficacy was maintained in 46% of the patients who continued treatment with anakinra and 40% of the patients who had switched from placebo.[3]

During the extension phase 29% of the patients discontinued treatment. Half of these withdrawals were caused by adverse events such as a flare-up of the arthritis or abnormal blood counts.[3]

Adverse effects also accounted for most of the withdrawals from a safety study of anakinra. This study randomised 1414 patients to take anakinra or placebo in addition to their other treatments. Approximately 78% of the patients completed six months of treatment. The most common adverse effect of anakinra was injection site reactions. Patients should vary the site of injection to try and reduce such reactions. Serious infections such as pneumonia occurred more frequently than with placebo.[4] Patients should have their white blood cell count checked before and during treatment.

Although the safety study[4] included patients taking other DMARDs, anakinra is only approved in Australia for prescription with methotrexate. This combination was compared with methotrexate in a six-month study involving 419 patients. Adding anakinra produced a response in 38–46% which was significantly greater than the 19% of patients who responded to methotrexate alone.[5]

While the trials show that anakinra has greater efficacy than placebo its benefits depend on how efficacy is measured. Several

trials used the American College of Rheumatology criteria for a 20% improvement (ACR20).[6] However, if the criteria for success is set higher the results are less impressive. For example, if the goal is a 50% improvement in the patient's symptoms, only 18% of patients will achieve it. If the goal is a 70% improvement, only 3% will achieve it after 48 weeks of therapy.[3]

As the response may be related to the dose of anakinra[5], it is important to know that some patients in the trials took more than the recommended daily dose of 100 mg. This dose was not specifically tested in some of the published trials.[2,3,5]

While the biological agents will benefit some of the patients who have not responded to DMARDs, the variations in study design mean the best option is not clear. Anakinra does not appear to be more effective than etanercept or infliximab, but comparative studies are needed.

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Atazanavir sulfate

Reyataz (Bristol-Myers Squibb)

150 mg and 200 mg capsules

Approved indication: HIV infection

Australian Medicines Handbook section 5.3.4

HIV infections are best managed with combinations of antiviral drugs.[1] As treatment may involve taking medication several times a day, there is an interest in simpler regimens. Atazanavir is a protease inhibitor which only needs to be taken once a day. The daily dose should be taken with food as this increases bioavailability. Steady state concentrations are reached in 4–8 days. Most of the dose is metabolised and then excreted in the faeces.

A dose-ranging study compared atazanavir with nelfinavir in previously untreated patients. The 467 patients also received lamivudine and stavudine. After 48 weeks approximately 35% of all patients had less than 50 copies of viral RNA/mL and CD4 cell counts had increased.[2]

Another study compared atazanavir with nelfinavir in 420 previously untreated patients who were also given didanosine and stavudine. After 48 weeks 36% of the patients taking 400 mg atazanavir daily and 39% of those taking nelfinavir had less than 50 copies of viral RNA/mL. CD4 cell counts increased in all treatment groups.[3]

In patients who have previously been treated with a regimen containing a protease inhibitor, atazanavir may be less effective than adding lopinavir and ritonavir to therapy with two nucleoside reverse transcriptase inhibitors. After 48 weeks 35% of the 144 patients taking atazanavir had less than 50 copies of viral RNA/mL compared with 53% of the 146 patients taking lopinavir and ritonavir.

If atazanavir is used in a combination with ritonavir a lower dose is prescribed because of a drug interaction. As atazanavir is metabolised by cytochrome P450 3A4 it has the potential for several other interactions. It should not be prescribed with calcium channel blockers, HMG-CoA reductase inhibitors ('statins'), ergot derivatives, sildenafil, midazolam and triazolam.

Atazanavir inhibits an enzyme involved in bilirubin conjugation. Many patients will therefore have elevated bilirubin concentrations and up to 11% may develop jaundice while taking atazanavir 400 mg daily.[2]

Other adverse effects reported in clinical trials include nausea, rashes and heart block. Hyperlipidaemia may be less of a problem than it is with other protease inhibitors. As with other protease inhibitors, HIV can become resistant to atazanavir.

