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EDITORIAL

Can we afford intensive management of diabetes?

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Index words: drug utilisation, general practice.

(Aust Prescr 2002;25:102–3)

The Commonwealth budget for 2001–02 included financial incentives for general practitioners to provide systematic care to their patients with diabetes. This initiative is likely to increase the number of consultations with general practitioners, specialists and allied health professionals, and the number of drugs used and tests ordered. The annual cost to the Pharmaceutical Benefits Scheme (PBS) and the Medicare Benefits Scheme of treating patients with diabetes will increase. This expenditure will be in addition to the funds allocated through the budget initiative. Furthermore, the number of patients being treated will continue to increase as the prevalence rises and we become better at detecting previously unrecognised cases. In Australia, in 2000, 770 000 people had diabetes. The direct annual healthcare costs of diabetes in 1995 were $1.4 billion[1] (approximately $1800 per patient).

With both the number of cases and the costs of care increasing, there will be increased pressure in the health system and on individual general practitioners to provide more intensive care to more diabetic patients. What is not clear is how this change in competing priorities for limited resources will unfold. For example, will there be more patients on waiting lists for specialists and allied health services, will other patients be displaced, or will more funds be put into these areas?

In this issue...

Medical advances will continue to increase expenditure on health care, but will we be able to afford 'best practice'? Brita Pekarsky and Ben Ewald say that the intensive treatment of diabetes may require the diversion of resources from other areas. Should we therefore limit the funding for Robyn Guymer's treatment of macular degeneration, or Stephen Clarke and Laurent Rivory's chemotherapy for colorectal cancer?

Information about how the funding for drugs is decided is currently secret. However, Lloyd Sansom is hoping to increase the transparency of the decision-making process of the Pharmaceutical Benefits Advisory Committee.

Transparency is also needed when informing patients about the risks of treatment. In the first of a series of articles on risk John McPhee focuses on the legal view of risk.

Some idea of the costs of treating a patient with diabetes can be gleaned from the Australian Co-ordinated Care Trials (1997–2000). These trials included a total of 1654 patients with diabetes recorded as the primary diagnosis. Although these patients represented 15% of the intervention group there was no analysis of the effect of co-ordinated care on their health. Using the data from 10 of these trials, the annual costs per patient for Medicare and PBS services varied across trials from $1900 to $3200.[2] These costs are indicative of those associated with best practice care for older patients with diabetes. More intensive monitoring has significant cost implications, as it will often lead to more intensive treatment of blood glucose, lipids and blood pressure.

The National Diabetes Strategy states that the UK Prospective Diabetes Study (UKPDS) provides evidence that intensive treatment significantly improves clinical outcomes and reduces diabetes-related complications. However, UKPDS showed that the benefits of intensive treatment of blood pressure are at least as great as the benefits of intensive treatment of blood glucose. Approximately six patients need to be treated intensively for blood pressure over 10 years to prevent one patient developing any complication, and 15 need treatment to prevent one diabetes-related death.[3] In contrast, only one case of microvascular disease (mostly retinopathy) was prevented for every 196 patients treated with intensive glucose control for 10 years. Reductions in macrovascular complications or death did not reach statistical significance.[4]

Increased intensive management of diabetes will increase the workload of general practice in differing ways across the country. In a region where there is a high ratio of general practitioners to patients, the additional work may be easily absorbed. However, in an area where there is a low ratio of general practitioners to patients, the increased demands will only be accommodated by displacement of other care provided by the general practitioner, or diversion of this workload to other staff. If a general practitioner sees fewer patients with coughs and colds, this may in fact be a desirable outcome, however if it is at the expense of other important services then any health gain in diabetes may be offset by losses in other areas.

There are opportunities to reduce both the impact on the general practitioner's workload and the costs to the practice of providing systematic care. These include using diabetes educators and practice nurses, and better information

management and decision support software. The budget initiative has the potential to improve the flexibility of funding, allowing practices greater scope in deciding how diabetes care is provided.

The additional costs of more intensive monitoring may be justified by future savings from a reduced need for hospitalisations to treat the complications of diabetes. The UKPDS included cost-effectiveness analyses for intensive blood glucose and blood pressure management. In both cases, more intensive management was found to be cost saving in the trial setting. It was expected to have additional costs, but still to be cost-effective in a community setting.[5,6] Whether the additional costs of more intensive management for a number of conditions would be considered to be cost-effective is unclear. The pharmaceutical and diagnostic test costs of each condition managed intensively are clearly additive, but the health benefits may not be. Furthermore, the UK results may not be generalisable to Australia.

The Australian example most frequently cited in the co-ordinated care trials was the patient who could not access cheap podiatry services, but then required an expensive hospital admission for the treatment of 'diabetic foot'.[2] The fund-holding model in the trials was intended to provide funding for the additional podiatry services which would be offset by the savings from reduced hospitalisation for complications. The evidence of either reduced hospital admissions or the subsequent savings was not apparent from the trials, partly because of their short duration and partly because improved care was more expensive. Despite up to 60% of all patients in some trials having diabetes, any impact on their health within the two-year period was not sufficient to generate the intended savings.

The only certain and immediate consequence of more intensive management of diabetes is increased pressure on the resources of both general practitioners and the broader healthcare system. Any health benefits for patients may not be for some years. General practitioners may be consistently referring patients to podiatrists, diabetes educators and ophthalmologists, but are these services available in all regions to low income patients? Will preventive advice on lifestyle changes be provided to patients at risk? Will other patients with other needs find themselves less able to access care? If there are insufficient resources to provide intensive management to all patients with diabetes, there will be some patients who will miss out on some or all aspects of this care. It may be that these are the very patients who would benefit most from improved management, better access to allied health services and preventive advice.

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Conflict of interest: none declared

Transparency and the Pharmaceutical Benefits Advisory Committee

Professor Emeritus Lloyd Sansom AO, University of South Australia, Adelaide, and Chair, Pharmaceutical Benefits Advisory Committee

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

Recent debate about the sustainability of the Pharmaceutical Benefits Scheme (PBS) has again raised the issue of transparency of the decision-making processes of the Pharmaceutical Benefits Advisory Committee (PBAC). The excellent editorial by Professor Eadie entitled 'The secrecy of drug regulatory information' widens the debate about the release of information about drugs into the public domain.[1]

There is no question that the public has a right to know the basis on which decisions are made for the approval or rejection of a drug for marketing and subsidy. In order for those decisions to be able to be debated and discussed, full disclosure of information at the time the decisions are made is needed. Professor Eadie raises a number of critical issues which may be seen by some as barriers to such action. However, they should not be seen as insurmountable, but simply as issues which need to be addressed in the development of a strategy towards the timely disclosure of relevant information.

The PBAC is committed to the release of information regarding its decisions. This includes the reasons for both positive and negative recommendations and in addition the reasons why a

drug has been recommended as a restricted or authority required benefit. It has been suggested that prescribing outside of subsidy-approved indications (i.e. leakage) is a major cause of the cost increases in the PBS. While such prescribing certainly does occur, the PBAC has never been in a position, at the time that a drug is approved for subsidy, to disclose the evidence on which decisions to include such restrictions were made or to be able to place the use of the drug in an appropriate clinical and cost-effective context. The PBAC is hopeful it will be able to initiate these reforms in the near future. However, as Professor Eadie clearly points out, there are matters of 'commercial-in-confidence' which must be acknowledged and attended to, and discussion with the pharmaceutical industry is essential to address their legitimate concerns on this and other issues. Notwithstanding these concerns the overriding consideration must be the right of doctors and the public to have access to information. It is the responsibility of regulatory authorities to provide it in a manner appropriate to each stakeholder group. There is no doubt that disclosure of information will make the decision makers more accountable, but that is how it should be in a transparent system.

The saying 'Don't tell me why it cannot be done but how it can be done' is appropriate in the context of this issue. Professor Eadie's comments are an excellent starting point.

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Conflict of interest: none declared

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Insulins in 2002

Editor, – Regarding insulin and metformin schedules – indeed one size does not fit all. Dr Pat Phillips' excellent update 'Insulins in 2002' (Aust Prescr 2002;25:29–31) nicely highlights inter-individual insulin requirements (e.g. a predicted daily range of 39 to 78 units of insulin for a 78 kg man).

When metformin is factored into the equation, the considerations become even more complex, as when for example a patient has mild diabetes-related renal dysfunction and/or chronic low-grade hepatitis B, both of which are relative contraindications to the use of metformin.

I am also currently looking after a man in his 70s who is mildly overweight, with borderline urea and creatinine, chronic hepatitis B with a slightly raised GGT but normal ALT concentration. His insulin requirements exceed 100 units per day, but metformin is being withheld out of concern for potential adverse effects.

In view of the potential value of metformin with insulin, would Dr Phillips care to comment further on the nuances of this interesting combination of drugs?

Ross Philpot

Consultant Physician

Adelaide

Dr P. Phillips, the author of the article, comments:

Dr Philpot correctly points out the advantages of continuing metformin when starting insulin in patients with type 2 diabetes. Metformin has actions independent of insulin secretion (by reducing gluconeogenesis and insulin resistance) and it has benefits in controlling weight.

However, metformin can cause potentially life-threatening lactic acidosis in patients at risk of metformin accumulation (renal impairment), hypoxic challenges (respiratory or cardiac failure) or reduced lactate clearance (impaired liver function).

The first patient described by Dr Philpot had 'mild diabetes-related renal dysfunction and/or chronic low-grade hepatitis B'. If the patient had one relative contraindication (moderate renal impairment, GFR 30–60 mL/minute) our guidelines[1] would recommend that low doses of metformin are appropriate (500–1000 mg/day). The situation should be reviewed regularly and metformin should be stopped if the patient were to develop an absolute contraindication.

In the second case it appears that the patient might have moderate renal impairment (GFR 30–60 mL/minute) but no functional liver impairment. A metformin dose of 500–1000 mg/day would seem appropriate and might reduce the necessary insulin dose and improve glycaemic control.

