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CONTENTS

Editorial

The impact of advertising prescription medicines directly to consumers in New Zealand: lessons for Australia

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Key words: drug industry, drug regulation.

(Aust Prescr 2006;29:30–2)

Advertising prescription medicines directly to consumers is allowed only in the USA and in New Zealand. Its effectiveness is attested to by the growth in advertising expenditure. More than US$4 billion was spent on direct-to-consumer advertising in the USA in 2004 and tens of millions are spent annually in New Zealand. As in the USA, direct-to-consumer advertising is 'allowed' in New Zealand by default rather than by design. Regulators failed to, or chose not to, enact legislation to stop it and the medical and public watchdog groups did not complain loudly enough until it was too late.

Freedom of speech, commercial freedom, providing valuable information on new medicines to consumers, and countering medical paternalism are the main arguments put forward by the proponents of direct-to-consumer advertising. These are summarised in a paper by the New Zealand Marketing Association which also contains an interesting appraisal of the current Australian situation.[1] Unfortunately, partial and unbalanced misinformation, which is the hallmark of New Zealand's direct-to-consumer advertising, is promotion clearly designed to drive choice rather than inform it.

Four years ago New Zealand general practitioners were abruptly awoken to the effectiveness of direct-to-consumer advertising. Overnight they had to cope with an unexpected and unwelcome increase in workload. Patients using the leading brand of beclomethasone appeared at surgeries in droves asking to switch to an orange inhaler (fluticasone), as a television advertisement had told them that their brown inhaler was to be withdrawn in a few weeks, to protect the ozone layer. In the view of many prescribers, the television advertisements contained several inaccuracies and raised patient anxiety unnecessarily as neither patients nor many general practitioners realised that generic beclomethasone would continue to be available. A senior company official would later admit that the timing of this campaign was chosen for marketing rather than environmental reasons. In particular, a generic equivalent to the company's inhalers was in the wings.

Many general practitioners were incensed at being pressured to switch well-controlled patients to what they considered to be a drug with little or no added therapeutic benefit.[2] Perhaps more worrying, the longer-term health effects of a near doubling of average daily doses of inhaled steroids (many prescribers seemed unaware of the potency of fluticasone) are yet to be quantified.

There was also a significant increase in cost to the New Zealand taxpayer from the switch in prescribing driven by direct-to-consumer advertising. At the time, fluticasone carried a premium on the equivalent dose of beclomethasone. In addition, the increase in effective dose by many prescribers not making the 2:1 switch in dose increased this price differential and the overall subsided cost. The true cost will never be made public as there was a confidential, out-of-court settlement days before a Fair Trading Act case (initiated by the Pharmaceutical Management Agency of New Zealand to recover the costs to the health budget) was due to start in the High Court.

In this issue…

From this month, patients with hepatitis C will no longer require a liver biopsy before accessing subsidised treatment. Robert Batey suggests how patients can be managed following removal of this restriction on prescribing the recommended regimen of antiviral drugs.

While hepatitis C affects thousands of Australians, obesity is much more prevalent. Ian Caterson reminds us that drug treatment is just part of the management.

Raising awareness of treatments for obesity has been the objective of advertising campaigns in Australia. Across the Tasman there are fewer restrictions on advertising. Les Toop and Dee Mangin alert us to the impact that directly advertising prescription drugs to the public has had on New Zealand. They are concerned that a trans-Tasman regulatory agency will not curb direct-to-consumer advertising.

The increase in workload from the television campaign was exacerbated by the start of a counter direct-to-consumer advertising campaign by a rival company. This company promoted its own red combination inhaler which the advertisements assured would 'kick asthma' and 'work better than your brown or orange inhaler'. Some general practitioners reported patients with well-controlled asthma presenting in quick succession, first demanding to switch to the orange inhaler and then asking for the red one!

A very brief television campaign for oral terbinafine for onychomycosis resulted in a rapid doubling of national prescription sales. Some general practitioners reported several patients appearing in the same surgery demanding treatment for minimal nail discolouration. Many general practitioners gave up the unequal struggle of repeatedly spending 15–20 minutes explaining why prescribing a modestly effective, but very expensive (to the taxpayer) and potentially hepatotoxic, drug for a minor cosmetic problem broke most of the principles of rational prescribing. It is easier after all just to write the prescription and keep the patient happy. Indeed compliance with requests seems to be the common response. Surveys of consumer experiences both in New Zealand and in the USA consistently show that when a patient asks for a specific drug by name they receive it more often than not.[3,4,5] This occurs even when the prescribers report they would not have prescribed the drug had it not been requested.[3,4]

In 2002, the heads of three of the four Departments of General Practice wrote to general practitioners setting out their intention to lobby for a ban on direct-to-consumer advertising and asking for colleagues to share their experiences. Within days more than half of all the general practitioners in New Zealand responded. The advertising and pharmaceutical industries were incensed and actively tried to discredit this advocacy.[2] Four out of five general practitioners writing back felt negatively about direct-to-consumer advertising. This feeling is reflected in the statements supporting a ban issued by all of the main New Zealand health professional bodies and a number of consumer groups.[3] The then Health Minister repeatedly stated a desire to heed this advice and to ban brand direct-to-consumer advertising.[6] The New Zealand cabinet supported exploring this through the trans-Tasman harmonisation process. Whether that promise can be fulfilled may now rest with yet another round of public consultations.

