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EDITORIAL

The Pharmaceutical Benefits Scheme: economic evaluation works ... but is not a panacea

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Index words: cost of drugs, drug regulation.

(Aust Prescr 2002;25:126–7)

For most of the first 50 years of its existence the Pharmaceutical Benefits Scheme (PBS) was free from significant public scrutiny or major controversy. More recently the PBS has come within the public gaze, with the dissolution of the Pharmaceutical Benefits Advisory Committee (PBAC) in 2001, controversial contested decisions regarding certain high profile drugs (e.g. sildenafil) and proposals to increase patient co-payments. With increased public scrutiny and debate (which is to be welcomed) it is useful to review briefly the operation of the PBS and consider ways in which it might be improved.

Pharmaceutical companies seeking to have a drug listed on the Schedule of Pharmaceutical Benefits are required to prepare a submission according to a comprehensive set of guidelines.[1] Since 1993 the guidelines have required the presentation of both economic and clinical data, so that comparative costs and benefits may be taken into consideration. Issues of cost are not considered until the clinical performance of a drug has been established so economic considerations are always placed within a clinical framework.

In this issue ...

The problems of providing medicines at an affordable cost, discussed by Ruth Lopert and David Henry, are not unique to Australia. Bernie O'Brien tells us that Ontario is dealing with similar dilemmas. Whether or not to subsidise a drug can be a difficult decision and Alan Evans (of Medicines Australia) says that the pharmaceutical industry would welcome more transparency in the process.

Even subsidised drugs attract co-payments so some patients attempt to save money by breaking their tablets. Roger Nation and Jennifer Marriott advise that dividing drugs can be dangerous.

Since glaucoma was last reviewed in *Australian Prescriber* many new drugs have been marketed in Australia. Ivan Goldberg compares these drugs with the traditional treatments for glaucoma.

As the Schedule is not a limited formulary, a drug such as an ACE inhibitor or non-steroidal anti-inflammatory drug, can be added even though several similar products are already listed. Generally, if a manufacturer is able to show that a drug is as effective as other listed drugs, and costs no more, it will be added to the list. Demonstrating equivalence of two therapies can be complex but once equivalence is satisfactorily established the comparison of costs is generally straightforward. The rule is that the average cost of treatment should not increase with the listing of the new drug. This is an example of cost-minimisation.

If a drug appears to have a therapeutic advantage (typically at a higher cost) over an appropriate comparator, the PBAC will attempt to determine the magnitude of that advantage and whether it is worth paying for. This is referred to as cost-effectiveness analysis. The interpretation of incremental cost-effectiveness is relatively straightforward where evidence of comparative efficacy is drawn from well-conducted head-to-head randomised controlled trials measuring major clinical end-points such as survival. It is more difficult when comparisons are based on surrogate end-points, when it may be necessary to ascribe a value to (for example) a reduction in blood pressure, or an improvement in spirometry.

Australia was the first country to introduce an explicit requirement for economic analysis as part of the process of selection of drugs for a publicly funded formulary. While other countries have since introduced similar requirements, the process is most highly developed and has been most closely reviewed in Australia. Through the application of economic evaluation and by virtue of the government's position as a monopsony purchaser, Australian drug prices are significantly lower than those in some overseas countries. On average, prices in the UK and Canada are 1.5 times greater and in the USA they are 2–3 times greater. By contrast, Australian prices are similar to those in France, Spain and New Zealand.[2] Despite this, PBS expenditure increased by more than 17% in 2001, to over $4 billion.[3] While the existing processes provide some control over prices they do not control prescription volumes or total costs.

The extent of use of a new drug depends on the epidemiology of the condition being treated, the degree to which patients seek treatment, and on uptake by prescribers. Numbers of

prescriptions depend, at least in part, on the intensity of promotion of the product. As economic evaluation is highly context-dependent, a drug that is cost-effective for a given indication and patient population may not be cost-effective if prescribed outside these settings. A useful example is ACE inhibitors. They are substantially more cost-effective in cardiac failure than in uncomplicated hypertension, where they offer no real advantage over beta blockers or thiazide diuretics and yet are significantly more expensive.[4]

In Australia, pharmaceutical companies spend large sums promoting their products. A drug may be promoted for any or all of the indications approved by the Therapeutic Goods Administration. PBS-listed indications are however often narrower. For example, advertisements for bisphosphonates used in osteoporosis are not required to mention that under the PBS the subsidy is confined to patients with a history of fracture following minimal trauma.

Leakage – the prescription of drugs outside PBAC-approved indications – is common. The overall cost of leakage is not known, but is likely to be high. When proton pump inhibitors were PBS-listed for severe grades of ulcerative oesophagitis a large proportion of PBS prescriptions were written for other indications.[5] This represents an 'opportunity cost'; in an environment where overall healthcare expenditure is capped, the funds to pay for leakage of PBS-listed drugs must be found from other programs. Ultimately, excessive use of expensive new drugs must reduce available funds for public hospitals and aged-care programs.

How can the situation be improved? There are a number of possible approaches to controlling the extent and costs of leakage. At a national level these include improving pharmaceutical company marketing and promotion, increasing the transparency of the decision-making process, and increasing the use of price-volume agreements or tiered pricing arrangements.

There is a strong case for requiring pharmaceutical promotion to provide information that is balanced to assist prescribers in choosing the best drugs for their patients. In the 2002–03 Budget, the government announced that it had reached agreement with pharmaceutical manufacturers to provide pertinent information to prescribers about medicines listed on the PBS.[6] In the course of their contact with doctors, medical representatives from drug companies are expected to inform them of the PBS prescribing requirements, and drug advertising material will henceforth include PBS prescribing information. It will be interesting to see how this works in practice.

There have been repeated calls for the PBS process to be made more transparent.[7] The operation of the PBAC is governed by the provisions of the National Health Act (1953), which require that the data submitted to the PBAC and the deliberations of the Committee remain confidential. Recently, the Department of Health and Ageing has published (on its web site) a quarterly summary of the PBAC's **positive** recommendations (including a brief summary of the basis on which each approval was made).[8] This is a welcome move, but the amount of information should be increased substantially, perhaps to the extent of including the comprehensive technical summaries prepared by the Economics Subcommittee of the PBAC. Currently, the identities of drugs that have been considered and rejected, and the grounds for rejection, remain confidential.

By contrast, in the UK this information is published by the National Institute for Clinical Excellence (NICE).[9] Consequently pharmaceutical companies, health professionals, consumer advocates, disease support organisations and the media have access to detailed information relating to the availability or non-availability of various healthcare interventions.

More extensive use could be made of price-volume agreements between the Government and manufacturers. Under these arrangements, the unit price of a drug is reduced when sales exceed a level that represents the limit of cost-effective use of the product. These agreements, which should be based on epidemiological and cost-effectiveness data, simulate market forces and share the cost of leakage between the manufacturer and taxpayers. An alternative would be to introduce a form of tiered pricing, in which the price paid to the supplier is based on the anticipated benefits of the drug when used in a range of indications or patient populations. Using the example of ACE inhibitors, this would mean that these drugs would attract a higher price when used in cardiac failure than they would in uncomplicated hypertension.

These suggestions are not a panacea and do not address the critical issue of prescriber behaviour. There appears to be a surprising readiness on the part of many prescribers to abandon well-established practices and enthusiastically embrace new drugs on the basis of promotional material, perhaps reflecting an insufficiently critical view of the superiority of new drugs. The recent tide of prescriptions for COX-2 inhibitors would suggest this is the case. Addressing the issue of prescriber behaviour is nevertheless fundamental because the future of the PBS and the welfare of patients who depend on access to affordable drugs lie in the hands of health professionals.

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Professor D. Henry was a member of the Pharmaceutical Benefits Advisory Committee from 1991 to 2000.

Cost-effective prescribing: trying to hit the target in Ontario and Australia

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SYNOPSIS

The Canadian province of Ontario does not subsidise prescription drugs for all of its citizens. Despite serving fewer beneficiaries, the Ontario system is facing the same financial pressures as the Australian Pharmaceutical Benefits Scheme. Both systems are using similar strategies to encourage the cost-effective use of drugs. Some drugs can only be prescribed for specific indications and others require the approval of the government before they can be prescribed. Ontario recently tried to limit its expenditure on new drugs to the costs forecast by the manufacturers. The outcome of this controversial policy is not yet known, but it emphasises the need for accurate information about prescribing patterns.

Index words: cost of drugs, Pharmaceutical Benefits Scheme.

(Aust Prescr 2002;25:128–30)

Introduction

In Canada and Australia expenditure on prescription drugs is growing. The government of Ontario in Canada annually spends close to Can$2 billion of taxpayers' money on prescription drugs. This is the equivalent of A$2.25 billion (A$1 = Can$0.88). As in Australia, an evaluation system has been established to ensure that medicines are used where they are most cost-effective. The Ontario experience has some lessons for and from Australia. Both countries are wrestling with the same problem: of designing a system that effectively guides prescribers to treat patients cost-effectively, yet maintains an appropriate degree of clinical freedom.

Drug subsidy in Ontario

Canada has a comprehensive national system of universal public health insurance for medical services similar to Australia. Unlike Australia, out-of-hospital prescription medicines are not covered by the national system and are considered a fiscal responsibility for each province. Consequently, in provinces such as Ontario there are multiple payers for drugs. For example, employed people commonly have prescription drug coverage as an employment benefit although they would share some of the costs. The public payer for drugs in Ontario is the Ontario Drug Benefits Program. This covers about 18% of the population of the province. The primary beneficiaries are those aged over 65 years and people with a specific catastrophic illness or low income.

Drug cost in Ontario

In 2000–01 the Ontario Drug Benefits Program had 49 million prescription claims from its 2.08 million beneficiaries for a total government cost of Can$1.9 billion. The majority of expenditure (67%) is for elderly people. A small percentage of claimants (5%) have annual claims over Can$3000 and account for 27% of all drug costs. The three largest categories of drug expenditures are cardiovascular (Can$422 million), antilipidaemic (Can$226 million) and gastrointestinal (Can$200 million). The 'top ten' drugs in terms of expenditures (Table 1) are similar to the top 10 drugs prescribed in Australia.[1] For example, in 2000–01 the lipid lowering drug atorvastatin was number one in Ontario (Can$87 million) and number two in Australia (A$280 million).

A major concern in Ontario is the increasing rate of growth of expenditure. In 2000–01 annual expenditure grew by 15% (Can$248 million) compared with only 2% in 1992–93. The introduction of 10 new products in 2000–01 accounted for 70% of expenditure growth. A significant impact (Can$45 million) resulted from the introduction of celecoxib and rofecoxib for treatment of arthritis.

Table 1

Top 10 drugs by cost in the Ontario Drug Benefits Program[2] and the Australian Pharmaceutical Benefits Scheme[1] 2000–01*

Rank	*In Ontario*	*In Australia*
1	atorvastatin	simvastatin
2	omeprazole	atorvastatin
3	amlodipine	celecoxib
4	enalapril	omeprazole
5	simvastatin	olanzapine
6	olanzapine	pravastatin
7	blood glucose test strips	sertraline
8	diltiazem	ranitidine hydrochloride
9	fluticasone propionate	insulin (human)
10	ranitidine	bupropion

* The Ontario Drug Benefits Program only covers 2 million people (approximately 18% of the population) whereas all Australians are covered by the Pharmaceutical Benefits Scheme.