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The evidence-relevance gap

Editor, – I was most impressed by the article 'The evidence-relevance gap – the example of hormone replacement therapy' (Aust Prescr 2002;25:60–2) in which Dr Neeskens gives a sensible and pragmatic approach to dealing with complex information thereby allowing the patient to put it in context for **her** situation. Too often we are confronted with population studies, but what do they mean to the individual person?

There are two other situations, one involving vast expense and the other some serious morbidity, which require similar scrutiny. The first involves the escalating use of 'statins' in the community at a cost which may result in limiting the ability of the Pharmaceutical Benefits Scheme to afford new drugs. Should we **really** be trying to reduce the cholesterol level to some magic number in every adult Australian, even those who are asymptomatic and without a relevant family history? And if so, for how long do we continue this therapy?

I frequently see patients in the 80–90 year-old age group presenting for surgery still religiously taking their prescribed statin. Is this necessary?

Secondly, the prescribing of warfarin with its dangerously low therapeutic index to prevent some perceived morbidity too often results in genuine catastrophes in the form of gastrointestinal or intracranial haemorrhage. Again, elderly patients present as emergencies requiring scarce blood products to reverse the coagulation defect before surgery can be performed. For how long do we keep prescribing this toxic drug? Presumably once patients have these major morbidities they are not started on warfarin again, so could it not be ceased before the disaster actually occurs?

Brian Duffy
Staff Specialist Anaesthetist
Queen Elizabeth Hospital
Woodville, SA

Editor, – Dr Neeskens is to be congratulated for his article 'The evidence-relevance gap – the example of hormone replacement therapy' (Aust Prescr 2002;25:60–2). I hope it will be a forerunner of articles testing the proposition that years of taking pharmaceuticals by basically well (i.e. symptomless people) is a good thing.

I know of no medicine that works which can be taken with impunity by everyone. We are all that little bit different.

The majority of trials are undertaken on people who have a problem (I include Framingham: it is surely not healthy to be under constant medical supervision). They are irrelevant to the majority.

B.W. Griffiths
Surgeon
Crescent Head, NSW

Editor's note:

Dr Neeskens is currently preparing another article for *Australian Prescriber*.

Dental patients receiving warfarin therapy

Editor, – We refer to 'Dental notes: Managing dental patients receiving warfarin therapy' (Aust Prescr 2002;25:69). This commentary is unfortunate because it presents the historical approach to managing patients on warfarin therapy and does not reflect current best practice.

The key issue is the risk:benefit analysis of ceasing warfarin and risking thromboembolism, versus reducing it and risking local wound bleeding. Any logical analysis clearly comes down on the side that if warfarin is indicated and has been appropriately prescribed, then one should leave it alone. The real and potential risks such as stroke or myocardial infarction are clearly catastrophic events, whereas at worst local wound bleeding is messy and inconvenient.

There is an extensive body of research which shows that the appropriate management of patients on warfarin who require dentoalveolar surgery is as follows:

- **preoperative** – check INR the day before the procedure to ensure it is within the therapeutic range for the patient. If greater than 4.0, advise the patient's physician and delay surgery until the INR is within the therapeutic range.
- **intraoperative** – the use of a local anaesthetic combined with a vasoconstrictor, plus a controlled, minimally traumatic surgical technique and local haemostatic methods are recommended. This includes irrigating the operative field with a 4.8% tranexamic acid solution. The sockets and mucoperiosteal flaps should then be sutured and oxidised cellulose gauze placed in the sockets.
- **postoperative** – the patients should be given a 4.8% tranexamic acid mouthwash with instructions to rinse with 10 mL of the solution for two minutes four times a day for 2–5 days.

There are some issues of supply, although most major hospitals on appropriate request from the patient's pharmacy, are happy to supply tranexamic acid. The pharmacy of the Royal Adelaide Hospital is certainly willing and able to provide appropriate advice on this.

It is appropriate for the patient's dentist and the treating general medical practitioner to review the patient's anticoagulation therapy. In our studies, we found over one-third of patients on warfarin either no longer met the clinical indications for this therapy, or had an inappropriate dosage and thus either a sub-therapeutic INR or an INR above 4.

Alastair N. Goss
Professor
and
Glen Carter
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FURTHER READING

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Professor Woods and Professor Savage, authors of 'Managing dental patients receiving warfarin therapy', comment:

We thank Professor Goss and Dr Carter for drawing attention to the management of minor oral surgery performed for patients taking warfarin. Certainly the procedure we recommend is based on the 'historical' approach, it is well tested, safe and effective. In this respect our recommendations are consistent with recommendations of Professor Goss and Dr Carter. Essentially, dental management of patients having warfarin therapy is a matter of co-operation between dentists and the physician managing the patient's coagulation.

Notwithstanding this comment, the use of tranexamic acid as a mouthwash is a promising development. The technique has been tested with a number of favourable reports in the literature. The present position however, for most dentists treating patients taking warfarin, is that they have no ready access to a tranexamic acid mouthwash, there is no proprietary tranexamic mouthwash available.

For the present, the majority of dentists treating patients having warfarin therapy have no ready access to or assistance from a teaching hospital and will in practical terms, have to rely on the 'historic' advice in the Dental Notes.

The heavy drinker in primary care

Editor, – I refer to the article 'The management of the heavy drinker in primary care' (Aust Prescr 2002;25:70–3). This article is excellent in its succinct coverage of alcohol problems in general practice. However, I do feel that there is an underemphasis on the risk of acute thiamine deficiency even in the general practice population.

In our unit we have recently admitted two male patients with signs of Wernicke's encephalopathy. These patients were both in their mid-forties and had no previous history of detoxification for alcohol dependence. Both patients had been transferred from other hospitals where they had been treated for alcohol withdrawal. The first patient had been a postoperative inpatient for five days before his transfer and had been treated for an acute confusional state with symptomatic medications. He improved within an hour of his first intramuscular injection of thiamine.

The second patient presented to a local hospital after having been hit by a car while intoxicated. Once he was medically stable he was transferred to our Drug and Alcohol Unit and was found to have a combination of confusion, ataxia, nystagmus as well as other cerebellar signs. He was so unwell he was transferred back to the local hospital but he recalls 'waking up' in the ambulance after a single 100 mg injection of thiamine.

The point is that this is an extremely serious but easily treatable condition. I would suggest that in Box 2 of Professor Whelan's article the use of thiamine be reiterated and if there is any doubt whatsoever about oral absorption or nutritional status that intramuscular thiamine be given daily for at least three days.

Kevin McNamara
Director
Drug and Alcohol Unit
Palm Beach/Currumbin Hospital
Gold Coast, Qld

Professor Greg Whelan, the author of the article, comments:

Dr McNamara rightly brings to our attention the importance of thiamine given prophylactically in the management of alcohol withdrawal.

The patients described by him are also seen in our hospital's Accident and Emergency service. All patients admitted with a history of heavy alcohol consumption, whether in alcohol withdrawal or not, are given an intravenous 'cocktail' of glucose and multivitamins, including thiamine.

The article in *Australian Prescriber* is aimed at producing guidance for general practitioners who manage patients in primary care, not in hospital. As noted, these patients are given thiamine 100 mg. Our practice is to give this orally unless we are concerned about absorption.

Medicinal mishaps

Editor, – The case reported in 'Medicinal mishaps' (Aust Prescr 2002;25:73) highlights the importance of obtaining an accurate medication history as part of the hospital admission process. Frequently this is 'easier said than done'. Obtaining an accurate medication history is often complex, time consuming and a fallible process. Reasons for this include:

- lack of patient knowledge of their medications
- lists from local doctors and patients that are out of date
- medication labels that are out of date or non specific ('mdu')
- transcription errors on residential care facility transfer letters
- neglecting to ask the patient what they are actually doing with their medications.

All patients should be encouraged to bring their medications to every hospital and clinic visit. Patients should be assisted by their pharmacist, local doctor or family member to maintain a current list if they are unable to remember their treatment themselves.

Glenn Valoppi
Pharmacy Resident
and
Simone Taylor
Senior Clinical Pharmacist
Emergency Medicine
Austin and Repatriation Medical Centre
Heidelberg, Vic.

Discontinuation of naproxen suspension

Editor, – Roche Products recently announced plans to discontinue production of naproxen suspension in Australia.[1] Their letter communicating these plans implies that rofecoxib suspension is a viable alternative. This is irresponsible, for several reasons, and demonstrates a clear lack of consideration of the best interests of children.

First, naproxen suspension is currently the most widely used non-steroidal anti-inflammatory drug (NSAID) in children with chronic arthropathies worldwide.[2] It has a well-established efficacy and safety profile in children. The liquid formulation also has a convenient dosage schedule (twice daily) and is affordable. The only other NSAID with demonstrated efficacy and safety in children currently available in liquid formulation in Australia is ibuprofen. However, its lower effectiveness, need for more frequent dosing and greater cost are disadvantages in chronic therapy. The discontinuation of naproxen suspension will therefore mean that children will be unfairly disadvantaged by having their already limited NSAID options even further restricted.

Second, children's risk of significant gastropathy with NSAID therapy is negligible.[3] There is therefore little rationale for considering a COX-2 inhibitor in the vast majority of children. Evaluable data regarding their safety/efficacy in children is

lacking. The question of whether there is **any** gastrointestinal safety advantage with COX-2 specific inhibitors[4], the emerging safety concerns in adults[5], and the considerably higher cost, mean that rofecoxib suspension cannot be considered a 'viable alternative' to naproxen suspension for children.

It is time to stop treating children as second class therapeutic citizens and time to start paying more serious attention to ensuring that they have fair and equitable access to appropriate medications.

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Dr David Kingston, Medical Director, Roche Products, comments:

The decision to discontinue production of Naprosyn (naproxen) suspension on a global basis was made because of the discontinuation of one of the flavouring agents. This meant extensive reformulation work, stability testing and then registering the new formulation on a worldwide basis. The low use of Naprosyn suspension led to the decision to discontinue production. This left Roche Australia with no source of Naprosyn suspension. We have been trying to interest some local companies in producing naproxen suspension but so far there is no agreement to do so.

We are sorry that it has not been possible to arrange an alternative supply of naproxen suspension but are continuing in our efforts.

Sensitivity and specificity – is your test reliable?