While atazanavir does have the advantage of a single daily dose, the best use of the drug in combination regimens, particularly in previously treated patients, will require further study.

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Cholera vaccine

Dukoral (Aventis Pasteur)

glass vials containing 3 mL for dilution

Approved indication: cholera immunisation

Australian Medicines Handbook section 20.1

Vibrio cholerae and *Escherichia coli* are responsible for many cases of diarrhoea around the world. Although cholera is endemic in some countries vaccination is not routinely recommended for travellers. Some vaccines have not been very effective.

This new product contains inactivated forms of three strains of *Vibrio cholerae*. It also contains a recombinant form of the binding portion of the cholera toxin. As this toxin is similar to the enterotoxin produced by the enterotoxigenic strains of *Escherichia coli*, the vaccine may have the ability to prevent some cases of traveller's diarrhoea.

The vial of vaccine is supplied with a sachet of sodium hydrogen carbonate which acts as a buffer. Patients dissolve the granules of the buffer in water then add the contents of the vial and drink the mixture. They should not have food or drink for one hour before and one hour after taking the mixture. The dose is repeated after at least a week, but children aged 2–6 years are recommended to have a third dose. Most people will be protected against cholera approximately one week after completing the course.

The vaccine was studied in Bangladesh as long ago as the 1980s. These studies found that for older children and adults two doses were as good as three. The protective efficacy of a two-dose regimen was 77% after a year. The protective efficacy then declines with time. If exposure to cholera continues, a booster is recommended after two years in adults and after six months in young children. Although there have been studies of the vaccine for the prevention of traveller's diarrhoea, this is not an Australian approved indication.

Patients may complain of loose stools and abdominal discomfort, but these adverse effects occur at similar frequencies in patients given a placebo. The clinical trials did not specifically assess interactions with other vaccines, but it is recommended that oral typhoid vaccines are not used within eight hours of cholera vaccine.

Although many Australians travel overseas there are only about six cases of cholera a year. The National Health and Medical Research Council advises that avoiding contaminated food and water is more important than vaccination against cholera.[1] Most tourists have a low risk of infection, but the vaccine may be considered for people at high risk, for example healthcare professionals working in endemic areas or refugee camps overseas.

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1. National Health and Medical Research Council. The Australian Immunisation Handbook. 8th ed. Canberra: Department of Health and Ageing; 2003.

Enfuvirtide

Fuzeon (Roche)

vials containing 90 mg/mL as powder for reconstitution

Approved indication: HIV infection

Australian Medicines Handbook section 5.3

Fusion inhibitors are a new class of drugs that prevent HIV from penetrating cells. By binding to an HIV transmembrane glycoprotein they stop the virus from fusing with the CD4 receptors on the patient's cells.

Enfuvirtide is given twice daily by subcutaneous injection. It reaches its peak concentration about four hours after the injection. As enfuvirtide is a peptide it is metabolised into amino acids. It has a half-life of approximately four hours.

Highly active antiretroviral therapy has improved the outlook for patients infected with HIV.[1] However, HIV can become resistant to antiviral drugs so that treatment fails to adequately suppress viral replication. Introducing a drug of a new class may help to regain control of the infection.

Clinical trials of enfuvirtide have included patients infected with HIV which had become resistant during at least three months of antiviral treatment. A trial, involving 512 Australian and European patients, randomly added enfuvirtide to an optimised regimen of other drugs for HIV. After 24 weeks the concentrations of viral RNA had fallen further in the patients given enfuvirtide than they had in patients who just took the optimised regimen. There were less than 50 copies of HIV RNA/mL of plasma in 12% of the patients given enfuvirtide compared with 5% of the control group. The CD4 cell count increased in both groups, but the rise was significantly greater in the enfuvirtide group.[2]

A similar randomised trial in the Americas also found that a regimen containing enfuvirtide had greater efficacy than the same regimen without enfuvirtide. The 328 patients who injected enfuvirtide had greater decreases in viral RNA and greater increases in CD4 count than the 167 patients who took the optimised regimen. After 24 weeks 20% of the enfuvirtide group had less than 50 copies of HIV RNA/mL compared with 7% of the control group.[3]

Injection site reactions were the commonest adverse reactions to enfuvirtide in the clinical trials. Patients may develop painful itchy nodules at the injection site. Although patients are told to rotate the injection sites they may develop a reaction in more than one place. Approximately 3% of patients withdrew from the trials because of injection site reactions.