The Drug Quality and Therapeutics Committee

Like the Pharmaceutical Benefits Advisory Committee in Australia, Ontario has a committee which advises the Minister of Health. This Drug Quality and Therapeutics Committee (DQTC) consists of 10 physicians and two pharmacists. It meets monthly to consider submissions made by pharmaceutical manufacturers for the listing of their products on the Ontario formulary. In addition to data on a drug's effectiveness and safety, the manufacturer is required to provide evidence of cost-effectiveness or 'value for money'. Guidelines were published in 1994 on the required form, content and conduct of such economic analyses.[3] Members of an economic subcommittee of DQTC carry out expert technical reviews of the economic analyses in the submissions.

Formulary listing options

The DQTC has several options open to it when recommending a drug for reimbursement. A drug can be listed on the formulary as a 'general benefit' which means it can be prescribed without restriction by any licensed medical practitioner. At the other extreme, a so-called 'Section 8' reimbursement means that the physician must make a written application to the Ministry of Health to justify the need to use the restricted drug. For example, the osteoporosis drug alendronate is a Section 8 benefit; the cost will only be reimbursed if the doctor documents that their patient has 'failed' therapy (e.g. poor efficacy or tolerability) with etidronate. In 2000–01 there were 2466 requests for reimbursement for alendronate under Section 8 of which 75% were approved at a cost of Can$788 000.

Between a general benefit and Section 8 is a category of reimbursement which is expanding rapidly. This 'limited use' category is a form of restricted reimbursement that requests the physician to prescribe the drug for patients meeting defined clinical criteria. The key difference between limited use and Section 8 is that it is simply an 'honour system' which trusts the physicians to follow prescribing guidance. There are many examples of limited use drugs, but the most recent debates have been about celecoxib and rofecoxib. Physicians are asked to only prescribe these drugs for patients with arthritis who have an increased risk of gastrointestinal bleeding because it is in these patients that the drugs are most beneficial and cost-effective.

The risk of 'leakage' and the need for drug utilisation review

Placing celecoxib and rofecoxib on the Ontario formulary under the limited use category exposes the government to financial risk if prescribers do not abide by the honour system and ignore the limited use criteria. For the government, the 'nightmare scenario' is that the aches and sprains adequately managed with cheap anti-inflammatory drugs get switched to more costly new drugs. In the Australian context I have heard this phenomenon referred to as 'leakage'; once a drug is subsidised for a specified indication and patient group, usage can 'leak' into other patient groups where the drug is less cost-effective. The risk of leakage raises questions of measurement and management. How can a government payer create systems for monitoring appropriate drug use and how should the risk of leakage enter into negotiations with manufacturers?

There are two ways in which drug utilisation review can be used to support limited use criteria. The first is using aggregate or patient-level administrative claims data to monitor trends in drug usage, substitution and other health care usage following formulary listing. For example, the extent to which celecoxib and rofecoxib will lead to reduced prescribing of gastro-protective drugs such as misoprostol is a component of cost-effectiveness models and will be watched keenly. The second method is the use of 'real-time' prescription advice and/or adjudication for reimbursement using office-based electronic medical records. The electronic medical record holds great promise for precisely determining a patient's eligibility for a limited use medicine, but it clearly poses some threats, both to the clinical freedom of prescribers and to the privacy of patients.

Risk management, envelopes and strategic bargaining

As part of the submission for listing provided to DQTC a manufacturer must make a forecast of how much of the drug will be prescribed over the next three years and how much this will cost. This forecast is known as a 'budget impact analysis' and the chief executive officer of each company, prior to listing, must provide a signed letter to the Ministry of Health declaring this forecast.

The forecast of drug expenditure has become a crucial part of the submission because the Ministry of Health has changed its approach to expenditure risk management. In an initial stance – which totally 'blindsided' the industry – the Ministry announced that it would only pay for a new medicine up to the expenditure forecasted in the submission. Faced with a storm of protest on this risk-shifting policy, the Ministry softened its position somewhat and established the Drug Utilization Advisory Committee as an advisory board on circumstances where a manufacturer 'overshoots' their forecast expenditure. It is too early to know how the Drug Utilization Advisory Committee will work and so the 'penalty' for overshooting the forecast remains unclear.

These recent policy developments on agreed expenditure envelopes have some important strategic implications for manufacturers making submissions. Essentially a manufacturer is now entering into a price-volume agreement with the government where it can control the price but has less than 100% control over utilisation once the drug is in the hands of prescribers. The risky business decision for the company is where to set its forecast expenditure for the drug, given two important unknowns: the precise extent of utilisation and the potential penalty for an overshoot in expenditure. It is also a game of strategy for the government which must decide to accept or reject the listing of a drug based on both the cost-effectiveness data and the uncertain forecast expenditure.

Lessons for and from Australia

Canada can learn from the centralised national system of drug review in Australia. The process of review and evaluation appears to be well organised and resourced by Federal government. In Canada there is duplication of effort as each province conducts its own review of clinical evidence and cost-effectiveness. Discussions are ongoing in Canada about the establishment of a single Federal agency for drug review. One advantage of having a single buyer of medicines, similar to Australia, is that it affords what economists call monopsony power – the government having more power to negotiate the terms of price and reimbursement.

The main lessons for Australia relate to Ontario's experience with the limited use designation which attempts to direct drug usage to patients for whom a medicine is most cost-effective. A member of the DQTC has recently criticised the limited use mechanism saying that there is no evidence that the policy is effective.[4] Producing 'evidence-based' prescribing guidance is the easy part – the difficulty is getting prescribers to comply. The related challenge is having the utilisation data systems in place to monitor how well the policy targets are being achieved. Ontario has made some progress in this respect and Australia needs to keep pushing for this necessary research infrastructure. Finally, whether you welcome or fear the 'brave new world' of the electronic medical record, it clearly holds great hope in the future as a means of real-time, office-based prescribing guidance and reimbursement adjudication. Concerns over prescriber freedom and patient confidentiality will no doubt be voiced as this technological innovation becomes a reality in the doctor's office.

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FURTHER READING

The Ontario Drug Benefits Program homepage
http://www.gov.on.ca/health/english/program/drugs/drugs_mn.html

The ODBP formulary
http://www.gov.on.ca/health/english/program/drugs/odbf/odbf_mn.html

Ontario guidelines on economic analysis for drug submissions
http://www.gov.on.ca/health/english/pub/drugs/drugpro/dsguide_mn.html

Dr O'Brien is a member of the economic subcommittee of the Ontario Drug Quality and Therapeutics Committee.

Transparency and the Pharmaceutical Benefits Advisory Committee

Alan H. Evans, Chief Executive, Medicines Australia, Canberra

Comment on Professor M.J. Eadie's editorial 'The secrecy of drug regulatory information' (Aust Prescr 2002;25:78–9)

Medicines Australia, which represents the prescription medicines industry in Australia, welcomes discussion on transparency of the evaluation process for new medicines.

Medicines Australia wrote to the Therapeutic Goods Administration (TGA) earlier this year suggesting the establishment of an industry/TGA project team to look at the evaluation process, including the issue of transparency. While the terms of reference for that project team are yet to be established, it is anticipated that consumers will have representation on that team. The project team is expected to consider the level of information that could potentially be made publicly available, the depth and detail of that information and the timing of the release of that information.

Caution should however be taken in making direct comparisons with the types and level of information available to consumers in the USA. The evaluation systems that give rise to the release of the minutes of expert committee reports in the USA vary from those in Australia on some key issues. For example, the evaluation of a new product in the USA includes a public hearing which both the public and the applicant are invited to attend. In Australia, the Australian Drug Evaluation Committee (ADEC) considers applications in closed sessions. Natural justice suggests that companies should have the opportunity to respond to the issues raised by the ADEC before the minutes are disclosed.

With respect to the release of pharmacological and clinical data, it should be noted that Article 39.3 of the World Trade Organization Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), to which Australia is a signatory, states that:

> Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use.

That said, Medicines Australia is currently considering the establishment of a Clinical Trials Register, similar to those established in the USA, whereby healthcare professionals, and members of the general public, can be made aware of the existence of clinical trials in certain disease states. While the availability of the results of those trials, both positive and negative, is also a consideration, Medicines Australia concurs with Professor Eadie's statement that this could undermine the publication, by the principle investigator, of these results in scientific journals and the like. This is a matter that needs to be discussed with the scientific community.

On the broader issue of transparency of the Pharmaceutical Benefits Advisory Committee (PBAC), Medicines Australia concurs with comments of Dr John Hewson, who is also President of the Arthritis Foundation of Australia, who recently said in the Australian Financial Review, 'Our Pharmaceutical Benefits Advisory Committee process needs to be much more transparent as to why a drug is or is not recommended for listing.'.

The decisions of the PBAC affect the quality of life of millions of Australians. Therefore it is clearly in the best interest of doctors, patients and the general public to ensure absolute transparency for the operations of the PBAC. This should include all aspects of its operations and include peer review.

And consistent with other government administrative actions, the decisions of the PBAC should be subject to appeal and review by the Administrative Appeals Tribunal.

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.

Warfarin and antiplatelet drugs

Editor, – We read with interest the article 'Warfarin, antiplatelet drugs and their interactions' (Aust Prescr 2002;25:81–5) and were disappointed that although the authors emphasise the risks of combining warfarin with aspirin, they fail to acknowledge the proven benefits of this combination in patients with prosthetic heart valves. A recent meta-analysis[1] showed that compared with anticoagulation alone, the addition of an antiplatelet drug reduced the risk of not only thromboembolic events (odds ratio 0.41, $p < 0.001$) but also total mortality (odds ratio 0.49, $p < 0.001$).

The old view that the combination is dangerous is still held by many doctors and pharmacists. We certainly agree with the authors' recommendation that with the combination, low-dose aspirin should be used and the INR 'kept at the lower end of the desired target', and that patients on the combination should be carefully monitored for possible bleeding complications, including gastrointestinal blood loss. However, the evidence that adding low-dose aspirin to warfarin reduces total mortality by 50% in these patients should not be ignored and needs wide dissemination.

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Managing constipation in children

Editor, – It was pleasing to see the article 'Managing constipation in children' (Aust Prescr 2002;25:85–7) as it is such a common problem. It was particularly pleasing to see the prominence given to the emotional aspects.

However, the article needs several comments. The first is the strong recommendation for oral bowel cleansing solutions and rectal medications. Oral cleansing solutions have significant risks in the presence of faecal impaction. Rectal medications frequently interfere with emotional management.

The article deals with stimulant aperients in the same paragraph as stool softeners. The two have very different indications. Stimulants such as senna and phenolphthalein often cause significant pain or incontinence due to increased muscle activity. Furthermore, their long-term use damages the intramural ganglion cells of the colon.

Stool softening agents are usually all that is needed for children with constipation unless there is an underlying organic cause. The vast majority of children who have no abnormality of the colon (albeit with a secondary fissure) require nothing more than stool softening. Dietary means alone are rarely enough in the first instance, but are important in long-term management. Paraffin oil, either plain or as an emulsion, is the only agent that will soften inspissated faeces. It is not absorbed so is safe to give in large doses and for prolonged periods. It takes 5–10 days to soften old hard faeces, but it will eventually do so and thereby avoid any anal

manipulations or general anaesthetic to perform manual evacuation. It has a reputation for interfering with absorption of fat-soluble vitamins, but I am unable to find a reliable reference for this.