The reliability of a test depends on the sensitivity and specificity. You should ask 'How am I using this test and how sensitive and specific is the test?'

The sensitivity of a test is defined as the proportion of people with disease who have a positive test. A test which is very sensitive will rarely miss people with the disease. It is important to choose a sensitive test if there are serious consequences for missing the disease. Treatable malignancies (*in situ* cancers or Hodgkin's disease) should be found early – thus sensitive tests should be used in the diagnostic work-up.

The specificity of a test is defined as the proportion of people without the disease who have a negative test result. A specific test will have few false positive results – it will rarely misclassify people without the disease as being diseased. If a test is not specific, it may be necessary to order additional tests to confirm a diagnosis.

It is useful for clinicians to know the sensitivity and specificity of common tests to help in deciding which tests to use to 'rule in' or 'rule out' disease. However, predictive values[1] are of more direct clinical usefulness, enabling the clinician to estimate the probability of disease **given** the test result. One problem is that predictive values are prevalence dependent, but the prevalence (likelihood) of disease can be increased by clinical signs, other tests and even clinical 'intuition'.

Finally, clinical signs and judgement should never be ignored in the face of a technological test result. For example, if a suspicious breast lump remains palpable, a negative mammogram should be ignored.[2] In such circumstances, clinical judgement should suggest biopsy, even though the test result was negative. Tests are to be used to assist clinicians, not to rule clinical decision-making.

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EXPERIMENTAL AND CLINICAL PHARMACOLOGY

New drugs for colorectal cancer – mechanisms of action

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SYNOPSIS

Several new drugs have recently been approved for the treatment of advanced colorectal cancer. Raltitrexed is a folate-based inhibitor of thymidylate synthase. Capecitabine is an orally active prodrug of 5-fluorouracil which undergoes some tumour selective activation. Irinotecan is the first registered topoisomerase I poison with activity against this tumour, whereas oxaliplatin is a platinum analogue. The lack of cross-resistance between these drugs has sparked preclinical and clinical studies of a multitude of combination regimens. These regimens may improve the outcomes for patients in the near future.

Index words: oxaliplatin, irinotecan, capecitabine, raltitrexed.

(Aust Prescr 2002;25:108–10)

Introduction

Colorectal cancer has long been considered as moderately resistant to chemotherapy. Previously 5-fluorouracil (5-FU) was the only proven treatment for this indication, but it has been slowly replaced by other drugs. It is hoped these newly the approved regimens will provide the building blocks for the combination chemotherapy of the future.

Anticancer drug mechanisms

Anticancer drugs act by a variety of mechanisms including:

- DNA damage by direct (e.g. alkylating agents), protein-mediated (e.g. topoisomerase poisons) and fraudulent base pathways (e.g. nucleoside analogues)
- interference with synthesis of vital co-factors and DNA/RNA/protein precursors (e.g. antimetabolites, asparaginase)
- interference with other cellular structures and processes (e.g. anti-microtubule drugs such as docetaxel, paclitaxel and Vinca alkaloids)
- inhibition of growth/anti-death signal (e.g. tyrosine kinase inhibitors such as imatinib mesylate, trastuzumab).

These mechanisms induce acute cell death (necrosis), programmed cell death (apoptosis), growth arrest or differentiation. Many anticancer drugs have multiple actions on the cell. For example, 5-FU is activated to 5-fluorodeoxyuridylate (also known as fluorodeoxyuridine monophosphate), which in the presence of a reduced folate co-factor inhibits the enzyme thymidylate synthase. This blocks the production of thymidine phosphate which is required for DNA synthesis. The 5-fluorodeoxyuridylate may also be fraudulently incorporated into DNA causing a form of DNA damage.

Mechanisms of action of new drugs active against colorectal cancer (Table 1)

Raltitrexed

Natural folates are vital co-factors for many cellular enzymes, specifically those that catalyse one carbon transfer reactions. Thymidylate synthase is a critical enzyme in the synthesis of the thymidine nucleotides required for DNA synthesis. This enzyme requires a reduced folate co-factor, 5–10-methylene tetrahydrofolate, to act as a carbon donor for the synthesis of thymidylate from deoxyuridylate. Raltitrexed has been specifically developed as a potent mimic of 5–10-methylene tetrahydrofolate and therefore inhibits thymidylate synthase. Many antifolate drugs are polyglutamated within cells. These polyglutamate forms are retained in the cells and, in the case of raltitrexed, this increases its potency and selectivity against thymidylate synthase.

Capecitabine

5-FU was until recently the only drug used extensively for advanced colorectal cancer in Australia (usually in combination with leucovorin). There is now some evidence to suggest that 5-FU is most active when given by prolonged intravenous infusion. This is not very convenient for patients because it

Table 1

Mechanism of action of drugs for the chemotherapy of colorectal adenocarcinoma

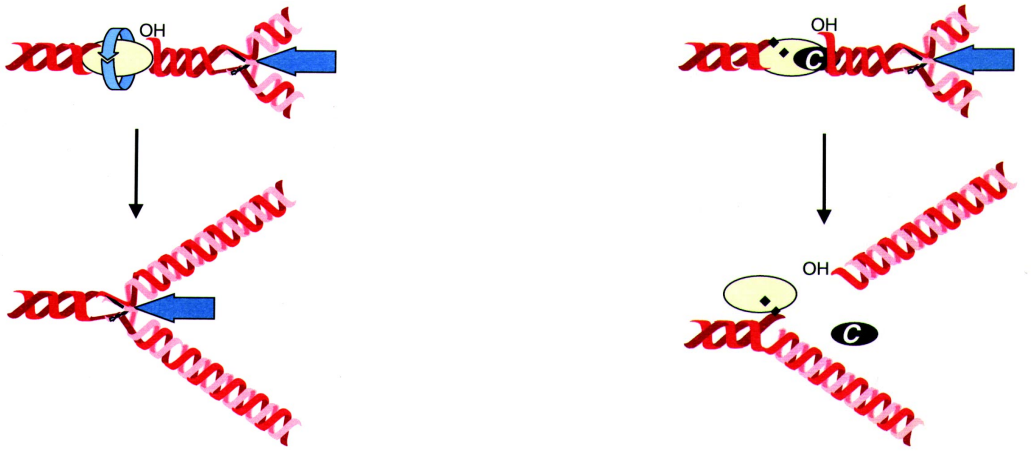
Drug	*Mechanism of action*
5-fluorouracil	Inhibition of thymidylate synthase (potentiated by addition of leucovorin)
	Incorporation of fraudulent bases into DNA and RNA
Raltitrexed	Direct inhibitor of thymidylate synthase
Capecitabine	As for 5-fluorouracil
Irinotecan	Topoisomerase I poison
Oxaliplatin	Bifunctional platinum alkylator of DNA

Fig. 1

Mechanism of action of topoisomerase I poisons

a. Normally, topoisomerase I introduces a nick in the DNA backbone allowing the rotation of one strand around the other. This releases the torsional strain which otherwise accumulates in front of the advancing replication fork (large arrow). The DNA break is extremely transient and is religated almost immediately at the same time that the topoisomerase I releases the other strand.

b. When a drug such as irinotecan is present (black oval with C), it binds to the topoisomerase I-nicked DNA complex. This prevents the religation of the nicked strand and the release of the enzyme. Eventually, the replication fork collides with the complex, causing the formation of a double-strand break.



requires protracted venous access and infusion devices. Oral treatment is not a viable alternative because the absorption of 5-FU from the gastrointestinal tract is low and unpredictable. This problem has led to the development of orally bioavailable 5-FU prodrugs, such as capecitabine.

Oral capecitabine undergoes sequential hydrolysis and deamination reactions in the liver to produce 5'-deoxy-5 fluorouridine. This is converted to 5-FU by thymidine phosphorylase (also known as platelet-derived growth factor). As this enzyme is abundant in tumour tissue there is some tumour specificity in the patient's exposure to 5-FU.

The adverse effects of treatment resemble those of 5-FU when given by protracted infusion. Hand and foot syndrome (plantar-palmar erythroderma) occurs commonly, the mechanism of which is unknown.

Other oral 5-FU prodrugs (e.g. S-1, UFT) have been the subject of extensive clinical trials, particularly in Japan. These are mostly combinations of 5-FU prodrugs with uracil, which is an inhibitor of dihydropyrimidine dehydrogenase, a ubiquitous enzyme that rapidly degrades 5-FU. This results in higher and more sustained concentrations of 5-FU in the tumour tissue. Surprisingly, these drugs do not appear to produce hand and foot syndrome to the same extent as capecitabine.

Irinotecan

Irinotecan is a water-soluble camptothecin analogue. Camptothecin was first isolated in extracts of the Chinese Happy Tree (*Camptotheca acuminata*) in the 1960s, but the mechanism of action and the anticancer potential have only recently been recognised.

Camptothecins function by 'poisoning' a nuclear enzyme, topoisomerase I. Topoisomerase I acts as a 'swivelase' in the cell, relieving topological problems (hence the name) that arise from the torsional strain that is introduced into long strands of DNA during processing (e.g. replication). This enzyme normally introduces a transient nick into one of the two strands of the DNA, which enables strand rotation and relief of the torsional strain. In the presence of camptothecins, the nick is stabilised which is equivalent to a single-strand DNA break (Fig. 1). Collision with a replication fork during DNA replication then leads to the formation of a potentially lethal double-stranded break. These breaks occur at concentrations of camptothecins that are usually much lower than those that inhibit topoisomerase I-mediated DNA relaxation. This is why these drugs are termed poisons and not inhibitors.

The anticancer activity of doxorubicin, mitozantrone, etoposide and amsacrine is partly mediated by a similar action on DNA. These drugs, however, act on topoisomerase II.