In addition to injection site reactions, adverse events tended to be slightly more frequent when enfuvirtide was added to the treatment regimen. Adverse reactions which occurred more frequently with enfuvirtide included peripheral neuropathy, pneumonia and depression. As enfuvirtide is a protein, patients can develop hypersensitivity reactions to its injection. More than 70% of patients treated with enfuvirtide had an adverse event

(other than an injection site reaction) resulting in the withdrawal of approximately 8% from the clinical trials.[2]

The clinical trials are ongoing and preliminary results suggest the effect of enfuvirtide is sustained for 48 weeks. However, the measures of efficacy are surrogate end-points so it will take longer to find out if enfuvirtide improves the clinical outcomes for patients. It is unclear when treatment should be stopped in patients who do not initially respond to enfuvirtide. We also do not know if significant resistance will develop later.

While enfuvirtide is an advance, its use will have to be rationed. There are many steps in the manufacturing process and this may limit the supply of the drug. Until supplies increase enfuvirtide will be an expensive treatment[4] (more than $20 000 for a year's treatment).

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Gadobenate dimeglumine

MultiHance (Bracco)

529 mg/mL in 5 mL, 10 mL, 15 mL and 20 mL vials

Approved indication: magnetic resonance imaging

Magnetic resonance imaging (MRI) can be enhanced by contrast agents. Gadobenate is a gadolinium-based compound that can be used as a contrast agent when imaging the liver or central nervous system.

Patients are given an intravenous dose in proportion to their body weight. Higher doses are used when imaging the central nervous system. Gadobenate is distributed in the plasma and extracellular space and will highlight areas where the blood-brain barrier has broken down. Most of the dose is excreted in the urine within 24 hours.

In a clinical trial involving 205 patients, with suspected lesions in the central nervous system, enhancement with gadobenate or gadodiamide produced similar quality images.[1] A comparison with gadopentetate, in patients with suspected liver tumours, found that gadobenate may have an advantage in delayed imaging.[2] While these studies assessed the diagnostic information provided by enhanced MRI, they do not say if the imaging made any difference to the patients' treatments.

The adverse effects of gadobenate include hypertension, tachycardia, injection site reactions, nausea and vomiting. Resuscitation equipment is required as patients may have an anaphylactic reaction to gadobenate.

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Treprostinil sodium

Remodulin (Orphan)

20 mL vials containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL

Approved indication: pulmonary arterial hypertension

Australian Medicines Handbook section 6.7.3

Pulmonary arterial hypertension is a rare condition and there has been criticism that Australian patients have not had access to effective therapy.[1] The approval of treprostinil will increase the options for patients with severe pulmonary arterial hypertension (bosentan and epoprostenol are already available), but hospitals will have to grapple with its cost.

Treprostinil is an analogue of prostacyclin, the natural substance which causes vasodilatation and inhibits platelet aggregation. The haemodynamic effects of treprostinil include reduced pulmonary and systemic vascular resistance.

The drug is given by continuous subcutaneous infusion. Infusion rates are adjusted over several weeks to achieve a balance between improved symptoms and adverse effects. Most of the dose is metabolised in the liver and then excreted in the urine. The half-life is 2–4 hours.

A double-blind trial compared treprostinil to placebo in 470 patients with pulmonary artery hypertension (New York Heart Association (NYHA) functional class II–IV). After 12 weeks there were haemodynamic improvements and a dose-related increase in exercise capacity in the treprostinil group.[2]

Approximately 8% of the participants discontinued treprostinil because of pain at the infusion site. This problem affected 85% of the patients.[2] In addition to problems related to the infusion system, common adverse events include diarrhoea, pain in the jaw, flushing and oedema. As treprostinil inhibits platelets, bleeding, such as gastrointestinal haemorrhage[2], can occur.