Apart from a small number of children with an organic cause or very resistant constipation, the majority of constipated children have a totally normal colon, so once sensation and motility are restored by getting rid of accumulated faeces, they will defecate quite satisfactorily if the stool is soft.

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Malaria prevention

Editor, – The article 'Malaria prevention in the expatriate and long-term traveller' (Aust Prescr 2002;25:66–9) was good but deficient in a few areas. I am a pharmacist living in a malaria endemic area of Nigeria. By virtue of this I am aware of other ways of managing malaria as we are faced with this terrible disease for a lifetime.

In the section on the malaria standby treatment regimens, attention was not drawn to the use of dihydroartemisinine – a novel drug developed from the malaria herb Qinghaosu in China. This drug happens to be the most effective and safest antimalarial compared to the others listed in the article. It has a very fast onset of action and adverse effects that are not debilitating.

I would emphasise the life cycle of the plasmodium parasite, as the dormant hypnozoites and gametocyte forms in the liver and blood respectively contribute significantly in reinfection and transmission of the diseases. The need for a radical cure when the expatriate or traveller returns home means there is a possible role for a drug like primaquine.

In conclusion, these aspects would definitely add the cherry on the cake and make the article well balanced.

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Dr Daniel O'Brien and Dr Beverley-Ann Biggs, authors of the article, comment:

We acknowledge the comments of Bamgboye Raymond regarding our article 'Malaria prevention in the expatriate and long-term traveller'. Indeed dihydroartemisinine is used widely throughout malarial endemic countries as a safe and effective treatment for malaria. However, our paper was written for Australian health practitioners, and as this medication is not currently registered for use in Australia, it was not included.

We also agree that treatment of malaria due to *Plasmodium vivax* and *Plasmodium ovale* requires consideration of eradication of the liver hypnozoites to reduce the chance of recurrent infection in those who have left the endemic area, and are unlikely to be re-exposed in the near future. However our article deals with emergency standby treatment for those developing malaria in endemic areas. Here there is little value in treatment with drugs such as primaquine due to the likelihood of reinfection.

Sensitivity and specificity – is your test reliable?

Editor, – The recent article on sensitivity and specificity (Aust Prescr 2002;25:107) is of concern in that it implies that sensitivity and specificity are invariant when applied to a particular disease state. This is not so. We give examples below.

Following occlusion of a coronary artery during myocardial infarction, cardiac troponin will be released. However, troponin is a protein and will not get into the circulation until some hours after the coronary occlusion has occurred. Thus samples collected early, say at two hours post-event, will have a poor diagnostic sensitivity for identifying myocardial infarction, while samples collected later, say at 12 hours post-infarction, will have a very high diagnostic sensitivity. These two clinical settings with very different sensitivities are not covered by the usual statement that 'cardiac troponin has a sensitivity for myocardial infarction approaching 100%'.

Consider the use of ferritin measurement to establish or exclude a diagnosis of iron-deficiency anaemia. A low ferritin concentration is considered to support the diagnosis of iron-deficiency anaemia. If samples are collected only in the general practice setting there will be very few 'false normal' results. If however, samples are collected in the acute hospital setting, where there is a relatively higher prevalence of liver disease with release of tissue ferritin, then there will be proportionately more people falsely identified as having 'normal' iron homeostasis. The apparent diagnostic sensitivity in these two populations, if compared to the best test available – bone marrow biopsy and quantitation of stored iron – would be quite different, because of the characteristics of the two populations.

Both of the examples above demonstrate that diagnostic sensitivity can vary for a particular disease state, and are one of the reasons why tests appear to perform differently in the reports in the literature. It is important to define very precisely the population that is being studied, when diagnostic sensitivity and specificity is being discussed.

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Splitting tablets

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SYNOPSIS

Patients split tablets for a variety of reasons, however there are problems associated with this process. Tablet-related factors include inaccuracy in splitting tablets and the resultant dose fluctuations, increased degradation of drug as a result of exposure to air and alterations in the dissolution rate of some formulations. Even when commercial tablet cutters are used the accuracy of splitting may be variable. Patients may experience difficulty in splitting tablets especially if their dexterity, eyesight or cognition is impaired. Compliance is likely to be decreased if the regimen requires tablets to be split. Although splitting tablets may potentially save the patient money the possible impact on the quality of medication use must be considered.

Index words: compliance, dosing, quality use of medicines.

(Aust Prescr 2002;25:133–5)

Introduction

Tablet splitting or dividing has been an accepted practice for many years as a means of obtaining the prescribed dose of a medication. Patients may be required to split tablets to:

- obtain the required dosage when a dosage form of the required strength is unavailable
- provide appropriate fractional doses in a flexible dosing regimen or in a gradually increasing or decreasing dosage regimen
- begin therapy with the lowest possible dose to decrease the incidence of adverse effects or to gauge an individual patient's response.

Elderly people or children who require reduced doses may not be able to use liquid formulations (or they may not be available on the Pharmaceutical Benefits Scheme). If suitable low-dose tablet formulations are unavailable, these patients may require tablets to be split to obtain the appropriate dosage.

Patients may save money if there is a price differential that makes halving tablets economically attractive. However, the process of splitting tablets causes a number of problems, some of which are patient-related while others are related to the tablet or formulation.

Tablet or formulation-related factors

Uneven breaking of a tablet may result in significant fluctuations in the administered dose. This may be clinically significant for drugs with a narrow therapeutic range[1], such as warfarin or digoxin. For many drugs, however, especially those with long half-lives and/or a wide therapeutic range, dose fluctuations are unlikely to be clinically significant.

Removing tablets from foil packaging or exposing uncoated tablet surfaces may increase the rate of degradation of the active drug. This has important ramifications as the patient may get a lower than intended dose and adverse effects may be increased by degradation products. The tablet dissolution rate and absorption characteristics may also be affected when tablets are split.[2] This applies particularly to coated and controlled-release tablets. While the cumulative dissolution may be similar between whole and halved tablets the initial rate of dissolution may be increased with unpredictable clinical consequences. Some sustained-release (extended duration) formulations can be halved without affecting their extended-release characteristics (e.g. isosorbide mononitrate, bupropion) while others cannot (e.g. felodipine (Agon SR), tramadol (Tramal SR)) and it is therefore important to check the product information of each specific brand if splitting tablets is considered. Many tablets are coated to mask the taste of the drug. Splitting may therefore expose a drug's taste. Table 1 provides a general guide, with limited examples, as to which tablets may not be suitable for splitting.

Tablets that are scored are usually considered by the manufacturer to be suitable for division and the majority of tablets are made this way. Not all tablets, however, are suitable

Table 1

Types of tablets that are not recommended to be split

Types of tablets that should not be split	*Examples (not a complete list)*
Unscored tablets	d-penicillamine (D-Penamine) acarbose (Glucobay 50 mg) metformin (Diaformin 850) tiludronate (Skelid)
Unusually thick or oddly shaped tablets	alendronate 40 mg (Fosamax 40 mg) finasteride (Proscar 5 mg) fosinapril (Monopril) amiloride (Midamor)
Film-coated tablets	nifedipine (Nifecard) donepezil (Aricept) tamoxifen (Nolvadex) azathioprine (Imuran 25 mg)
Enteric-coated tablets	valproate (Epilim 200 mg, Epilim 500 mg) diclofenac (Voltaren) mesalazine (Mesasal) pantoprazole (Somac)
Some time-release and extended-release tablets	felodipine (Agon SR) cefaclor CD 375 mg (all brands) potassium chloride (KSR, Slow K, Span K) tramadol (Tramal SR)

Table 2

Factors contributing to increased inaccuracy of tablet splitting

Tablet factor contributing to inaccuracy	*Examples (not a complete list)*
Small size	digoxin (Lanoxin-PG) temazepam (Temaze)
Irregular shape	fosinapril (Monopril) lamotrigine (Lamictal) alendronate (Fosamax) auranofin (Ridaura)
Scored on one side only	alprazolam (Kalma) benztropine (Cogentin) selegiline (Eldepryl) clozapine (Clozaril)

for splitting and this should be considered when the recommendation to split the tablet is made. The degree of inaccuracy may be associated with tablet size, shape and type of scoring (Table 2). Some tablets, even with a score line, may not break easily into two pieces of equal size.[1] The length of time that drugs remain stable after splitting also needs to be considered as the drug may not be stable when the cut surface is exposed to air for even short periods (up to 24 hours) let alone tablets pre-cut for doses a week or more in advance. This may be of importance if a carer, district nurse or pharmacist has to split tablets in advance for patients unable to manage the task.

The storage of split tablets is not well discussed in the literature. Anecdotal evidence suggests that many patients, or their carer, nurse or pharmacist, split a number of tablets in advance. Patients store split tablets in bottles that previously contained the same medication, different medication or some other substance, or in the same bottle as whole tablets or in a dosage administration aid. Issues of concern relate to labelling of storage containers and the time that split tablets are exposed to air and light before use with the possible detrimental effect on stability. For example the instability of soluble aspirin limits the usefulness of the unused half of a split tablet. If only half the tablet is taken the unused half should be immediately discarded.

Patient-related factors

Tablets can be split manually into two portions by either breaking with the fingers along a scored line, cutting with a knife or using a specially designed tablet cutter. Substantial dexterity in positioning and holding the tablet is needed. Uneven division of the tablet or a degree of wastage can occur as some tablets may crumble or break into more than two parts.

Commercially available tablet cutters should increase the accuracy of tablet splitting, but these devices require a degree of manual dexterity in loading the tablet.[3] Irregularly shaped tablets may be difficult to load and may not easily be split into equal halves. Dividing a tablet into quarters is even more difficult and is likely to incur a greater rate of tablet wastage and inaccuracy in final dosage.[4]

Liquid formulations may not be suitable alternatives for elderly patients as measuring volumes of liquid formulations also requires dexterity and good eyesight. These formulations also preclude the use of dosage administration aids such as dispenser packs. Splitting tablets may be the only option when a reduced dose is needed.

Old age or diseases such as arthritis and Parkinson's disease can cause impaired manual dexterity or decreased grip strength that renders the process of splitting tablets extremely difficult.[5] Even if a tablet cutter is used it may not improve accuracy if the patient is functionally impaired. Cognitive impairment may make remembering instructions to split a tablet for a particular dose difficult, especially if dosage regimens are complex, such as tapering or increasing doses, or if more than one tablet is to be split.

Another issue of concern is whether difficulty splitting tablets may adversely affect patient compliance with drug regimens, as patients may skip or double doses rather than split tablets and retain unused halves. Complex regimens involving split tablets may be expected to decrease patient compliance. Studies have shown that patient compliance is not decreased by use of split tablet regimens[6,7], although the results should be interpreted with caution because of selection bias.

Cost considerations

While splitting tablets may appear cost-effective, there may be adverse consequences relating to the treatment of the patient's condition. Any savings from splitting tablets may be offset by drug wastage and potential negative effects on the quality use of medicines.

Conclusion

The decision to split tablets should be made after due consideration. The following recommendations may be used as a guide:

- Check the product information before recommending tablets be split
- In general only scored tablets should be split
- Patients should be assessed for their ability to understand and comply with regimens involving split tablets
- A tablet cutter can be used to improve accuracy, but patients must be instructed in its proper use
- Patients should be advised about appropriate storage of split tablets.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 151)

1. Splitting tablets can accelerate the degradation of the active ingredient.
2. If a soluble aspirin tablet is split the half which is not used immediately should be discarded.