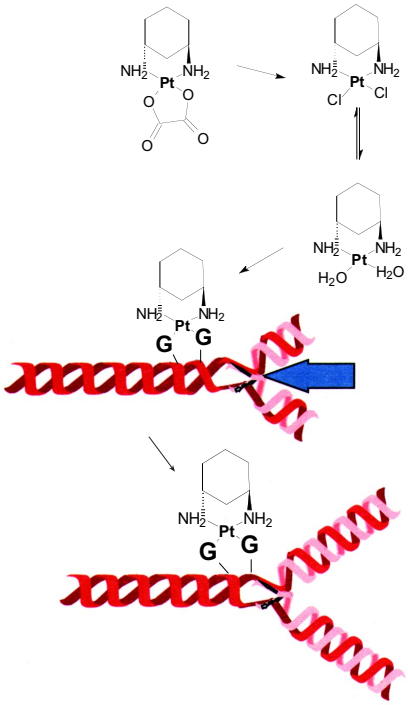
Irinotecan is a prodrug and requires activation to the metabolite SN-38. This metabolite is then conjugated in the liver to an inactive glucuronide by the enzyme UDP glucuronosyl transferase 1A1. The activity of this enzyme is deficient in people with Gilbert's disease. It is relatively common (1 in 5) and those individuals so affected have greatly reduced capacity for conjugation of SN-38 so they have an increased risk of severe toxicity when treated with irinotecan. Although Gilbert's disease is not a specific contraindication for irinotecan, affected patients should be treated with great caution.

Irinotecan is also an inhibitor of acetylcholinesterase and patients may experience an acute onset of cholinergic-like symptoms including lacrimation, sweating, abdominal cramping and diarrhoea during or within minutes of the end of infusion. The acute diarrhoea should not be confused with a delayed diarrhoea which can arise 3–10 days after treatment.

Fig. 2

Interference of oxaliplatin with DNA processing

Oxaliplatin (top left) is activated to a bis-aquated species through a number of reactions. The bis-aquated species then reacts with neighbouring guanine residues either on the same or neighbouring strands of DNA. In the illustrated case, an inter-strand link is depicted (i.e. a bridge is formed between the two strands of DNA). This prevents the strand separation required for DNA processes such as replication, thereby blocking the replication fork (large arrow). It is thought that the bulky di-amino cyclohexane residue of the adduct prevents or slows considerably the DNA repair machinery which otherwise removes such aberrant structures.



Oxaliplatin

Oxaliplatin is a diaminocyclohexane platinum derivative with a broad spectrum of activity which includes colorectal cancer. It undergoes rapid non-enzymatic activation with the displacement of the oxalate ring by two chlorines and subsequent formation of a variety of aquated species. These species react with macromolecules within the cell (Fig. 2). Specifically, the bis-aquated diaminocyclohexane platinum is a bifunctional alkylator capable of reacting with adjacent guanine residues in DNA. This provides either intra- or inter-strand DNA cross-links, which interfere with DNA processing. The lack of cross-resistance with cisplatin in tumour cell models may be due to the retained bulky diaminocyclohexane side chain which projects into the minor groove of the DNA (when intrastrand cross-links are present). This may sterically inhibit the nucleotide excision and mis-match repair machinery that normally removes such adducts.

Treatment with oxaliplatin may lead to a neurotoxicity that is distinct from that caused by cisplatin. There is a transient peripheral neuropathy (paraesthesia and dysaesthesia) of the extremities and perioral regions which can be triggered or aggravated by exposure to cold. New research has suggested that chelation of intracellular calcium by the oxalic acid released during the activation of oxaliplatin may play a role in this unusual adverse effect.

Combinations

The lack of cross-resistance between the thymidylate synthase inhibitors (5-FU, capecitabine, raltitrexed), oxaliplatin and irinotecan means that they could potentially be combined. Indeed, the clinical data gathered so far indicate a definite role for combination regimens in the treatment of advanced colorectal cancer. Oxaliplatin, for example, is only registered for use in combination with 5-FU and leucovorin.

Summary

Recently, several conventional cytotoxic drugs have been registered for use in the management of advanced colorectal cancer. These drugs do not represent a revolution in the treatment of this disease, but they target novel processes (irinotecan), are less prone to deactivation (oxaliplatin), are more selective (raltitrexed) or enable oral therapy (capecitabine). Combining these drugs has additive or synergistic effects in cell culture. These combinations, because of their largely non-overlapping toxicities, are being studied in clinical trials of advanced disease and post-surgical adjuvant treatment.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 123)

1. Capecitabine enables cancer cells to be exposed to 5-fluorouracil without the need for prolonged intravenous infusion.
2. Patients may be more prone to the adverse effects of oxaliplatin in cold weather.

EXPERIMENTAL AND CLINICAL PHARMACOLOGY

New treatments for advanced and metastatic colorectal cancer – clinical applications

Stephen Clarke, Associate Professor, Senior Staff Specialist in Medical Oncology, Central Sydney Area Health Service, Sydney

SYNOPSIS

In the last five years several new drugs have become available for the treatment of patients with advanced colorectal cancer. These drugs include raltitrexed, capecitabine, irinotecan and oxaliplatin. They have resulted in improved tumour response rates compared with older treatment regimens using 5-fluorouracil. Combinations of these drugs provide hope for future palliation of this common cancer.

Index words: raltitrexed, capecitabine, irinotecan, oxaliplatin.

(Aust Prescr 2002;25:111–3)

Introduction

Colorectal cancer affects 1 in 20 Australians with Australia, New Zealand and the United States having the highest incidences of this disease in the world. Approximately 25% of patients will have advanced disease at presentation and, in spite of locally effective surgery, another 25% of patients will relapse postoperatively. Large numbers of patients could therefore benefit from effective palliative treatments.

For a long time chemotherapy was not offered to patients with advanced or metastatic colorectal cancer. This was partly because this cancer is commonest in patients over 60 years old who were thought to be at greater risk of toxicity from chemotherapy, and also because the drugs available were not particularly effective. However, there is now evidence that chemotherapy prolongs survival for patients with advanced colorectal cancer compared to best supportive care. In addition, for patients responding to therapy the increment in survival can be more than 18 months.

Standard chemotherapy

The most commonly used chemotherapy for colorectal cancer has been 5-fluorouracil (5-FU) which has been available since 1957. 5-FU has multiple mechanisms of cytotoxicity including the inhibition of thymidylate synthase. The toxicities and efficacy of this drug vary significantly with the mode of administration. Short intravenous injections (bolus schedules) produce unpredictable adverse effects with mucositis, diarrhoea and leucopenia predominating.

The activity of 5-FU is increased by the co-administration of folinic acid which enhances the inhibition of thymidylate synthase. A bolus schedule of 5-FU and folinic acid given for five days in a row and repeated every 28 days (the Mayo Clinic Schedule) has been the most favoured regimen, because of survival advantages in randomised trials compared to 5-FU alone. In the elderly and infirm patient, this regimen is often altered to a weekly injection for six out of eight weeks because of a lower incidence of severe mucositis. However, this regimen has not been shown to be superior to 5-FU alone.

5-FU may also be administered as an intravenous infusion, of varying duration. This improves response rates and tolerance although there is no difference in survival. Bolus schedules of 5-FU produce antitumour responses in 10–20% of patients treated while infusional regimens achieve response rates of 20–30% (based on a greater than 50% fall in the product of tumour diameters on CT scan). There is a much lower incidence of mucositis and myelosuppression with infusional regimens. The commonest adverse effects are related to redness and peeling of the palms and soles (plantar-palmar erythroderma) and to complications from the central venous catheters required to enable outpatient administration of treatment.

The toxicities of most anticancer treatments are usually maximal 7–14 days after treatment. This is true for both established drugs and the newer anticancer treatments. Patients should be asked to contact their local doctor or oncologist if toxicities occur. Routine monitoring usually consists of a complete assessment of the patient's health, and a full blood count and biochemistry on the day of treatment. Reductions of 20–50% of the initial dose will be made if severe toxicity has occurred in a previous cycle of treatment.

In the last five years a number of new treatments have become available for patients with advanced colorectal cancer. The effectiveness of these drugs needs to be compared with that of 5-FU (Table 1).

Raltitrexed

Raltitrexed is a folate analogue which inhibits thymidylate synthase. It is given as a 15 minute intravenous infusion every three weeks. It is subsidised by the Pharmaceutical Benefits Scheme (PBS) for the treatment of patients with advanced or recurrent colorectal cancer.

Table 1

Summary of phase III trials of new treatments in colorectal cancer

Drug or combination	*Response rate*	*Median survival time compared to 5-FU*	*Impact on overall quality of life compared with 5-FU*
Raltitrexed	15–20%	Equivalent	Equivalent (less mucositis and myelosuppression)
Capecitabine	20–25%	Equivalent	Equivalent (all toxicities less except hand-foot changes)
Irinotecan/5-FU	35–39%	Superior (2–3 months)	Equivalent/better (less myelosuppression/mucositis)
Oxaliplatin/5-FU	51%	Equivalent	Equivalent (more myelosuppression/neuropathy)

The principal toxicities associated with raltitrexed are fatigue, myelosuppression and occasionally severe diarrhoea. The combination of neutropenia and severe diarrhoea may be life-threatening. It should be treated with aggressive resuscitation and intravenous antibiotics active against Gram negative bacteria. Patients at greater risk of severe toxicity in whom dose reduction should be considered include those with impaired renal function, low serum albumin and poor day to day functioning (performance status). However, in such patients the likely benefit from treatment is very low and it may be prudent not to treat these patients with chemotherapy. If a patient experiences the combination of diarrhoea and myelosuppression, even in a mild form, they may experience much worse toxicities with subsequent treatment. Dose reductions may be appropriate in these patients.

In large comparative studies raltitrexed has produced equivalent response and survival rates to bolus schedules of 5-FU and folinic acid.[1] Patients had a lower incidence of myelosuppression and mucositis. However, a more recent randomised study, which compared raltitrexed to two different infusional forms of 5-FU, found increased toxicity and a lower quality of life in patients given raltitrexed. Although overall survival was similar there was an increase in treatment-related deaths (approximately 6% for patients treated with raltitrexed and less than 1% for patients on the infusional arms).[2] These excess deaths are thought to be due to a combination of neutropenia and diarrhoea. While drug-induced deaths have been uncommon in the Australian experience with raltitrexed, these results show that it should be used with care. The future for raltitrexed in colorectal cancer may rest with combinations with other active drugs such as oxaliplatin and irinotecan.