Although dyspnoea improved during treatment with treprostinil, the increase in exercise capacity was small. At the start of the study the patients could walk 326 metres in six minutes. The median increase after treatment was 10 metres. Sicker patients tend to improve the most so treprostinil is only approved for patients in the NYHA III–IV functional class.

While it is unknown if treprostinil will have a similar effect on

survival as epoprostenol, it has the advantage of not requiring intravenous infusion. It is possible to change patients from epoprostenol to treprostinil, but this has only been reported in patients with life-threatening complications of intravenous treatment.[3] Treprostinil has not been compared with bosentan, an oral endothelin receptor antagonist, which is considerably cheaper.

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NEW COMBINATIONS

Combined diphtheria, tetanus, acellular pertussis, hepatitis B and inactivated polio vaccine

Infanrix penta (GlaxoSmithKline)

0.5 mL in pre-filled syringe

Combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio, and *Haemophilus influenzae* type b vaccine

Infanrix hexa (GlaxoSmithKline)

0.5 mL in pre-filled syringe, with a vial containing 10 microgram *Haemophilus influenzae* type b vaccine

Approved indication: immunisation

Australian Medicines Handbook section 20.1

The development of new vaccines has increased the potential to prevent childhood illnesses. The expanded range of vaccines has, however, created the difficulty of children needing multiple injections at one time. Multivalent vaccines may help to overcome this problem.

These two products have been approved for primary immunisation at two, four and six months of age. They both contain the same antigens as the currently marketed Infanrix HepB, but also contain inactivated strains of polio virus. To prepare a hexavalent vaccination, the suspension of five vaccines is injected into a vial containing a pellet of haemophilus vaccine. The vaccines are then mixed until the pellet is dissolved and the resulting suspension is then drawn up for injection.

Three injections of the pentavalent vaccine, two months apart, produce an antibody response in more than 99% of babies. This response is as good as that seen when the vaccines are given separately. There is a similar response to the hexavalent vaccine, apart from a 96% response rate to the *Haemophilus influenzae* type b component.

Although the multivalent vaccines induce an immune response, limited information is available about their effectiveness at preventing infections. Their efficacy is considered to reflect that of their components. For example, the diphtheria, tetanus and acellular pertussis component is said to have an efficacy of 84% in protecting against whooping cough. Although the two products have been approved for use as boosters at 18 months, the current Australian Standard Vaccination Schedule does not include booster doses at that age.[1]

As with all vaccines, the health professional giving the intramuscular injection should be ready to deal with an anaphylactic reaction. Adverse reactions to these multivalent vaccines resemble those of their components. The most common reactions are pain at the injection site and irritability. Approximately 20% of children will develop fever.

The National Immunisation Program does not fund all the vaccines in the Schedule and the vaccines used vary between States.[1] While these multivalent vaccines may help to simplify primary immunisation, protecting children against other diseases will still require multiple injections at 12 months of age.

Reference

1. National Health and Medical Research Council. The Australian Immunisation Handbook. 8th ed. Canberra: Department of Health and Ageing; 2003. http://www.immunise.health.gov.au/handbook.htm [cited 2004 Nov 8]

Combined diphtheria, tetanus, acellular pertussis and inactivated polio vaccine

Infanrix IPV (GlaxoSmithKline)

0.5 mL in pre-filled syringe

This vaccine is similar to the above products, but contains fewer antigens. While it can be used for primary immunisation against diphtheria, tetanus, pertussis and polio, its components fit in with the recommended vaccines for four-year-old children.

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

† At the time the comment was prepared, a scientific discussion about this drug was available on the web site of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int).

NEW FORMULATION

Esomeprazole

Nexium IV (AstraZeneca)

vials containing 42.5 mg for reconstitution

NEW STRENGTHS

Cephazolin sodium

Cefazolin Sandoz (Sandoz)

2 g powder for injection

Rasburicase rys

Fasturtec (Sanofi-Synthelabo)

glass vials containing 7.5 mg powder

Trandolapril

Gopten (Abbott)

4 mg capsules

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