Cisapride: more restrictions

Concerns about cardiac arrhythmias led to restrictions being placed on the prescription of cisapride.[1] There are few gastrointestinal conditions which require treatment with cisapride.[2] It should only be tried if patients with gastroparesis or severe gastro-oesophageal reflux have not responded to other drugs.

The manufacturer has now decided to withdraw the highest strength of cisapride tablets (20 mg). It has also revised the product information.

All patients now require measurements of renal function and ECGs before and during treatment. They should be followed up at least every three months. As interactions may prolong the QT_c interval, patients taking cisapride should be regularly asked if they are taking any other medicines.

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Book review

Therapeutic Guidelines: Analgesic. Version 4. Melbourne: Therapeutic Guidelines Limited; 2002. 358 pages.
Price: $33, students $25.30, plus postage.*

Milton Sales, General Practitioner, Adamstown, NSW

Analgesic guidelines can be used in two ways – as a detailed and useful resource about the physiology and pharmacology of pain and its management, and as an occasional resource for looking up specific disease states or painful conditions.

The list of contributors to Therapeutic Guidelines: Analgesic is impressive, and the writing style is concise and easy to read. It brings together the current understanding of the physiology of pain including pathways, neurotransmitters and pharmacology – what works where and how. There is also discussion of the psychology of pain.

Analgesics, adjuvants, physical therapies and psychological issues are all covered in this comprehensive review of all types of pain syndromes, to give a thorough overview of each topic.

This is demonstrated by considering the handling of the topic of headache, a common presenting problem for general practice. It starts with the presentation of warning signs for serious causes of headache, and has a table to help distinguish the benign causes of headache and their features.

Then discussed in detail with pathophysiology and management, are tension headache, migraine, cervical headache, occipital neuralgia, opioid addiction, drug induced headache, post-traumatic headache, cluster headache, chronic paroxysmal hemicrania, ice-pick headache, cough, exertional and sexual headache, and post-lumbar puncture headache. Facial pain and eye pain are handled separately in their own chapters.

In each case, discussion of the cause, and non-pharmacological and pharmacological management is detailed. There are also clear diagrams of neck exercises to show patients.

Other features include tables of drug interactions with all the significant classes of analgesics, pregnancy and breastfeeding classifications, tables of disease modifying antirheumatic drugs, local anaesthetic doses and characteristics, and the Glasgow Coma Scale. The management of cancer pain and palliative care issues are also included.

The index is accurate and effective, and combined with the straightforward chapter headings enables easy navigation.

This is a comprehensive resource that would suit a variety of levels from medical student to consultant. It can be read from cover to cover and used as a quick resource during a consultation. There are few texts that cover the range of analgesic topics in this depth. It is a valuable addition to the Therapeutic Guidelines series.

* For more information contact Therapeutic Guidelines Limited – 1800 061 260 or sales@tg.com.au

Insulin delivery devices

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SYNOPSIS

Everyone with type 1 diabetes requires insulin from diagnosis and more than 30% of people with type 2 diabetes eventually need insulin because of progressive failure of pancreatic beta cells. People with type 2 diabetes are often reluctant to commence insulin and some will require assistance with their injections. Over the past five years a number of new insulin delivery systems have become available that can make insulin administration easier. A number of factors, including patient preference, influence the choice of device. A thorough assessment of the individual's self-care capacity is important and appropriate education is imperative when starting insulin.

Index words: diabetes, injections.

(Aust Prescr 2002;25:136–8)

Introduction

Insulin is a very effective drug and is vital treatment for people with type 1 diabetes. Type 2 diabetes is an insidious disease with progressive destruction of the insulin-producing beta cells.[1,2] Eventually more than 30% of patients require insulin to attain their blood glucose targets.[3] Many people with type 2 diabetes are reluctant to start insulin for a number of reasons including fear of needles, fear of hypoglycaemia, weight gain and believing they only have a mild form of diabetes.[4]

Historically, patients injected insulin using glass syringes with detachable needles. They had to boil the syringes and needles between injections and store them soaked in alcohol to keep them sterile. These needles were large, and injections were painful. The advent of the disposable plastic 'diabetic syringes' with a fixed needle represented a considerable advance and injections were less painful. They did, however, have a number of disadvantages, and doses and administration practices were often inaccurate. This was partly because of the range of insulins available and the need to mix each dose of short- and longer-acting insulin in the same syringe at the time of injection. The advent of biphasic insulin made drawing up insulin doses easier and less confusing for patients.

The last five years have seen an increase in the range of insulin delivery devices (Table 1). These devices have revolutionised insulin self-care, but have also placed extra burdens of choice on people with diabetes, and they do not necessarily improve compliance. One of the most significant advances has been the production of short, fine needles as they considerably reduce injection pain. In practice, patients report that blood glucose testing is more painful than insulin injections.

Choosing an appropriate insulin device

Education about all aspects of managing diabetes and counselling about living with the disease are essential and should include the patient's family and others who may be involved in the patient's care. Diabetes educators have an important role in teaching people to use insulin delivery devices. It is important that patients are given the opportunity to handle the types of devices available and choose the one that best suits their needs. Issues to consider are the person's:

- **vision and ability to see the dose indicator numbers.** Most devices, other than syringes, have an audible click for each one or two units of insulin dialled up. This can help people with impaired vision maintain their independence. Magnification aids are available with some insulin devices. The InnoLet device currently has the largest and clearest dose indicator of any device.
- **ability to perform the fine motor skills** required to load insulin cartridges into the device and dial up a dose. InnoLet and NovoLet are preloaded disposable devices that eliminate the need to load insulin into the device. NovoLet is not the device of choice for people who need large doses because it is easy to misdial and under- or overdose.
- **ability to manage the device.** This includes loading and checking the accuracy of the dose, cleaning and maintaining the device, and recognising the signs of malfunction and knowing what to do about them.
- **ability to give the injection correctly.** Most trials indicate that insulin pens are accurate, providing the patient is educated appropriately and their technique and the performance of the device are monitored regularly.
- **willingness to monitor their blood glucose.**

Diabetes education centres usually have a range of products available to help people choose appropriately before they buy a device and to ensure they can use it correctly.

Are short needles an advantage?

Short, fine needles (7–8 mm long and 29–31 gauge) look less menacing and most people prefer to use them. They also avoid inadvertent intramuscular injection. People who continually give intramuscular injections may be more prone to wide swings in blood glucose because insulin is more rapidly absorbed from muscle than from subcutaneous tissues.[5,6] Shorter needles significantly reduce this risk especially if patients are taught to pinch up and inject into a fold of skin.

Table 1

Currently available insulin devices

Device	*Issues to be aware of*	*Advantages*	*Disadvantages*
Syringes			
30, 50 and 100 unit sizes	There is still a place for syringes Patients need to be able to recognise different dose increments on different sized syringes	Can be used with all available insulins	Needles are usually longer than those on other devices
Insulin 'pens'			
Two brands are available in Australia; NovoNordisk, which has six devices and Lilly, which has one. 'Pens' are not suitable for people who need to mix insulins.			
NovoNordisk devices – can only be used with NovoNordisk insulins			
NovoPen 3	Dose range 2-70 units Small, fine needles available Pen is reusable	Accurate dosing Has a function to check the accuracy of the device	Replacing the 3 mL insulin cartridge can be difficult
NovoPen Demi	Similar to NovoPen 3, but dose increments in ½ unit possible	Useful for children and insulin sensitive patients who require very small doses	
NovoLet	Disposable prefilled devices Contain 3 mL of insulin Range of insulins available Uses small, fine needles Dose range up to 78 units	May benefit people while travelling	Can be confusing to use and dose errors often occur especially with large doses
Innovo	Dose range 1-70 units Accurate dosing Uses 3 mL cartridges Range of insulin available Reusable device Battery-operated, batteries last about 4 years then the device needs to be replaced Small, fine needles	Display indicates that insulin is being delivered, the number of units delivered, the dose given and the time elapsed since the previous dose was delivered Helps people who forget whether they have taken their insulin	Can be difficult to use, especially if large doses are needed – the plunger is difficult to depress
InnoLet	Dose range 1-50 units Accurate dosing Small, fine needles Device is disposable Contains 3 mL of insulin	Clear easy-to-see numbers on the dose dial, which is an advantage for vision impaired people Easy to use for people with limited manual dexterity	Only Protaphane and Mixtard 30/70 insulin available, at this stage Larger than other devices – takes up storage space in the fridge
Pen Mate	Automatic needle insertion device Used with NovoPen 3 Hides needle and injects insulin quickly and automatically	May benefit children and people with needle phobia	
FlexPen	Prefilled Contains 3 mL of insulin	Single dose setting mechanism	
Lilly device – can only be used with Lilly insulin			
Huma*Pen*	Dose range 0-60 units Small, fine needles Takes 3 mL cartridges Pen is reusable	Insulin cartridge is easy to change	May not be available for new patients
Other devices			
Insulin pumps	Provide continuous basal insulin with a facility for giving bolus doses with meals Use only short-acting insulin Use small, fine needles	Can achieve close to normal insulin profile	Expensive Require considerable expertise and time to be used effectively
Jet injectors	No needle required Not widely used Force insulin through the skin under pressure	May benefit people with needle phobia	Bruising is common Sterilisation issues Expensive

What about reusing needles?

As syringes and needles are now supplied at no cost through the National Diabetes Supply Service in most Australian States, there is no cost incentive to reuse syringes. Reused needles are more likely to bend, and are subject to microscopic tip damage that causes local trauma. When they are left on pens, they act as a conduit to the outside allowing air to enter the insulin cartridge resulting in dose inaccuracies.[7] Safe disposal of sharps is an important consideration and should be part of the education process.

Monitoring

With time people's injection technique can become inaccurate because they have changed devices, take less care or have physical changes such as visual loss or changes in their fine motor skills. Insulin injection technique should be checked regularly if hypoglycaemia occurs frequently, if they develop a complication or if they change devices. Injection sites should be checked as part of this assessment. Children should be assessed as they begin to take responsibility for their own injections.

The future

Most people would prefer not to inject. This may become a reality in the future depending on the results of trials currently underway using inhaled insulin. In the longer term, oral insulin and/or insulin patches may become an option.

Conclusion

Most currently available insulin devices are safe and accurate. Individuals need to be carefully assessed, educated appropriately and permitted to 'try before they buy'. There is still a place for insulin syringes and some patients prefer to use them.

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FURTHER READING

Novo Nordisk Australia
http://www.novonordisk.com.au/view.asp?ID=659

LillyDiabetes.com
http://www.lillydiabetes.com/products/pens.cfm

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 151)

3. More than 30% of patients with type 2 diabetes will eventually need to inject insulin.
4. New insulin delivery devices have longer needles to enable easier intramuscular injections.

Managing healthy women at risk of breast cancer

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SYNOPSIS

Early detection with effective treatment has reduced mortality in some groups of women with breast cancer, however reducing the risk of breast cancer is clearly an important goal. Several risk factors for breast cancer have been identified. The most important of these are ageing and a positive family history. Models incorporating these risk parameters are available to help identify women who may benefit from the various risk reduction approaches. Optimal breast cancer prevention strategies in high-risk women are still to be determined and are the subject of ongoing clinical trials.

Index words: tamoxifen, raloxifene, mammography.