Capecitabine

Capecitabine is an orally administered 5-FU prodrug. Its final enzymatic activation is mediated by thymidine phosphorylase. This enzyme has a higher concentration in tumours than in normal tissues, so it may have a selective action. Capecitabine was developed to mimic continuous infusions of 5-FU so it is taken twice daily. Initial randomised phase II trials of capecitabine compared intermittent (two weeks on and one week off) with continuous therapy, with or without the addition of folinic acid. The treatment with the best therapeutic index was intermittent capecitabine given without folinic acid. This regimen has been used subsequently.

The principal adverse effect of capecitabine is plantar-palmar erythroderma. If this is mild, treatment requires no adjustment or only transient interruption, but more severe cases require a dose reduction. Toxicities such as nausea and vomiting, mucositis and diarrhoea are uncommon. Severe neutropenia occurs in less than 10% of patients treated. Capecitabine may cause mild abnormalities of liver function including an elevation in bilirubin. It may also cause a rapid escalation of INR in patients taking warfarin and some patients may need to be changed to other forms of anticoagulation.

Two large international randomised studies comparing capecitabine with the Mayo Clinic Schedule of 5-FU and folinic acid have reported equivalent response and survival data for the two treatment arms.[3,4] There was markedly less leucopenia, diarrhoea and mucositis in the patients taking capecitabine.

Capecitabine is available on the PBS for patients with advanced or recurrent colorectal cancer. In the future it will probably replace infusional 5-FU in combination with radiotherapy for patients with rectal cancer and will be used as part of combination therapy in advanced disease. Single drug capecitabine will remain as a suitable palliative therapy for elderly and infirm patients with advanced colorectal cancer.

Irinotecan

Irinotecan acts on topoisomerase to prevent religation of breaks in DNA. It may be given as a weekly intravenous injection for four out of six weeks or at a higher dose every three weeks.

Irinotecan may produce severe toxicity, with delayed onset diarrhoea requiring rehydration occurring in over 30% of patients. This can be ameliorated with the use of high-dose loperamide, 4 mg initially and 2 mg every two hours at the first sign of severe diarrhoea, continuing until the patient has been free of diarrhoea for 12 hours. If the diarrhoea does not settle, intravenous hydration should be considered and if neutropenia co-exists, start antibiotics active against Gram negative organisms. Less commonly an acute, early

onset, cholinergic mediated diarrhoea may occur, but this settles with atropine. Other toxicities include neutropenia and alopecia. Patients who have had pelvic radiotherapy have been excluded from trials of irinotecan, because of concerns that this might cause more severe diarrhoea, so these patients should be treated with caution. Irinotecan is probably not a treatment which should be lightly instituted in frail and/or elderly patients.

Irinotecan is currently available on the PBS for patients with advanced and recurrent colorectal cancer who have failed therapy with fluoropyrimidines.[5,6] There are data to suggest that the combination of irinotecan and 5-FU may be an optimal first-line therapy for patients with advanced colorectal cancer.[7,8]

As a second-line therapy, irinotecan treatment produces significantly improved survival compared to either best supportive care or infusional 5-FU. Approximately 20% of patients will have evidence of a major tumour response. When used first-line, two randomised studies have shown that the combination of irinotecan and 5-FU produces responses in approximately 50% of patients and provides a survival advantage of several months compared to patients treated with 5-FU and folinic acid. The median survival for patients with advanced colorectal cancer using combination therapy approaches 18 months.

Oxaliplatin

Oxaliplatin is a platinum derivative which has activity in colorectal cancer, somewhat surprisingly given that cisplatin is inactive. The toxicities produced by oxaliplatin are also different from those seen with cisplatin. Nausea, vomiting and renal impairment, which are dose limiting with cisplatin, are not such major problems with oxaliplatin. The principal and dose limiting toxicity is a predominantly sensory peripheral neuropathy. Initially these symptoms are transient and associated with cold, but after 4–5 months of treatment the symptoms become constant. Slow improvement occurs after cessation of treatment. In addition to the peripheral neuropathy, a cold-related laryngopharyngeal dysaesthesia may occur which can be alarming to patients. Apart from the neuropathy, the main other toxicity associated with oxaliplatin is mild myelosuppression.

Oxaliplatin has been used in European countries for some years and has recently been made available on the PBS for second-line treatment of patients with colorectal cancer. This is somewhat surprising given that there is a lack of data, especially randomised trials, for this indication. However, there are phase II results which show a 10–20% response rate for oxaliplatin in patients who have failed 5-FU. Data also show anti-tumour activity in patients whose cancers had previously progressed on 5-FU, suggesting some synergy between oxaliplatin and 5-FU. In first-line use, the combination of 5-FU and oxaliplatin produces response rates of approximately 50%. However, randomised data have not shown a survival benefit over 5-FU and folinic acid, although the trials comparing these regimens were not powered to detect survival differences.

Conclusion

The treatment options have increased in the last five years for patients with advanced and metastatic colorectal cancer. The new drugs have resulted in improved response rates without worsening of patient quality of life. There are also suggestions of modest improvements in overall survival. Hopefully these treatments may result in improved palliation of this common condition and lead the way to more effective adjuvant treatments in the future.

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Dr Clarke has acted as a consultant to Sanofi-Synthelabo.

Self-test questions

The following statements are either true or false (answers on page 123)

3. Diarrhoea can be a life-threatening complication of raltitrexed.
4. Oxaliplatin is more active than cisplatin against colorectal cancer.

Perceptions of risk – a legal perspective

John McPhee, Consultant in Health Law, Clinical Ethics and Health Law, Faculty of Health, University of Newcastle, Newcastle, New South Wales

SYNOPSIS

The decision whether or not to undergo medical treatment is usually that of the patient. In order to make such a decision the patient needs information about the risks and benefits of any proposed course of treatment. The High Court of Australia has said that the patient must be informed about material risks. It has said that material risks are those risks to which a reasonable person in the patient's position or that particular patient would attach some significance. Therefore in deciding which risks to disclose to the patient the doctor must attempt (as much as is practicable) to view the procedure from a patient's perspective. Necessarily this must be an individual judgement based on what is reasonably known about the person before them. This judgement must be made within the particular circumstances of the consultation.

Index words: adverse effects, informed consent.

(Aust Prescr 2002;25:114–5)

The 1992 decision in *Rogers v. Whitaker* (1992) 175 CLR 479 established in Australian law the standard of care required when a doctor gives information to patients about risks of proposed procedures (although '[t]he decision in *Rogers v. Whitaker* has been received with some consternation by the medical profession'[1]).

In *Rogers v. Whitaker* the question to be decided by the court was whether an ophthalmic surgeon should have warned his patient of the one in 14 000 chance of a complication, sympathetic ophthalmia and subsequent risk of blindness, arising from a proposed procedure. The High Court affirmed the decisions of the New South Wales Supreme Court and the New South Wales Supreme Court of Appeal that the doctor should have warned his patient of this remote risk. In reaching this conclusion the High Court stated the standard to be adopted by doctors when advising patients of risk. The joint judgement of the majority of the court * stated:

> 'The law should recognize that a doctor has a duty to warn a patient of a material risk inherent in the proposed treatment; a risk is material if, in the circumstances of the particular case, a reasonable person in the patient's position, if warned of the risk, would be likely to attach significance to it or if the medical practitioner is or should reasonably be aware that the particular patient, if warned of the risk, would be likely to attach significance to it.' (at 490)

* Gaudron J delivered a concurring judgement.

This case confirmed that Australian courts would not be bound by common professional practice (evidence before the court revealed that many doctors in the ophthalmic surgeon's position would not tell their patients about the risk of sympathetic ophthalmia). The test then is 'what risks would a reasonable person in the patient's position want to be told about before they would undergo the procedure'. This is recognition that in the usual circumstances the choice of whether to undergo a procedure is that of the patient and in order to make this decision they need to know something about the risks that may be involved. Justice Kirby has pointed out that the Australian cases 'emphasise that it is the patient who ultimately carries the burden of the risks'.[2]

The judgement also recognises that some patients may have special concerns, different perhaps from the 'reasonable' person. If this is known (or should have reasonably been known) by the medical practitioner then any additional risks should also be disclosed.

Recently the High Court has had an opportunity to review *Rogers v. Whitaker* in the case of *Rosenberg v. Percival* [2001] HCA 18 (5th April 2001). In this case a dental surgeon failed to warn his patient appropriately about risks associated with a sagittal split osteotomy. Following the procedure the patient suffered severe temporomandibular joint complications. In this case (as in *Rogers v. Whitaker*) the patient asserted that if she had been appropriately warned about the risks associated with the procedure she would not have undergone it at that time. Each of the High Court judges who decided this case (on appeal from the Western Australia Supreme Court of Appeal) delivered a separate judgement, but all affirmed the principle stated in *Rogers v. Whitaker*.

The cases also assume that the doctor will know something about the patient beyond, perhaps, the immediate complaint that brings the patient to the doctor. However, it should be noted that courts take into account the circumstances of the interaction between doctor and patient. In *Rosenberg v. Percival* the Chief Justice warned that:

> [r]ecent judgments in this Court have drawn attention to the danger of a failure, after the event, to take account of the context, before or at the time of the event, in which a contingency was to be evaluated. This danger may be of particular significance where the alleged breach of duty of care is a failure to warn about the possible risks associated with a course of action, where there were, at the time, strong reasons in favour of pursuing the course of action.[3]

If a patient were to decline to undergo the treatment because of their unwillingness to accept a risk (after being appropriately informed) then they must bear the consequences of such a decision. Doctors also have a responsibility to make it clear to the patient which of any alternative modes of treatment they recommend. They may do this forthrightly although not to the extent that the advice becomes coercive.

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FURTHER READING

Space does not permit a more extensive analysis of *Rosenberg v. Percival*, however the judgement is available from the web at: http://www.austlii.edu.au/au/cases/cth/high_ct/2001/18.html

For a critical view on the recent High Court cases, see Mendelson D. Liability for negligent failure to disclose medical risks. J Law Med 2001;8:358-67.