(Aust Prescr 2002;25:139–41)

Introduction

Approximately 1 in 13 (8%) Australian women will develop breast cancer by the age of 75 years. It is the commonest cause of death from cancer in Australian women. Although the cause of breast cancer is unknown there are numerous risk factors. Being female and ageing are the two main risk factors for developing the disease. The presence of a family history is also an important and well-established risk factor. Weaker risk factors include early age at menarche, nulliparity and age of menopause.

The majority of breast cancers are sporadic occurring in women without a family history. Only a small proportion (5–10%) of all breast cancers occur in women with a very strong family history and a proportion of these are attributable to germline mutations in single highly penetrant cancer susceptibility genes, such as BRCA1 or BRCA2. Some 'familial clusters' of breast cancer may result from interactions of multiple genes and environmental factors or single low penetrance cancer susceptibility genes. Importantly, most women with a family history of breast cancer do not carry germline mutations in single highly penetrant cancer susceptibility genes.

Breast cancer risk management strategies

Several important medical decisions, particularly risk reduction strategies, may be affected by a woman's underlying risk of breast cancer. Management in this situation should involve comprehensive quantitative risk assessment, counselling appropriate to the individual's risk, the opportunity for genetic testing where appropriate, and advice regarding specific management strategies.

Quantifying breast cancer risk

Many of the known risk factors for breast cancer may interact, so evaluating the risk conferred by combinations of risk factors is challenging. Several risk prediction models are available and provide an epidemiological basis for counselling women with a family history.[1,2] The Gail model, developed in the USA, incorporates family history, reproductive factors, and history of benign breast disease. A software program of this assessment tool is available from the National Cancer Institute web site*. Little Australian data exist on which to base familial risk assessments. Care needs to be taken in using tables based on American data as the underlying breast cancer rate is one-third higher in the USA.

The Australian National Breast Cancer Centre (NBCC) has established a set of easily understood criteria to define those at increased risk based on family history†. Assessing family history in detail helps estimate a woman's risk of developing breast cancer as well as the probability of inheriting a mutation in a known cancer-predisposing gene. There are three NBCC criteria.

Category 1

These women have no family history or a weak family history (for example, one first-degree relative diagnosed with breast cancer at 50 years or older). This group covers 95% of the population and their lifetime risk of developing breast cancer is between 8 and 12% (compared to 8% for the general population).

Category 2

These women have a moderately increased risk. There may be one or two first-degree relatives diagnosed with breast cancer before the age of 50, or two or more distant relatives on the same side of the family with breast or ovarian cancer. Fewer than 4% of all women are at moderately increased risk and their lifetime risk for developing the disease is 12–25%.

Category 3

Less than 1% of the female population are at potentially high risk. They usually have several (three or more) closely affected relatives with breast cancer occurring at relatively young ages. There may also be bilateral or multifocal breast cancer, and the occurrence of ovarian cancer in the family. Inherited

* http://bcra.nci.nih.gov/brc

† http://www.nbcc.org.au/pages/info/resource/nbccpubs/advice.htm

predisposition in these families is possible and may be the result of a mutation in an autosomal dominant breast cancer susceptibility gene such as BRCA1 or BRCA2. For women who carry mutations in these genes the lifetime risk of breast cancer may be as high as 40–80%, and of ovarian cancer 10–60%. These families should be referred to cancer genetic clinics for genetic counselling and consideration of genetic testing.

Breast cancer prevention strategies

Chemoprevention

Tamoxifen can prevent second primary breast cancers. There are also extensive molecular, cellular and animal data to show that it acts as an effective oestrogen antagonist in the breast. Tamoxifen has therefore been studied in several randomised trials for the primary prevention of breast cancer.

The Breast Cancer Prevention Trial was a randomised placebo-controlled trial involving over 13 000 women at high risk of developing breast cancer.[3] After a mean follow-up period of four years, tamoxifen had reduced the incidence of breast cancer by 49%. However, this beneficial effect was confined to oestrogen receptor positive tumours and there were more serious adverse events, including endometrial cancer, vascular events (stroke, pulmonary embolism, deep vein thrombosis) and cataracts, in the tamoxifen group. Despite these problems the trial led to the Food and Drug Administration in the USA approving tamoxifen for the reduction of breast cancer risk in women whose risk of developing breast cancer is equal to the minimum eligibility criteria for the trial. These women were at least 35 years of age with a five year predicted risk of breast cancer development of at least 1.66% (calculated by the Gail model).

The preliminary results of the International Breast Cancer Intervention Study (IBIS)[4] also suggest that tamoxifen has some effect in preventing breast cancer, but not on overall mortality. This trial involved 7139 women aged 35–70 years including Australian women. All the women had risk factors for breast cancer indicating at least a two-fold relative risk for ages 45–70, a four-fold relative risk for ages 40–44, and an approximately 10-fold relative risk for ages 35–39. After a mean follow-up of 50 months, there was a 32% (8–50%) reduction in breast cancer incidence associated with tamoxifen (69 versus 101, $p = 0.013$). Endometrial cancer was increased about two-fold (11 versus five), but this was not significant ($p = 0.2$). Thromboembolic events were significantly increased (43 versus 17, odds ratio = 2.5 (1.5–4.4), $p = 0.001$) and the effect was particularly apparent following surgery (20 versus 5 events, $p = 0.004$). There was a non-significant increase in deaths from cancers other than breast, thromboembolic events, and cardiovascular causes, giving rise overall to a significant excess of deaths in the tamoxifen arm (25 versus 11, $p = 0.028$).

The overall risk:benefit ratio for the use of tamoxifen in prevention is still unclear, and continued follow-up of the patients in the current trials is essential. In Australia at this time primary chemoprevention is not an approved indication for tamoxifen use.

Raloxifene acts on oestrogen receptors and antagonises the effects of oestrogen in the breast and uterus. Preliminary reports (albeit from studies with osteoporosis as the major end-point) suggest that raloxifene may be associated with a reduced risk of developing breast cancer in postmenopausal women (at average or below average risk).[5] This suggestion is based on a relatively small number of breast cancers. It is therefore premature to recommend raloxifene to lower the risk of developing breast cancer outside of a clinical trial. There is currently no evidence to conclude that raloxifene will reduce the risk of dying from breast cancer for women who do not have breast cancer. Currently, a large number of postmenopausal women are entering, or are continuing to be followed in, randomised clinical trials evaluating raloxifene's effect on a wide range of clinical end-points. Results from such studies may influence future recommendations regarding raloxifene use.

Prophylactic surgery

Bilateral prophylactic mastectomy is a controversial clinical option for women who are at increased risk of breast cancer. High-risk women, including women with a very strong family history of breast cancer (NBCC category 3) and BRCA 1/2 mutation carriers, must make a decision with the primary focus on risk reduction or early detection.

Prophylactic mastectomy may significantly reduce, but does not completely eliminate the risk of breast cancer. There are no randomised clinical trials to ascertain efficacy in preventing disease or reducing mortality. The trade-offs of prophylactic mastectomy are substantial. It is an irreversible procedure with potential physical and psychological sequelae. Furthermore the reduction in breast cancer risk achieved by prophylactic mastectomy is likely to depend on a woman's underlying risk of the disease. A decision analysis involving women who were carriers of BRCA1 or BRCA2 mutations found that the benefit of prophylactic mastectomy differed substantially according to the breast cancer risk conferred by the mutations.[6] For women with an estimated lifetime risk of 40% (approximately four times the population risk), prophylactic mastectomy would add almost three years of life, whereas for women with an estimated lifetime risk of 85% the procedure would add more than five years.

Breast cancer screening

The preventive options currently available for Australian women at increased risk for breast cancer are limited. Early detection (screening) strategies are an important consideration. There is general agreement that screening mammography reduces breast cancer mortality for women older than 50 years.[7,8] Its value for women younger than 50, regardless of risk status, remains controversial. The National Program for the Early Detection of Breast Cancer's current policy is to offer mammograms to asymptomatic women aged over 40 years at their request. The program provides women aged 40–49 years with advice of the limited evidence for the benefits of screening in women of their age. They are also given information on the possible adverse effects of screening,

such as over-diagnosis, radiation exposure and false positive results. The women may then make an informed decision on whether to participate in the program.

If screening women before 50 years of age does reduce breast cancer mortality, the women who stand most to benefit from beginning screening then are those at higher risk of the disease, particularly the 15–20% of women who have a family history of breast cancer. Thus a policy of offering early screening to these high-risk women seems reasonable. A number of promising early detection options are being evaluated. They include digital mammography, magnetic resonance imaging and ductal lavage and may prove to be more sensitive tests in this group of women.

Conclusion

Studies suggest that many women overestimate their breast cancer risk, however the great majority of Australian women can be reassured that they are at, or at most only slightly above, population risk.[9] This means that most will not develop breast cancer in their lifetime. Breast cancer is a serious disease and an important cause of premature mortality and morbidity. It is important to encourage women to participate in mammographic screening programs. At present risk reduction strategies for women at high risk are limited and require further investigation in the context of clinical trials.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 151)

5. Most women with breast cancer have a strong family history of the disease.
6. Tamoxifen can reduce the risk of breast cancer but can increase the risk of endometrial cancer.

Book review

Therapeutic Guidelines: Neurology. Version 2. Melbourne: Therapeutic Guidelines Limited; 2002. 191 pages.
Price: $33, students $25.30, plus postage.*

Ursula Russell, General Practitioner, Shepparton, Vic.

The 2002 edition of Neurology, the red book in the series, is another fine example of the art of therapeutic review. The guide is a highly readable, highly practical document. For a busy general practitioner the topics are pertinent and thoroughly explored, the topic headings guide you to relevant information with ease and the Therapeutic Guidelines' format of italicising the drug gives you the quickest opportunity for reviewing a favourite section.

A very good section is the headache section; there is nothing like a good review of evidence for helping to make some clarity of a problem that in my practice seems less than clear. Likewise the sections on facial pain and neuropathic pain are highly relevant for my practice. The sections on epilepsy and stroke, involuntary movements and central nervous system infections are not so commonly needed in my 'part time' world, but I feel confident that I could call on the relevant and up to date information quickly and easily. Another highlight of the 2002 version is the pictorial exposition of some of the manoeuvres for vertigo and motion sickness.

In summary: a very good and workable guideline for the busy general practitioner.

* For more information contact Therapeutic Guidelines Limited – 1800 061 260 or sales@tg.com.au

Drugs for glaucoma

Ivan Goldberg, Eye Associates and Glaucoma Service, Sydney Eye Hospital and the Save Sight Institute, University of Sydney, Sydney

SYNOPSIS

Older drugs for glaucoma reduce intra-ocular pressure, but often have unpleasant adverse effects. They still have a role in therapy, but there are now newer drugs which overcome some of the problems. The topical carbonic anhydrase inhibitors decrease the secretion of aqueous humour, while lipid-receptor agonists increase uveoscleral outflow. Alpha$_2$ agonists use both mechanisms to reduce intra-ocular pressure. If a patient needs more than one drug to control their glaucoma, the new drugs generally have an additive effect when used in combination regimens.

Index words: beta blockers, carbonic anhydrase inhibitors, lipid-receptor agonists.

(Aust Prescr 2002;25:142–6)

Introduction

Glaucoma is the second commonest cause of visual disability in the world.[1] It affects between 70 and 90 million people, with about 10% of them becoming blind in both eyes.[2]

In the last decade there has been an increase in the number of drugs available to treat glaucoma. However the key strategy remains the reduction of intra-ocular pressure. Many of the older drugs remain available so we need to assess how the new drugs fit in with them and which drugs should be replaced.

The old staples

Beta blockers, adrenergics, miotics and systemic carbonic anhydrase inhibitors were the four families of antiglaucoma drugs. Most are still available (Tables 1 and 2).

Beta blockers

Beta blockers remain the most commonly prescribed antiglaucoma drugs, but their usage is falling relative to the newer preparations. Timolol can be instilled once or twice daily with equal effect for most patients. Betaxolol is needed twice daily and its ocular hypotensive efficacy is not as marked. While betaxolol possesses calcium channel blocking properties, which offer anti-vasospastic and anti-apoptotic potential, these effects have not been proven clinically to reduce glaucomatous visual loss.

With remarkably few topical adverse effects (surface irritation or conjunctival hyperaemia in a small number of patients), timolol and levobunolol inhibit the rate of aqueous production by about 40%. This drops the intra-ocular pressure by 20–25%, which is more than the 15–20% drop with betaxolol. With longer-term use of timolol or levobunolol, tachyphylaxis is not uncommon and the pressure slowly rises. Withdrawing the drug for a few months often re-establishes its efficacy.

The main problem with timolol or levobunolol is their potential for systemic adverse effects. These are the same as the adverse effects of oral beta blockers, the most important of which are bronchoconstriction, bradyarrhythmias, and an increase in falls in the elderly.

As betaxolol is relatively selective for beta$_1$ receptors it should pose less respiratory risk. Its pharmacokinetic properties (higher plasma binding and larger volume of distribution) also make it less likely to provoke other systemic effects.

Miotics

Miotics (pilocarpine and carbachol) are rapidly falling out of favour. While their ocular hypotensive efficacy is undisputed, and their systemic safety margin wide (abdominal cramping or diarrhoea are rarely reported), their use is declining because of their local effects and the need to instill them up to four times daily. As parasympathomimetics, these drugs lower intra-ocular pressure by stimulating the ciliary muscle to exert a physical tug on the trabecular meshwork. This stimulation also causes browache and accommodative spasm (the fluctuating myopia is very distracting particularly for younger patients). Constriction of the sphincter pupillae produces miosis, which dims vision especially in older patients with cataracts. The miosis is uncosmetic, and creates technical problems from poor mydriasis if cataract extraction surgery is needed after years of instillation.

Adrenergic agonists

Dipivefrine is the only non-selective adrenergic agonist still available. Relatively low hypotensive efficacy, not infrequent surface irritation and frank allergic blepharoconjunctivitis have translated its unattractiveness (even when nothing better was available) into unpopularity. Safer than the now unavailable adrenaline products, it is still prescribed occasionally, and, like beta blockers and miotics, is additive in its effect with all the other older drugs.

Systemic carbonic anhydrase inhibitors

Acetazolamide is the only remaining systemic carbonic anhydrase inhibitor in Australia. It is still the most potent ocular hypotensive medication available, and can drop intra-ocular pressure by 25–40%. Other than rare transient myopia, no ocular adverse effects occur. Systemic adverse effects are legion – anorexia, nausea, abdominal cramping, diarrhoea, anergy, weight loss and paraesthesiae. As acetazolamide is related to sulfonamides, allergic reactions (including Stevens-Johnson syndrome) and aplastic anaemia have been a concern.[3]

Table 1

Clinically important pharmacological properties of antiglaucoma medications

	Concentration	*Instillation frequency*	*Duration of effect*
Inhibit aqueous inflow			
Beta blockers			
$\underline{\text{Beta}_1}$			
Betaxolol	solution 0.5% suspension 0.25%	2/day	12–18 hours
$\underline{\text{Beta}_1 \text{ and beta}_2}$			
Timolol	solution 0.25%, 0.5% gel 0.25%, 0.5%	1–2/day	12–24 hours
Levobunolol	solution 0.25%	1–2/day	12–24 hours
Systemic carbonic anhydrase inhibitors			
Acetazolamide	250 mg tablets	½–4 tablets/day	6–12 hours
Topical carbonic anhydrase inhibitors			
Dorzolamide	solution 2%	2–3/day	8–12 hours
Brinzolamide	suspension 1%	2–3/day	8–12 hours
Enhance conventional aqueous outflow (via trabecular meshwork)			
Miotics – direct parasympathomimetics			
Pilocarpine	solution 0.5%, 1%, 2%, 3%, 4%, 6%	2–4/day	4–12 hours
Carbachol	solution 1.5%, 3%	2–4/day	4–12 hours
Adrenergic drugs – may increase uveoscleral aqueous outflow as well			
Dipivefrine	solution 0.1%	2/day	12–18 hours
Enhance uveoscleral (unconventional) outflow			
Lipid-receptor agonists			
Latanoprost	0.005%	once daily	24–36 hours
Travoprost	0.004%	once daily	24–36 hours
Bimatoprost	0.03%	once daily	24–36 hours
Unoprostone	0.15%	2/day	12–18 hours
Dual action (aqueous inflow inhibition and uveoscleral outflow enhancement)			
Alpha_2 agonists			
Brimonidine	0.2%	2–3/day	8–12 hours
Fixed combinations			
Timolol/dorzolamide	0.5% / 2%	2/day	12 hours
Timolol/latanoprost	0.5% / 0.005%	once daily	24 hours

Table 2

Possible additive effects between different classes of antiglaucoma drugs

	Beta blockers	*Adrenergics*	*Miotics*	*Systemic CAIs**	*Topical CAIs**	*Alpha_2 agonists*	*Lipid-receptor agonists*
Beta blockers	–	+	+++	+++	+++	+++	+++
Adrenergics	+	–	+++	+++	+++	–	–
Miotics	+++	+++	–	+++	+++	+++	++
Systemic CAIs*	+++	+++	+++	–	–	+++	+++
Topical CAIs*	+++	+++	+++	–	–	+++	+++
Alpha_2 agonists	+++	–	+++	+++	+++	–	+++
Lipid-receptor agonists	+++	–	++	+++	+++	+++	–

* CAIs carbonic anhydrase inhibitors
– Not recommended
\+ Partially additive
++ May be additive, but not invariably
+++ Fully additive

Renal calculi are not uncommon. When necessary, acetazolamide should be used for as short a term as possible.

The new drugs

While the ultimate goal of a universally effective, totally safe and perfectly tolerable drug has not been realised, the newer drugs represent a series of distinct advances (Table 1).

Lipid-receptor agonists and related drugs

Latanoprost was the first of this class to be generally available, and it climbed rapidly to the position of most frequently prescribed drug for glaucoma, despite complaints about its cost. For the majority of patients, one drop of latanoprost 0.005% once daily will lower intra-ocular pressure by 27–34%.[4] This allows it to replace multidrug therapy in many patients.[5] This has an immediate flow-on benefit in terms of compliance, convenience and overall cost. No significant loss in the reduction in intra-ocular pressure has been found after 24 months of treatment.[6] With their long duration of action, latanoprost and similar drugs ensure better control of intra-ocular pressure throughout the day and night.

Latanoprost increases the flow of aqueous fluid through the ciliary muscle and through the sclera into the orbit, thereby enhancing uveoscleral or 'unconventional' outflow. Probably because of its unique mechanism of action, latanoprost is additive with all other antiglaucoma drugs with the possible exception of miotics, particularly in patients who have been using high concentrations of miotics for years.

Travoprost is available in Australia. There is also bimatoprost, whose manufacturer cites evidence that it activates a different class of lipid receptors and belongs to a different class of drugs (prostamides).

Slight conjunctival hyperaemia and a new adverse effect, increased iris pigmentation, were the main adverse events in all clinical trials of lipid-receptor agonists. Patients with hazel or mixed colour irides seem most predisposed; the iris colour changes are irreversible, but not progressive once the drug has been withdrawn.[7] These effects have also been reported with unoprostone, travoprost and bimatoprost. Darker, thicker and longer eyelid lashes ('luscious lashes' – quite popular with some patients) are almost invariable, and are reversible once the drug has been discontinued.[8] These local effects may be more common with travoprost and bimatoprost than with latanoprost. The ocular hypotensive effect of these two is at least as good as that of latanoprost as currently constituted, and may be slightly better.

Other less common adverse effects, which have emerged following marketing, include anterior uveitis and cystoid macular oedema. Confined mainly to patients with already predisposed pseudophakic or aphakic vitrectomised eyes, these problems are unusual, and usually diminish with drug withdrawal. As adverse effects may only emerge some time after marketing any new drug, clinicians need to consider whether any symptoms or problems experienced by patients using such a drug are causally related to that drug.

Alpha$_2$ agonists

Based on clonidine, apraclonidine and brimonidine are the two topical alpha$_2$ selective agonists available in Australia. Stimulation of alpha$_2$ receptors lowers intra-ocular pressure, whereas alpha$_1$ receptor activation produces adverse effects such as mydriasis, eyelid retraction and vasoconstriction.

Apraclonidine is 30 times less selective than brimonidine for the alpha$_2$ receptor. As it also often causes tachyphylaxis and allergic blepharoconjunctivitis, apraclonidine is not recommended for chronic control of glaucoma. Apraclonidine remains very useful in controlling an attack of angle-closure glaucoma and in preventing possible spikes of intra-ocular pressure after anterior segment laser surgery.[9]

Brimonidine reduces intra-ocular pressure by inhibiting aqueous production and increasing uveoscleral outflow. The former mechanism is thought to be more important early in treatment while the latter is more significant during prolonged treatment. The mean peak effect of brimonidine is a 24% reduction in intra-ocular pressure and the mean trough effect is a 15% reduction.[10] Little if any tachyphylaxis has been reported after two years of treatment. After four years of instillation by patients who have responded to brimonidine, the trough effect increases to approximate the peak.

Common adverse events of alpha$_2$ agonists include conjunctival hyperaemia (11%), allergic blepharoconjunctivitis (cumulative over four years to 25%), foreign body sensation and stinging. Dry mouth, headache, fatigue and drowsiness may be experienced, particularly if the patient is instilling the drops without adequate no-blinking/nasolacrimal duct occlusion techniques (see Fig. 1).

Monoamine oxidase inhibitors are a contraindication to the use of brimonidine. It should be used with caution in patients taking tricyclic antidepressants, barbiturates, sedatives, beta blockers, calcium channel blockers or other systemic antihypertensive drugs.

While the adverse effect profile of brimonidine is generally favourable, it depends critically on an intact blood-brain barrier. In infants and younger children this is not the case and topical brimonidine can cause profound systemic hypotension, apnoea, convulsions and cyanosis. It is absolutely contraindicated in children under the age of six, and relatively contraindicated in older children.

Topical carbonic anhydrase inhibitors

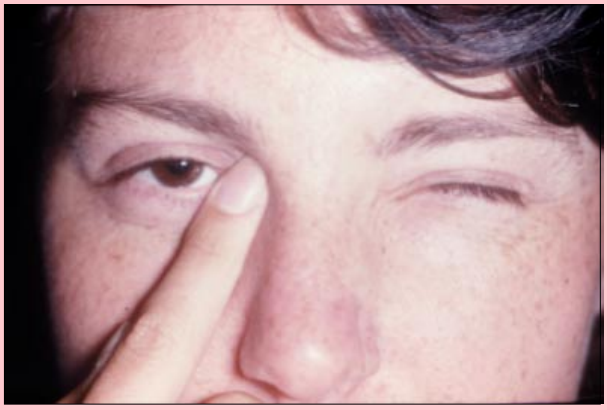
The topical carbonic anhydrase inhibitors, dorzolamide and brinzolamide, reduce intra-ocular pressure by 15–24% with less apparent systemic effects than acetazolamide, and reasonable surface comfort.[11] Both drugs seem to have very similar pharmacological and clinical profiles. They need twice or even three times daily instillations and are only occasionally satisfactory as monotherapy. Mostly they are useful as adjunctive drugs – when added to timolol, for example, a further 15–20% reduction in intra-ocular pressure can be anticipated.[12] They are not as effective as systemic carbonic

Fig. 1

Duct occlusion techniques

Simple eyelid closure AND digital occlusion of the tear duct for at least two minutes after eye drop instillation reduces systemic absorption of any topical drug by up to two-thirds. Thereby, the safety margin of any instilled medication can be expanded significantly.