Conflict of interest: none declared

National Prescribing Service *Medicines Line* 1300 888 763

The National Prescribing Service has launched *Medicines Line*, a national telephone service providing information for the general public. For the cost of a local call, people will be able to ask questions about their medicines, including over-the-counter and complementary medicines.

Medicines Line is staffed by drug information specialists and will aim to provide independent evidence-based information. It will focus on information about drugs. *Medicines Line* will not give opinions on clinical management or the appropriateness of someone's medication.

Callers will be encouraged to discuss the information with their own general practitioner or community pharmacist, as they will be best placed to help interpret the medicines information in the context of the person's health. When the caller gives permission, a copy of the information provided to them will also be forwarded to their general practitioner or community pharmacist.

The service will be operated from the Mater Hospital, Brisbane, by a consortium that includes the Pharmaceutical Society of Australia. *Medicines Line* will complement the existing NPS Therapeutic Advice and Information Service for health professionals.

Contact details for the two NPS telephone services are

for consumers: *Medicines Line* 1300 888 763

for health professionals: *Therapeutic Advice and Information Service* 1300 138 677

Patient support organisation

Retina Australia

Retina Australia is a national peer support organisation concerned with retinal diseases, including macular degeneration. Through its State and Territory branches Retina Australia offers voluntary peer support to sufferers of retinal disease. It publishes a wide range of information on retinal disease, some of which is available on its web site. Retina Australia also raises funds for scientific research into the causes, prevention and cure of retinitis pigmentosa and other retinal dystrophies.

The National President of Retina Australia has described living with a visual disability in *A degree of vision* (Personal paper), Lancet 2000;356:1517–9.

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Drug treatment of macular degeneration

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SYNOPSIS

Many new therapies for age-related macular degeneration are under investigation as current treatment options are very limited. Photodynamic therapy is a new, effective and safe treatment for a select group of patients with choroidal neovascularisation associated with age-related macular degeneration. This treatment involves the selective accumulation of a photosensitive dye (verteporfin) within the abnormal vascular tissue rather than the surrounding normal tissue. When light of a specific wavelength is applied to the macula those areas containing greater amounts of dye undergo greater damage. This approach is superior to conventional argon laser photocoagulation where collateral thermal damage to vital structures limits its usefulness.

Index words: eye, photodynamic therapy, verteporfin.

(Aust Prescr 2002;25:116–9)

Introduction

Age-related macular degeneration (AMD) is a progressive, late-onset disease affecting central vision. It is currently the leading cause of irreversible blindness in Australia with 37% of registrable blindness (excluding refractive errors) being due to AMD compared to 21% due to glaucoma.[1] Early signs of the disease are present in 15% of the population aged 50 years and older, and by 90 years of age more than two-thirds of the population are affected. The prevalence of AMD is predicted to double in the next 30 years. The high prevalence, the anticipated increase in the ageing population and the very limited treatment options make AMD one of the greatest challenges in ophthalmology today.

Risk factors

The pathogenesis of AMD remains largely unknown. Environmental risk factors probably impact on the patient's genetic background.[2]

Twin and family studies as well as population-based genetic epidemiological studies have shown that genetic factors play an important role in the aetiology. However, the actual degree of hereditability of AMD is still unknown.

The potential environmental risk factors are numerous, however smoking is currently the only factor consistently associated with AMD.[3] Long-term smoking at least doubles the risk. Other putative risk factors include hypertension, atherosclerosis, high serum cholesterol and dietary fat intake, light exposure, iris colour and a low intake of antioxidant vitamins. The Age Related Disease Study reported that high doses of multiple vitamins and zinc could marginally slow the progression of AMD in a sub-group of patients, although the high doses required (5–15 times recommended daily supplements) posed significant concerns about the adverse effects after long-term administration.[4]

Pathology

The early stages of macular degeneration can be recognised by the formation of drusen, yellow deposits, in the centre of the macula. They are very common and are not usually associated with visual symptoms. Significant visual loss occurs when a complication of the drusen develops, either a choroidal neovascular membrane, 'wet AMD' or atrophic 'dry AMD' (Fig. 1).

In neovascular AMD, abnormal blood vessels from the choroid grow up under the retina. This choroidal neovascular membrane causes acute loss of vision when transudate or haemorrhage accumulates beneath the retina, leading ultimately to a fibrous scar. This results in progressive and irreversible loss of central vision and often becomes bilateral over a period of years. The membranes are classified according to their appearance on a fluorescein angiogram (see box).

In atrophic AMD the retina slowly becomes atrophic over months to years and as such central vision is gradually lost. The majority of AMD is atrophic, however most of the patients with severe visual impairment have neovascular AMD.

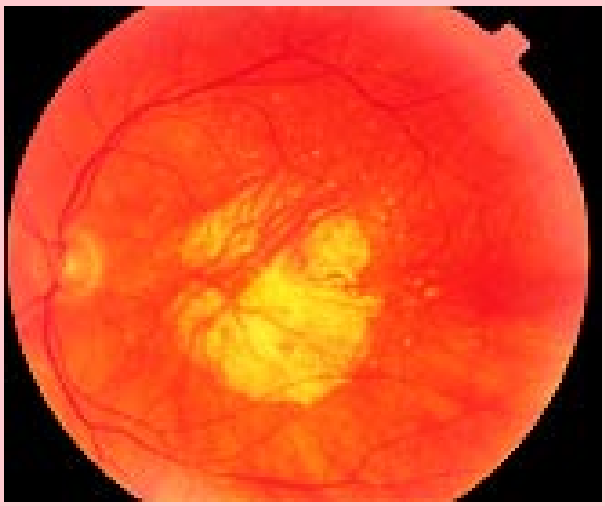
Classification of choroidal neovascular membranes by fluorescein angiography

A classic lesion appears as a well demarcated area of uniform hyperfluorescence early in the angiogram with leakage of fluorescein later to obscure the boundaries of the lesion through the mid and late phases of the angiogram.

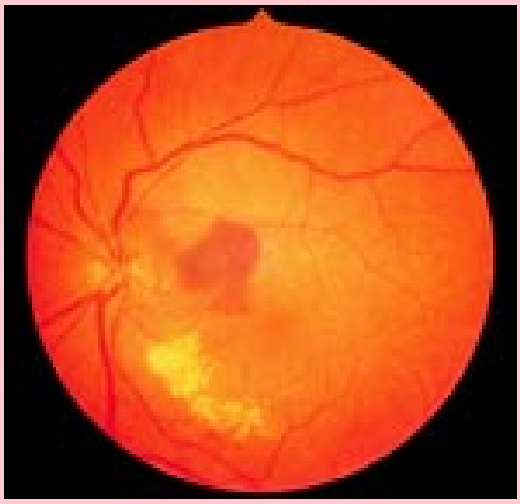
An occult (no classic component) lesion has poorly demarcated boundaries of fluorescein leakage from an undetermined source at the level of the retinal pigment epithelium in the late frames of the angiogram.

Fig. 1

a. A fundus photo depicting atrophic or 'dry' AMD



b. The central lesion in this fundus photo is depicting choroidal neovascularisation of the macula or 'wet' AMD



Treatment

The aim of treatment is to try and stop further loss of vision as once vision is lost it is usually not regained. We therefore need to screen people more effectively so that those at risk can be identified and educated about monitoring vision at home and the need for prompt referral. It is imperative to pick up symptoms of choroidal neovascularisation as soon as possible. Patients at high risk can be asked to observe an Amsler grid (square grid of lines) every few days to pick up changes as soon as they occur. Any sudden distortion of straight lines or missing parts of the chart should prompt swift action.[5]

Laser treatment

Large scale randomised clinical trials during the 1990s showed that argon laser photocoagulation was of benefit in neovascular AMD if the membranes were well defined on fluorescein angiography (classical membrane). The aim of photocoagulation is to limit the destructive effects of the choroidal neovascular membrane by using coagulative necrosis to destroy the entire neovascular complex. Heat conduction causes collateral damage to surrounding structures including the retina. Laser photocoagulation is therefore really only applicable if the abnormal blood vessels do not occupy the very centre of vision (subfoveal).

By the time patients with choroidal neovascularisation present to an ophthalmologist less than 20% will have a lesion that is suitable for conventional laser treatment. The vast majority of patients have subfoveal involvement at presentation. The use of laser photocoagulation for these subfoveal lesions is controversial. Despite immediate loss of acuity, long-term follow-up of more than two years shows treatment does have some benefit. Nevertheless the sudden iatrogenic acquisition of a dense central scotoma gives the patient no time to adapt to the loss of central vision. Whilst argon laser photocoagulation remains the treatment of choice for choroidal neovascular membranes outside the fovea it has really failed to reduce the rates of blindness from AMD. This together with the fact that there is no proven treatment for atrophic AMD highlights the need for new treatments.

Photodynamic therapy

In photodynamic therapy a non-toxic light-sensitive compound called a photosensitiser is given intravenously and then subsequently activated by beaming light of an appropriate wavelength to the target area. There is a preferential concentration of the photosensitiser in the target tissue and light is directed towards this target area. Neither the light nor the drug is harmful to tissues when applied independently, but in combination they cause cellular destruction. The destructive mechanisms are complex and not well understood. They involve cellular, vascular and immunological actions, thereby differing substantially from the thermal damage caused by laser photocoagulation.

Although photodynamic therapy is a new technique, randomised clinical trials show it can reduce the risk of vision loss in cases of AMD with a choroidal neovascular membrane under the central fovea.[6,7]

Photodynamic therapy is a two-step process that can be performed as an outpatient procedure. The first step involves a 10-minute intravenous infusion of the light-activated drug (verteporfin). Five minutes later the non-thermal laser (689 nm) is beamed for 83 seconds at 600 mW/cm to the lesion to achieve the desired light dose of 50 mJ/cm^2. The treatment size is the greatest linear dimensions of the lesion plus a 1 mm margin. Photoexcitation of the photosensitiser produces free radicals which cause structural and functional damage to cell membranes and other structures leading to cell death. The photodynamic damage to endothelial cells activates platelets leading to thrombus formation and vascular occlusion.[8]

Verteporfin

Verteporfin is a photosensitive drug derived from porphyrin. Its absorption maximum is in the ultraviolet A range (680–695 nm) so it can be activated by a non-thermal diode laser at wavelengths that can penetrate blood, melanin and fibrotic tissue. Once in the circulation verteporfin complexes with low density lipoproteins (LDL). As the number of endothelial LDL receptors is increased in neovascularisation, verteporfin preferentially accumulates in neovascular tissue. This increases the selectivity of photodynamic therapy for choroidal neovascular membranes and not other retinal vessels. The aim of verteporfin therapy is to occlude the abnormal vessels selectively while maintaining perfusion in deeper choroidal vessels and overlying retinal vessels. Unlike conventional laser treatment there is no immediate loss of vision at the site of verteporfin activation.