(The photo shows the two techniques separately. Ideally the patient uses both techniques on the same eye.)



anhydrase inhibitors and they should not be prescribed simultaneously with acetazolamide.[13]

Corneal disease, particularly the stromal oedema effects of endothelial dysfunction, can be aggravated by topical carbonic anhydrase inhibitors. In healthy eyes, this does not seem to be a problem. The most common ocular adverse events with dorzolamide are stinging (less with brinzolamide), burning and eyelid inflammation. Allergic conjunctivitis leads to about one patient in 20 discontinuing treatment over 12 months. Conjunctival hyperaemia and follicles occur in up to 20% of users. Continued use seems to be associated with a declining rate of problems.

Following drainage surgery and treatment with systemic carbonic anhydrase inhibitors, hypotony and cilio-choroidal detachment have been reported. These adverse effects appear to be less frequent with dorzolamide.

Fixed combinations

To improve convenience and thus compliance, there is a trend to introduce fixed combinations of old and new drugs. While the combination of timolol with pilocarpine has been with us for many years, the combination of timolol and dorzolamide has recently been introduced. There will soon be a combination of latanoprost with timolol. Combinations of brimonidine and timolol, as well as travoprost and timolol are also on their way.

New choices – new responsibilities

All that we do in our management of patients depends on the balance between possible benefits versus potential harm. For the vast majority of our patients, medical therapy of glaucoma remains the first and ongoing strategy. Being asymptomatic, chronic and incurable (but generally controllable) diseases, the glaucomas by their very nature encourage non-compliance. It is the treatment which produces adverse effects, engenders inconvenience and costs, and diminishes quality of life. Instructing the patient in techniques to reduce the rate of systemic absorption of any topical ophthalmic drug, significantly widens its safety margin. Ideally all patients instilling eye drops of any sort should be shown how to perform this simple manoeuvre (see Fig. 1).

The number of new drugs which reduce intra-ocular pressure improves efficacy and safety margins, but even more importantly, allows us a greater choice for each individual patient. To exercise that choice meaningfully, we need the evidence of likely strengths and weaknesses of each of these medications, and how they interact with one another (Table 2) and with other drugs being used for concomitant disease.

Since latanoprost was introduced, it has steadily displaced the non-selective beta blockers as first-line therapy. The availability now of travoprost, and soon of bimatoprost, extends the number of patients who have a good chance of responding well to one of these drugs. Their once-daily instillation and wide safety margin should improve compliance. Brimonidine is usually a second-line drug, but may be used instead of beta blockers as first choice, particularly in the presence of pulmonary and/or cardiovascular disease. Topical carbonic anhydrase inhibitors are often introduced as third-line drugs. All can be used adjunctively.

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FURTHER READING

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 151)

7. Alpha$_2$ agonists cause a greater reduction in intra-ocular pressure than lipid-receptor agonists.
8. Latanoprost should not be used in combination with a topical beta blocker in the treatment of glaucoma.

Patient support organisation

Glaucoma Australia

Glaucoma Australia aims to minimise sight disability from glaucoma by:

- increasing community awareness and understanding of glaucoma and the need for regular eye checks
- supporting glaucoma patients and their families particularly with information
- funding glaucoma research.

Glaucoma Australia disseminates a newsletter and information about new developments in glaucoma medicines, diagnostic equipment and therapeutic procedures. Glaucoma Australia Support Groups in most States provide, through guest speakers, education and information on glaucoma, and members offer mutual support to glaucoma sufferers, their families and friends.

Contacts

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For details on glaucoma meetings in South Australia, Tasmania and Victoria contact the Glaucoma Australia Melbourne office, phone (03) 9404 2974.

Australian Medicines Handbook, 4th edition 2003

The fourth edition of the Australian Medicines Handbook, due for release in December 2002, has been comprehensively updated to include new drugs and new evidence. Information on vaccines has been substantially expanded in this edition and a new section on acute coronary syndromes included. It is available as a book, CD-ROM, CDs for multiple users, and on-line via Health Communication Network.

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$99 student price – book only (with student identification)

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New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial 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.

Caspofungin acetate

Cancidas (Merck Sharp and Dohme)

vials containing 50 mg or 70 mg as lyophilised powder

Approved indication: aspergillosis

Australian Medicines Handbook section 5.2

Immunosuppressed patients, including patients treated with large doses of corticosteroids, are at risk of invasive aspergillosis. They are usually treated with amphotericin. If this does not work then caspofungin can be considered.

Caspofungin is from a new class of drugs which inhibit the synthesis of the glucan component of the fungal cell wall. Although caspofungin is active against species of candida it is only approved for aspergillosis as this was the indication that was granted fast-track approval by the Food and Drug Administration in the USA.

The drug is reconstituted in 0.9% saline or water for injection then given by slow intravenous infusion. A loading dose is given on the first day. On the following days a smaller single dose is given by infusion until the patient improves. Caspofungin is slowly metabolised with only small amounts appearing unchanged in the urine. The dose should be reduced in patients with hepatic impairment.

As caspofungin is reserved for patients who are refractory to or intolerant of other antifungal drugs, its approval has been based on only 58 patients with invasive aspergillosis. Most of the patients had a haematological malignancy or had received a transplant. There was a favourable response in 34% of the people who were refractory to other drugs. Responses were lower in patients with extrapulmonary aspergillosis.

Common adverse reactions in the study included nausea, vomiting, fever and flushing. Some patients developed complications such as phlebitis at the site of infusion. Caspofungin can decrease haemoglobin and increase liver enzyme concentrations. It should not be prescribed with cyclosporin because of the risk of altered hepatic function.

Although only a minority of patients will respond, this is a better outcome than could be expected for patients who are refractory to other drugs. It is unknown if resistance to caspofungin will develop.

Drospirenone/ethinyloestradiol

Yasmin (Schering)

3 mg drospirenone/30 microgram ethinyloestradiol 28 tablets (21 active tablets packaged with 7 placebo tablets)

Approved indication: contraception

Australian Medicines Handbook section 17.1.3

Drospirenone is a new progestogen. It has actions which are similar to those of progesterone.

A fixed combination of drospirenone and ethinyloestradiol is contraceptive. It has been studied in several open trials including a comparison with the combination of ethinyloestradiol 30 microgram and desogestrel 150 microgram (Marvelon). A total of 627 women took one of the pills for 26 cycles. There were three pregnancies with each drug. The incidence of breakthrough bleeding and dysmenorrhea was the same for both pills. Approximately 21% of women will have spotting during the first six cycles of treatment with drospirenone/ethinyloestradiol. Adverse events prompted 11% of the women to withdraw from the study.[1]

The contraindications and precautions for the combination resemble those of other combined pills. Common adverse events include headache, breast pain and nausea.

Drospirenone has been claimed to have antiandrogenic and antimineralocorticoid properties, but the clinical significance of these effects is uncertain. In the comparative study women taking the pill containing drospirenone did not put on as much weight. After two years of treatment mean weight gain was 0.4 kg compared to 0.98 kg with the desogestrel-containing pill. There was no significant difference in the incidence of premenstrual symptoms.[1]

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Drotrecogin alfa

Xigris (Eli Lilly)

5 mg and 20 mg vials

Approved indication: severe sepsis

Australian Medicines Handbook section 7

Protein C is involved in the inactivation of the coagulation cascade. The activated form of protein C has an antithrombotic effect and a deficiency of protein C can lead to thrombosis (see 'Investigations for thrombotic tendencies' Aust Prescr 1999;22:63-6).

In serious infections inflammatory cytokines can trigger coagulation, so activated protein C has an important role in modulating the procoagulant effect of inflammation. Patients with severe infections may be unable to activate protein C and those with low concentrations of protein C have a poor

prognosis. Trials have therefore investigated whether adding an infusion of recombinant activated protein C (drotrecogin) to the treatment of these seriously ill patients will improve their outcomes.

A multinational double-blind trial enrolled 1690 patients with severe sepsis causing dysfunction of at least one organ system. The 850 patients given drotrecogin were compared with 840 patients who received an infusion of saline for 96 hours. One month after the infusion 25% of the patients given drotrecogin were dead. This outcome was significantly better than for the placebo group as 31% of those patients died.[1]

The danger of giving a recombinant anticoagulant is bleeding. One in four patients given drotrecogin had some bleeding and 3.5% had a serious haemorrhage. Two patients died of intracranial haemorrhage during the infusion.[1] Drotrecogin is contraindicated in patients with a recent history of brain or spinal surgery, head trauma or haemorrhagic stroke. Patients with a bleeding tendency or peptic ulceration are particularly at risk of serious haemorrhage.

There is no antidote to drotrecogin, but as the half-life of endogenous activated protein C is relatively short, stopping the infusion will reduce the concentration within a few hours. In most patients the drug is undetectable two hours after the end of the infusion.

The clinical trialists concluded that one life would be saved for every 16 patients treated with drotrecogin. However, the patients have to be carefully selected to achieve this benefit. Many patients with a potential risk of bleeding were excluded, for example, patients who had taken warfarin or more than 650 mg of aspirin. Drotrecogin is likely to be expensive.

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Epoprostenol sodium

Flolan (GlaxoSmithKline)

vials containing 500 microgram as freeze-dried powder

Approved indication: primary pulmonary hypertension

Australian Medicines Handbook section 7.1

Primary pulmonary hypertension is a serious, but rare, condition. A rise in pulmonary artery pressure leads to right ventricular failure and death. The median survival time is less than three years, so patients may die while waiting for a transplant.

Treatment regimens include anticoagulants and the use of vasodilators to reduce pulmonary vascular resistance. Epoprostenol (formerly known as prostacyclin or prostaglandin I_2) is a vasodilator which also inhibits platelet aggregation.

In an eight-week randomised trial, 11 patients with primary pulmonary hypertension were given a continuous infusion of epoprostenol. Compared with 12 patients who received conventional therapy, the infusion group had reductions in pulmonary artery pressure and total pulmonary resistance. Both groups were able to walk further after treatment.[1]

All the patients who completed the study were able to continue treatment with epoprostenol in an uncontrolled trial. This found that the survival of patients with severe symptoms (New York Heart Association class III or IV) increased. Their three-year survival rate was 63% compared with 41% in a group of historical controls.[2]

Improved survival was also seen in a prospective study of 81 patients with class III or IV heart failure. All 41 of the patients given epoprostenol survived, but eight of the 40 people in the control group died during the 12-week study.[3]

Epoprostenol is too unstable to be given orally. Its intravenous half-life is less than six minutes so it has to be given by continuous infusion. In the clinical trials each patient used a portable infusion pump connected to a central venous catheter. The infusion should not be stopped suddenly as the patient can deteriorate within minutes. Adjustments to the infusion rate must be done under observation so that heart rate and blood pressure can be monitored for several hours.

As epoprostenol is a vasodilator its acute adverse effects include hypotension, flushing and headache. Other common adverse effects reported in the clinical trials include tachycardia, jaw pain, myalgia, nausea and diarrhoea.

The indwelling catheter is a risk for infection and more than 20% of patients may develop local infections. In the long-term trial the drug delivery system was implicated in half the deaths.[2] Patients must therefore be taught how to prepare the drug and how to care for their catheter to minimise the risk of sepsis.

Epoprostenol may have an effect on coagulation, but as the patients are also usually taking anticoagulants they should already be being routinely monitored for signs of bleeding. The clearance of digoxin is temporarily reduced by epoprostenol.

Although treatment with epoprostenol has risks, it appears to improve survival and quality of life.[3] Its haemodynamic effects may delay the need for transplant surgery and improve the outcomes for people who need to have surgery. Epoprostenol is also being studied in patients with other causes of pulmonary hypertension, such as scleroderma.

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3. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334:296-301.

Gadoteric acid

Dotarem (Aspen Pharmacare Australia)

0.5 mmol/mL in 10 mL vials

Approved indication: magnetic resonance imaging

Gadolinium-containing products can be used to enhance the contrast in magnetic resonance imaging (MRI). Gadoteric

acid is inert, but has paramagnetic properties. It can be used in whole body imaging and for brain imaging if the blood-brain barrier is abnormal.

Most of the gadoteric acid is excreted unchanged in the urine within 24 hours. There are no data on giving the product to patients with renal failure.

After intravenous injection of gadoteric acid the most common adverse reactions are headache, paraesthesia and nausea.

In the absence of studies large enough to detect significant differences, it is unknown if gadoteric acid has any advantages over similar contrast agents.

Olopatadine hydrochloride

Patanol (Alcon Laboratories)

1 mg/mL eye drops in 5 mL dispensers

Approved indication: seasonal allergic conjunctivitis

Australian Medicines Handbook section 11.3.2

Topical antihistamines are useful in the treatment of allergic conjunctivitis, but until recently levocabastine has been the only single drug available in Australia. Prescribers now have the option of using olopatadine, an H_1 receptor antagonist which also inhibits the release of histamine from mast cells.

Patients instil one or two drops of olopatadine twice a day. Very little of the drug enters the circulation and the quantity that is absorbed is largely eliminated unchanged in the urine.

Olopatadine has been compared with other treatments for allergic conjunctivitis, but many of these alternatives are not available as ophthalmic formulations in Australia. In studies lasting a few weeks olopatadine has compared favourably with drops of azelastine, nedocromil, ketotifen and ketorolac. Some studies have found that patients get more relief with loratadine and olopatadine than with loratadine tablets alone. Olopatadine may help patients whose main complaint is itchy eyes.

Adverse reactions to olopatadine drops include dry eyes, blurred vision, burning and stinging. Some patients may complain of altered taste.

To determine the role of olopatadine in Australian practice will require comparative studies with levocabastine, although the drugs may compete on price. If olopatadine is prescribed, treatment should not exceed 14 weeks.

Pegfilgrastim (pegylated filgrastim)

Neulasta (Amgen)

syringes containing 6 mg/0.6 mL

Approved indication: neutropenia

Australian Medicines Handbook section 14.2.1

Granulocyte colony stimulating factor (G-CSF) promotes the production of neutrophils. Recombinant forms of G-CSF (filgrastim, lenograstim) can be used to treat neutropenia and are useful for patients receiving aggressive chemotherapy (see 'Granulocyte colony stimulating factor (G-CSF)' Aust Prescr 1994;17:96-9).

Recombinant G-CSF has to be given as a daily injection or infusion until the patient recovers. The half-life of filgrastim is approximately three hours, however the addition of a polyethylene glycol molecule extends this to 15–80 hours. This enables patients to be treated with only one subcutaneous dose in each cycle of chemotherapy.

The prolonged half-life of pegylated filgrastim (pegfilgrastim) is brought about by reduced renal clearance. As pegfilgrastim clearance also involves it binding to receptors on neutrophils, clearance will increase as the patient recovers from neutropenia.

A single dose of pegfilgrastim has been compared with daily filgrastim in 310 patients receiving chemotherapy for breast cancer. There were no significant differences in the duration and severity of the neutropenia. Febrile neutropenia developed in 9% of the patients given pegfilgrastim and 18% of those given filgrastim.[1]

The adverse effects of pegfilgrastim are similar to those of filgrastim. More than one in four patients will develop bone pain and this can be severe enough for some patients to need opioid analgesia. Serious adverse effects of filgrastim such as splenic rupture, adult respiratory distress syndrome and anaphylaxis have not yet been reported with pegfilgrastim.

Pegfilgrastim will probably not be significantly cheaper than filgrastim, but its less frequent administration makes it more convenient to use.

REFERENCE

1. Holmes FA, O'Shaughnessy JA, Vukelja S, Jones SE, Shogan J, Savin M, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 2002;20:727-31.

Tenofovir disoproxil fumarate

Viread (Gilead Sciences)

300 mg tablets

Approved indication: HIV infection

Australian Medicines Handbook section 5.3

Patients with HIV are now treated with combinations of antiviral drugs (see 'New approaches in the treatment of HIV infection' Aust Prescr 1998;21:44–6). The combination each patient uses may need to be changed when resistance develops. There are no drugs which will eliminate multiresistant HIV, but tenofovir can be added to the patient's usual regimen.

Tenofovir is an analogue of adenosine monophosphate. By competing with the usual substrate of HIV reverse transcriptase it inhibits the enzyme. This stops the conversion of viral RNA into DNA.

Early trials showed that tenofovir could reduce plasma concentrations of viral RNA. It was therefore tried in patients who had evidence of ongoing viral replication despite antiretroviral therapy. In a dose-ranging study tenofovir or a placebo was added to the combination therapy of 186 patients. After 24 weeks, 19% of the patients taking tenofovir had less than 400 viral copies/mL and 11% had less than 50 viral

copies/mL. In the placebo group only 7% of patients achieved less than 400 viral copies/mL.

A larger trial added 300 mg tenofovir to the treatment of 368 patients while another 182 patients had a placebo added. After 24 weeks 40% of the patients taking tenofovir and 11% of the patients taking placebo had less than 400 viral copies/mL. Only 1% of the placebo group had less than 50 copies/mL compared with 19% of the tenofovir group.

As tenofovir is not well absorbed the tablets contain tenofovir disoproxil fumarate. This compound is a prodrug which is rapidly converted in the liver and plasma. It should be taken with food as this increases bioavailability. Most of a dose is excreted in the urine as tenofovir. Unlike some antiretroviral drugs, tenofovir does not inhibit cytochrome P450, but it does compete with other drugs excreted by renal tubular secretion. These competing drugs include ganciclovir, valaciclovir and aciclovir. Tenofovir can increase the concentrations of didanosine by more than 40%, but the mechanism is unknown.

As some renal toxicity (e.g. phosphaturia) occurred in animal studies, kidney function should be monitored. These studies also reported osteomalacia, but the significance of this finding for patients is not yet known. Most of the adverse effects of tenofovir are gastrointestinal (nausea, vomiting, flatulence and diarrhoea).

There are no long-term safety data for tenofovir and its efficacy is based on surrogate end-points. Although there has been little viral resistance to tenofovir so far, the benefits of tenofovir are still uncertain. In the dose-ranging study the effect of tenofovir on CD4 lymphocytes was not significantly different from that of placebo.

Valganciclovir

Valcyte (Roche)

450 mg film-coated tablets

Approved indication: cytomegalovirus retinitis

Australian Medicines Handbook section 5.3.1

Immunosuppressed patients, particularly those with AIDS, are at risk of cytomegalovirus infection. This can cause a retinitis which may result in blindness. Patients can be treated with ganciclovir, but, as its oral bioavailability is low, treatment has to begin with two or three weeks of intravenous therapy. Valganciclovir is a prodrug of ganciclovir which allows induction therapy to be given orally.

The bioavailability of valganciclovir is approximately 60%, but this can be increased by taking the drug with food. As valganciclovir is converted to ganciclovir in the gut wall and liver, very little reaches the systemic circulation. Ganciclovir is mainly excreted in the urine, so the dose of valganciclovir should be reduced in patients with renal impairment.

A randomised trial studied the progression of newly diagnosed cytomegalovirus retinitis after four weeks of treatment. Seventy patients were treated with intravenous then oral ganciclovir and 71 patients took oral valganciclovir. The retinitis progressed in approximately 10% of each group. After four weeks all the patients took valganciclovir for maintenance. The retinitis progressed after a median time of 125 days in the patients induced with ganciclovir and 160 days in the valganciclovir group.[1]

As ganciclovir has many adverse effects it is not surprising that there are frequent adverse reactions in patients given valganciclovir. Diarrhoea, nausea and vomiting are common. As neutropenia occurs in 27% of patients and anaemia in 26%, frequent blood counts are indicated. Taking too much valganciclovir can cause fatal bone marrow suppression. It is therefore vital to remember that valganciclovir tablets should not be substituted, one for one, for oral ganciclovir capsules.

Patients with cytomegalovirus retinitis may prefer to begin their treatment with oral rather than intravenous therapy. As well as the convenience, valganciclovir avoids the morbidity associated with giving intravenous ganciclovir. However, the available information does not say if patients can be induced with valganciclovir then switched to oral ganciclovir for maintenance therapy.

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NEW FORMULATIONS

Meningococcal C C-CRM197 conjugate vaccine

Menjugate (CSL)

0.5 mL vials

Meningococcal C polysaccharide conjugate vaccine

NeisVac-C (Baxter)

0.5 mL pre-filled syringes

Sirolimus

Rapamune (Wyeth)

1 mg tablets

NEW STRENGTHS

Efavirenz

Stocrin (Merck Sharp & Dohme)

600 mg tablets

Ipratropium bromide

DBL Ipratropium (Mayne Pharma)

500 microgram/mL solution for inhalation

Testosterone

Androderm (Mayne Pharma)

24.3 mg transdermal patch (delivers 5 mg testosterone/day)

NEW COMBINATION

Eprosartan mesylate/hydrochlorothiazide

Teveten Plus (Solvay)

tablets containing 600 mg eprosartan mesylate/12.5 mg hydrochlorothiazide

NEW PROPRIETARY BRANDS

Alprazolam

Alprax (Arrow)

0.25 mg, 0.5 mg, 1 mg and 2 mg tablets

Benztropine mesylate

Benztrop (Pharmalab)

2 mg tablets

Cephalexin

Cephalexin-BC (Biochemie)

125 mg/5 mL powder for oral suspension

Doxycycline

Doxy-50 Acne Pack (Douglas)

50 mg tablets

Epirubicin hydrochloride

Epirubicin hydrochloride injection (Mayne Pharma)

2 mg/mL solution in 5 mL, 10 mL and 25 mL vials

Gabapentin

Pendine (Alphapharm)

100 mg, 300 mg and 400 mg capsules, 800 mg tablets

Methylphenidate

Douglas-Methylphenidate (Douglas)

10 mg tablets

Mirtazapine

Mirtazon (Arrow)

30 mg tablets

Norfloxacin

Roxin (Arrow)

400 mg tablets

Tramadol hydrochloride

Zydol (Arrow)

50 mg capsules

Answers to self-test questions

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

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