Early clinical trials showed that there was an immediate reduction in the fluorescent leak on angiography after treatment with verteporfin, however the effect was temporary. The leaks returned after 4–12 weeks. Re-treatment is therefore necessary for long-term benefits. Treatments are, on average, required every three months in the first 12 months and then twice in the second 12 months. One difficulty with this treatment is knowing when to stop. The present guidelines recommend that the treatment be continued, albeit at longer intervals, until there is no leak on the angiogram. At this stage it is not known if it is safe to stop before this occurs.

Clinical trials

Two phase III studies assessed the long-term safety and efficacy of verteporfin.[6,7] The TAP study looks at photodynamic therapy for patients with classic choroidal neovascularisation while the VIP study looked at occult neovascularisation in AMD. So far, these studies show a modest benefit at two years in reducing the risk of moderate to severe visual loss.

The TAP study enrolled people with subfoveal choroidal neovascularisation that had a component that was defined as classic on the angiogram. For the purposes of the study, if at least 50% of the lesion had classical characteristics it was defined as predominately classic. Occult lesions were defined as no classic component and when less than 50% of the lesion had a classic appearance it was defined as minimally classic. In the study, the placebo group received a 30 mL solution of 5% dextrose in water over 10 minutes rather than the active photosensitiser, before the laser treatment was given.

The primary outcome was avoiding a loss of visual acuity of at least three lines on a modified ETDRS (early treatment diabetic retinopathy study) chart (approximately two lines lost on a standard Snellen chart). This outcome was achieved by 61% of the treated group and 46% of the placebo group over the first 12 months ($p < 0.001$). The patients with the best outcome, in a sub-group analysis, had a predominantly classical lesion on angiography; 67% of the treated group had a visual loss of less than three lines compared to 39% in the placebo group. Predominantly classical lesions constitute less than 25% of those with subfoveal choroidal neovascular membranes. There was no difference in minimally classical lesions and too few in the no classic component group to analyse meaningfully. In the VIP study the analysis of the 100% occult group, or no classic group, found a non-significant difference at 12 months of 49% of the treated group losing less than three lines of vision, compared to 46% of the placebo group.

After two years in the TAP study the predominantly classic group still showed a benefit of treatment with loss of less than three lines occurring in 59% of the treated compared to 31% of the placebo group. There was no significant difference in the minimally classic group (Table 1). In the VIP study, after two years 46% of patients with occult lesions treated with verteporfin had lost less than three lines of vision compared to 33% of the placebo group. These results provide the evidence to suggest that verteporfin treatment should be made available to people with predominantly classical membranes and, less convincingly, to those with no classic component in the membrane. There appears to be no benefit of this treatment for lesions with a minimally classical component.

Verteporfin appears to be reasonably safe. There are reports of infusion-related back pain and photosensitivity reactions in 2–3% of patients. All patients must avoid sunlight for 48 hours after the treatment as they can suffer severe sunburn if they are exposed to the sun before the photosensitive dye is eliminated. The pharmacokinetic profile is slightly altered in patients with mild hepatic impairment as biliary clearance is the main route of elimination. However, there was not an associated increase in skin photosensitivity in these patients. There is no experience of verteporfin in people with moderate to severe liver impairment, therefore caution should be taken and measures to prevent photosensitivity reactions should be adhered to longer. It is possible that the concomitant use of other photosensitive drugs (such as tetracyclines, sulfonamides, thiazide diuretics) may increase the potential for photosensitive reactions.

Table 1

Efficacy of verteporfin in photodynamic therapy

Primary visual outcome results at two years by sub-group analysis (less than three lines of vision lost)[6]

Type of neovascularisation	*Verteporfin treated group*		*Placebo*		
Predominantly classic	59%	(94)	31%	(26)	$p < 0.001$
No classic	46%	(104)	33%	(38)	$p < 0.23$
Minimally classic	47.5%	(96)	44.2%	(46)	$p < 0.58$

(Number of eyes = number of patients)

In Australia verteporfin dye costs $2000 per vial. Since June 2002 the Commonwealth Government has decided to subsidise verteporfin for patients with predominantly classic neovascularisation. Ophthalmologists will have to send in their angiograms for assessment by a panel to gain this subsidy for the patient. At present there is no subsidy for purely occult, or no classic neovascularisation.

There are reports of a 5% risk of sudden severe visual loss after treatment in the group with no classic component. This is important considering the smaller benefit likely from treating this sub-group.

Experimental medical treatments

With the number of people in the at risk age group set to double in the next 25 years we need to look for more effective ways to manage AMD. New photosensitisers such as SnET2 (tin ethyl etiopurpurin) and lutetium texaphyrin are currently being investigated. Angiogenesis inhibitors are being studied in the hope that they can stop choroidal neovascularisation. Vascular endothelial growth factor (VEGF) plays an important role in the retinal and iris neovascularisation caused by retinal ischaemia as in diabetic retinopathy. Evidence is accumulating to implicate VEGF as a principal angiogenic growth factor contributing to the pathology of AMD. A large multicentred randomised controlled trial of intravitreal injections of an anti-VEGF is underway.

Conclusion

Clinical trials have shown that verteporfin therapy reduces the risk of at least moderate visual loss compared to placebo for at least two years in patients with predominantly classic choroidal neovascular membranes who present with subfoveal lesions. Verteporfin does not repair already damaged tissues, but might prevent further growth of the membranes. Photodynamic therapy adds a technique to the ophthalmologists' armamentarium for some lesions in AMD for which there is virtually no other proven treatment. Conventional laser photocoagulation treatment still remains the best choice for nonfoveal, classic choroidal neovascularisation. As phototherapy reduces the risk of vision loss rather than restoring vision, it is essential to identify the development of choroidal neovascular membranes as quickly as possible so the patient can be treated while their visual acuity is still good. Verteporfin is not a 'miracle cure', but it is at least a step in the right direction. Patient education is crucial to try and avoid unrealistic expectations from the treatment. There are still unsolved issues with photodynamic therapy such as the optimal treatment regimen and the effect on the patient's quality of life.

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Dr Guymer is a research fellow supported by the Royal Victorian Institute for the Blind.

Self-test questions

The following statements are either true or false (answers on page 123)

5. Most cases of age-related macular degeneration are caused by abnormal blood vessels growing from the choroid.
6. Patients should avoid sunlight for 48 hours after treatment with verteporfin.

Message to all 2002 graduates in medicine, pharmacy and dentistry

If you are graduating in Australia this year and you wish to continue receiving *Australian Prescriber* to assist with your postgraduate training, please complete and send the distribution form on the inside back cover of this issue, or register on-line at www.australianprescriber.com at Contact Us.

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How we write about new drugs

J.S. Dowden, Editor, Australian Prescriber

The 'New drugs' section of *Australian Prescriber* has been a consistent feature of the journal since 1975. Health professionals value its brief, unbiased comments about recently marketed products. These comments will continue to be published, but following the acquisition of *Australian Prescriber* by the National Prescribing Service[1,2] there have been some changes in the way the 'New drugs' section is prepared.

When the journal was published by the Department of Health, the editors had access to the drug evaluations prepared by the Therapeutic Goods Administration. As the editors were usually senior medical advisers to the Drug Evaluation Branch they were able to see all the (published and unpublished) research evidence submitted by pharmaceutical companies applying to have their drugs approved for use in Australia.

As the National Prescribing Service operates independently of the Department of Health and Ageing, it does not have access to the research evidence held by the Therapeutic Goods Administration. This is because the applications containing the evidence are considered to be 'commercial-in-confidence'.[3]

To overcome this barrier *Australian Prescriber* is increasingly using information published by the European Medicines Evaluation Agency and the US Food and Drug Administration. Although it would be better to have access to Australian assessments of new drugs, these overseas regulatory authorities currently have less restriction on making information available.

The 'New drugs' comments in *Australian Prescriber* continue to draw information from the medical literature and databases such as the Cochrane Collaboration. Although only a few key references are published in the 'New drugs' section many more are considered when preparing the comments. When dealing with published clinical trials there is, however, a risk that only the trials with positive results have been published.[4]

Sometimes the results of an unpublished trial can appear in the product information for the drug. The product information also contains helpful information about a drug's pharmacology and adverse effects.

The Editor prepares draft 'New drugs' comments using the available sources of information. These drafts are then considered by the Editorial Executive Committee. This peer-review process helps to ensure the comments are correct and relevant to clinicians. The 'New drugs' comments are not intended to be a comprehensive review of a product, but should help health professionals decide if they need to find out more information for their own practices.

Now that new drugs are often reported by the general media before health professionals are informed about them, *Australian Prescriber* is speeding up the dissemination of its 'New drugs' comments. Instead of waiting for the next issue to review a new product, a 'New drug' comment will be published on the *Australian Prescriber* web site as soon as the drug is marketed. This will help to ensure *Australian Prescriber* remains a helpful and trusted source of drug information.

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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.

Amisulpride

Solian (Sanofi-Synthelabo)

100 mg, 200 mg and 400 mg film-coated tablets

Approved indication: schizophrenia

Australian Medicines Handbook section 18.2

Amisulpride is a benzamide antipsychotic which antagonises dopamine receptors. It binds to the D_2 and D_3 dopamine receptors, but has little affinity for muscarinic or serotonin receptors. This pattern of activity differs from that seen with atypical antipsychotics.

The oral formulation has a bioavailability of 48%, but is not extensively metabolised. Most of the drug is excreted unchanged, with an elimination half-life of 12 hours. Clearance is reduced in patients with renal impairment.

A meta-analysis of trials which compared amisulpride with conventional antipsychotic drugs found that it had greater efficacy in patients with acute schizophrenia.[1] Amisulpride has been compared with haloperidol in patients with chronic schizophrenia. After one year, a study of 60 inpatients found no significant difference in overall efficacy, but there was a trend suggesting amisulpride may be more beneficial for

negative symptoms.[2] Another larger study (488 patients) also found that amisulpride had a greater effect than haloperidol on negative symptoms.[3]

Like the atypical antipsychotics, amisulpride causes fewer extrapyramidal adverse effects than conventional drugs. Its extrapyramidal effects are dose related. Common adverse effects include insomnia, anxiety, agitation and weight gain. The release of prolactin may result in problems such as galactorrhoea and amenorrhoea. There is a potential for amisulpride to cause torsade de pointes as it prolongs the QT interval. Amisulpride is therefore contraindicated in combination with other drugs which cause QT prolongation. Caution is also advised if the patient is taking diuretics or other drugs which may cause hypokalaemia.

While amisulpride has effects which are similar to those of the atypical antipsychotics, there is little information about the relative benefits. One eight-week study found amisulpride and risperidone had similar efficacy in acute schizophrenia.[4]

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Modafinil

Modavigil (CSL)

100 mg tablets

Approved indication: narcolepsy

Australian Medicines Handbook section 16.8.3

In addition to disturbing sleep, narcolepsy is associated with excessive sleepiness during the day. A multiple sleep latency test can help to confirm the diagnosis.[1] Treatment of daytime sleepiness may require the use of psychostimulants. Modafinil now offers an alternative to dexamphetamine and methylphenidate.

The mechanism of action of modafinil is unclear. It does not bind with receptors for noradrenaline, dopamine or serotonin.

Patients take a single dose in the mornings. This is rapidly absorbed with the peak plasma concentration being achieved within four hours. Modafinil is eliminated mainly by metabolism, with most of the metabolites being excreted in the urine. Cytochrome P450 3A4 may be involved in the metabolism so there is a potential for interactions with inducers and inhibitors of this enzyme. Modafinil may also induce its own metabolism.

Two clinical trials compared different doses (200 mg and 400 mg) of modafinil with placebo.[2,3] Several tests such as the Epworth sleepiness scale[1] were used to assess the outcomes. Both doses of modafinil improved the patients' symptoms, but not all of the changes were significantly greater than placebo.[3]

During these trials approximately 5% of patients withdrew because of adverse effects. Common adverse reactions while taking modafinil included headache, nausea and nervousness. Like other stimulants, modafinil has some euphoric effects so there is the possibility that it could be abused.

While the 400 mg dose is well tolerated it has no significant advantage over the 200 mg dose. Approximately 60% of patients will improve with 200 mg daily (38% of patients will improve with a placebo). Some of the significant improvements may be of questionable clinical relevance. For example, patients can stay awake for five minutes if they are taking a placebo and for eight minutes if they are taking modafinil. Continuous treatment may result in reduced plasma concentrations of modafinil when it induces it own metabolism. As the double-blind clinical trials only lasted for nine weeks it is not known if modafinil is effective in long-term treatment of narcolepsy. It has no role in patients complaining of a general tiredness or lack of energy.

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Peginterferon alfa-2b

Peg-Intron (Schering-Plough)

vials containing 50, 80, 100, 120 and 150 microgram as powder for injection

Approved indication: chronic hepatitis C

Australian Medicines Handbook section 14.2.2

The treatment of choice for chronic hepatitis C is ribavirin in combination with interferon alfa-2b.[1] This interferon has to be given by injection three times a week. To reduce the frequency of injections interferon alfa-2b has been conjugated with polyethylene glycol to produce peginterferon which has a reduced renal clearance.

Peginterferon is injected once a week. The site of the subcutaneous injection should be varied with each dose. Plasma concentrations reach a maximum 15–44 hours after the injection and are sustained for 48–72 hours. The elimination half-life of interferon alfa-2b is about seven hours and renal clearance accounts for 80% of the total clearance. Conjugation with polyethylene glycol reduces renal clearance to 30% of the total and increases the elimination half-life to 40 hours.

The efficacy of peginterferon has been assessed in 1219 previously untreated patients with chronic hepatitis C confirmed by liver biopsy. Patients were randomised to receive interferon alfa-2b three times a week or a weekly injection of one of three different doses of peginterferon. They were treated for 48 weeks. Six months after completing treatment, 12% of the patients taking interferon alfa-2b had

undetectable concentrations of hepatitis C RNA and normal concentrations of alanine aminotransferase (see 'Hepatitis C: diagnosis and monitoring' Aust Prescr 1999;22:91–4). This response was significantly less than the 18–25% of the patients who responded to peginterferon.

Although all the doses of peginterferon were efficacious, the recommended dose is 0.5 microgram/kg. The dose may be doubled for patients infected with genotype 1 virus. (This genotype is associated with a poor response to interferon.) If the virus is still present after six months of treatment, peginterferon should be stopped.

Peginterferon causes more injection site reactions than interferon alfa-2b, but overall the pattern of adverse reactions is similar. Common complaints are flu-like symptoms in the first few weeks of treatment, headache, tiredness, myalgia and fevers. As granulocytopenia occurs in 4–7% of cases, patients with fever require investigation. Thrombocytopenia can also occur. Patients should have their eyes examined before treatment as the interferons can cause ophthalmological problems such as retinal haemorrhages. Interferon alfa-2b may also exacerbate psoriasis. Some patients develop depression during treatment, so a previous history of a serious psychiatric condition is a contraindication to treatment. While peginterferon is used to treat chronic hepatitis, it is not recommended for patients with severe hepatic dysfunction.

Although more patients respond to peginterferon than interferon alfa-2b the response rate is much lower than the 43% seen with the combination of interferon alfa-2b and ribavirin.[1] Another trial therefore studied the effectiveness of peginterferon in combination with ribavirin.

This open trial randomised 1530 previously untreated patients to take either interferon alfa-2b and ribavirin or one of two regimens of peginterferon alfa-2b and ribavirin. The patients were treated for 48 weeks then followed up for another 24 weeks. Viral RNA was undetectable in 47% of the patients given interferon alfa-2b or the lower dose regimen of peginterferon alfa-2b. In patients who had taken a higher dose (1.5 microgram/kg/week) of peginterferon the response was 54% – a statistically significant advantage. This regimen was also advantageous for patients with the genotype 1 virus. A sustained virological response was found in 42% compared with 33% of the patients given interferon alfa-2b. The higher dose, however, resulted in more frequent adverse reactions including neutropenia.[2]

Although the high dose regimen produces a bigger response in patients with genotype 1 virus it has no significant advantage over lower doses or interferon alfa-2b for patients infected with other genotypes. Identifying the best regimen will require further research to clarify the most effective dose of ribavirin. Despite these issues, the combination of peginterferon alfa-2b and ribavirin may become the treatment of choice for chronic hepatitis C, if it is found to be cost-effective.

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Reboxetine mesylate

Edronax (Pharmacia)

4 mg tablets

Approved indication: major depression

Australian Medicines Handbook section 18.1

Reboxetine inhibits the reuptake of noradrenaline, but has little effect on the reuptake of serotonin or dopamine. This gives it a relatively selective mechanism of action on neurotransmission. The resulting increased concentration of noradrenaline in synapses may help some patients with depression.

Although short-term studies show that reboxetine improves depression more than a placebo, the difference is not always statistically significant. An eight-week study of 347 elderly patients found that reboxetine had similar efficacy to imipramine.[1] Another eight-week study of 168 patients showed no significant differences in the overall efficacy between reboxetine and fluoxetine.[2]

A multicentre study investigated what happened to 283 patients during longer-term treatment. Patients who had responded to six weeks' treatment with reboxetine, were randomised to continue therapy or switch to a placebo. After 46 weeks 56% of the patients switched to placebo had relapsed compared with only 22% of those who continued reboxetine.[3]

Doses of reboxetine are rapidly absorbed. The half-life is 13 hours and a steady state is reached within five days. If there has been no response to the starting dose, it can be increased after three weeks. A lower starting dose is recommended in the elderly. Lower doses are also appropriate for patients with renal or hepatic impairment as the drug is eliminated in the urine and by metabolism.

The metabolism of reboxetine involves cytochrome P450 (CYP3A4). Inhibitors of this enzyme, for example ketoconazole, will increase plasma concentrations of reboxetine.

In the comparison with imipramine, adverse events occurred in 68% of the patients taking reboxetine and 71% of those taking impramine.[1] Comparison of reboxetine and fluoxetine shows that adverse events occur in approximately 67% of patients taking either drug.[2] The adverse effects of reboxetine include dry mouth, constipation, insomnia, dizziness and tachycardia. ECG changes appear in 15% of elderly patients taking reboxetine. Hypotension can occur, but is less likely than in patients taking imipramine.[1]

Prescribers should be cautious about prescribing reboxetine to patients with glaucoma, prostatic hypertrophy/difficult micturition, cardiovascular disease or a history of seizures.

As depression often requires months of treatment, it would be reasonable to wait until more long-term safety data are available before prescribing reboxetine. A comparative study with venlafaxine, which inhibits the reuptake of serotonin as well as noradrenaline, would be informative.

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NEW STRENGTHS

Azathioprine

Azamun (Douglas)

25 mg tablets

Ipratropium bromide

Apoven (Douglas)

500 microgram/mL solution for inhalation

Chem mart Ipratropium (Faulding Healthcare)

500 microgram/mL solution for inhalation

GenRx Ipratropium (Faulding Healthcare)

500 microgram/mL solution for inhalation

Healthsense Ipratropium (Faulding Healthcare)

Terry White Chemists Ipratropium (Faulding Healthcare)

500 microgram/mL solution for inhalation

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Quinapril/hydrochlorothiazide

Accuretic (Pfizer)

tablets containing 10 mg quinapril/12.5 mg hydrochlorothiazide and 20 mg quinapril/12.5 mg hydrochlorothiazide

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2. True
3. True
4. True
5. False
6. True

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