Even if brand advertising can be banned via the trans-Tasman agreement, both countries (and many others) will still be faced with the growing problem of regulating 'disease awareness' advertising which is seen by many as direct-to-consumer advertising by the back door.[7]

The Australia-US Free Trade Agreement could be a step towards less regulation in Australia. The Australian Consumers' Association website lists some of the tricks used to circumvent the current Australian regulations, with several examples of back door direct-to-consumer advertising.[8] All of this would be fine if direct-to-consumer advertising actually informed consumers, but the evidence suggests it does not. The recent and ongoing debacle with COX-2 inhibitors and the increased harm resulting from the extensive and misleading direct-to-consumer advertising in the USA have reawakened calls for stricter regulation of drug promotion around the world.

New Zealand has adopted a system of 'self-regulation' for all drug promotion. This includes a much publicised, industry-run, pre-vetting service, the Therapeutic Advertising Pre-vetting System (TAPS). On the strength of TAPS, central regulators (Medsafe) have relinquished any active monitoring role. As expected, given their diametrically opposed perspectives, the pre-vetting process is simultaneously lauded by the industry and decried as ineffective by those with a public health focus. It is very brief and importantly does not involve any technical pre-vetting of the accuracy or balance of the scientific basis for the claims. Larger companies can, on payment of a fee, apply to pre-vet their own advertisements.

Complaints about advertising to consumers can be made to an industry-funded advertising standards authority complaints board.* The identity of complainants is publicised and the process can be daunting for individual consumers and organisations alike.[9] Penalties for breaching the code are limited to withdrawing advertisements, usually after the offending material has had its impact and finished its run. Direction to publish corrective statements is rare. The New Zealand pharmaceutical industry organisation also has its own code of conduct on promotion which considers complaints about all promotion of medicines. This can impose minor financial penalties which are occasionally invoked, usually following a complaint from a competitor. The recently proposed advertising regime under the joint trans-Tasman agency developed by the Interim Advertising Council[10] will in our view be ineffective without a mechanism for independent technical and scientific pre-vetting (very expensive), tight monitoring and stiff penalties for violations. Without these three crucial components we have little confidence that anything will change, with partial, unbalanced and misleading promotion predominating. It seems unlikely that anything will really change while the policy of user pays and self-regulation of medicines promotion remains.

Neither self- (New Zealand) nor central (USA) regulation has been able to control direct-to-consumer advertising. Australia would do well not to let the genie out of the bottle. In the two countries where no one thought to provide a cork it is proving very difficult to get it back in. It is important that prescribers who are at the sharp end of direct-to-consumer advertising make their views known now, before the lobbyists influence the politicians to further liberalise an increasingly hands-off

* See www.asa.co.nz for a description of the Advertising Standards Authority, including TAPS

approach which allows industry to set its own standards.

In summary, what both New Zealand and Australia need is greater and more accessible independent consumer health information, not impossible to regulate, industry-sponsored direct-to-consumer advertising.

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Further reading

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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.

Eplerenone

Editor, – I read with interest the new drug review of eplerenone (Aust Prescr 2005;28:130–1). This review contains a number of statements that require clarification.

First, it is stated that gynaecomastia and breast pain still occur with eplerenone (as has been a major adverse effect of spironolactone). This is a somewhat disingenuous interpretation of the data as in fact no study has shown an excess of these events with eplerenone compared to placebo. As with any adverse effect, there is a spontaneous background event rate that is not further added to by eplerenone therapy.

Next, it is implied that because spironolactone reduces relative risk of death by 30% in patients with severe heart failure it is a more effective drug than eplerenone, that 'only' reduced risk of death by 15% in post-myocardial infarction (MI) heart failure patients. Again, making comparisons regarding the impact of therapies **across** trials is poor science and tells us nothing about the relative merits of individual drugs because of the differing disease states and background treatments in the differing trials.

Finally, and most importantly, it is stated that spironolactone is well known and inexpensive and 'thus unlikely to be superseded until more data about eplerenone are available'. This statement clearly implies that the two drugs can be used interchangeably for the same clinical indication. Just as eplerenone should not be given to patients with severe heart failure (because it has not as yet been tested in such a patient population) the same is true of spironolactone

in post-MI heart failure. The suggestion that these drugs are interchangeable challenges fundamental principles of evidence-based prescribing and should be utterly rejected.

Henry Krum
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Professor Krum has been a consultant to Pfizer, manufacturer of eplerenone.

Editorial comment:

Gynaecomastia may take several months to develop. While the frequency has not increased during studies of heart failure, it has been higher than with placebo in studies of hypertension. According to data reviewed by the US Food and Drug Administration 1% of men taking eplerenone for hypertension developed breast symptoms.[1]

While the selectivity of eplerenone may explain why it has less effect on sex hormones than spironolactone, it is not clear if this results in greater efficacy. If the efficacy depends on aldosterone antagonism then spironolactone should also be effective. Spironolactone is known to be effective in heart failure, but, as Professor Krum highlights, the supporting evidence does not come specifically from patients who start treatment 3–14 days after an acute myocardial infarction. This has resulted in the cost-effectiveness of eplerenone being compared to placebo rather than spironolactone.[2]

As 50 patients need to be treated with eplerenone for a year to prevent one death, there is a need to find out if spironolactone could be more cost-effective. We would encourage a comparative trial of eplerenone and spironolactone, although there may be no incentive for the manufacturers to carry out this comparison.

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Balsalazide sodium

Editor, –The New drug comment about balsalazide sodium (Aust Prescr 2005;28:104–6) described the use of this product by citing two 1998 studies which compared it to mesalazine in double-blind trials with ulcerative colitis patients.[1,2] I wish to bring to your attention that the conclusions of these studies are not generalisable to the mesalazine products available in Australia, since the mesalazine product used in these studies (Asacol) is not marketed in this country. Asacol has a different coating from the mesalazine products marketed in Australia.

There are several mesalazine formulations available globally, which have different coatings and therefore different release mechanisms[3,4,5] which may lead to different therapeutic efficacy. These different formulations are also supplied in different strengths. The only two oral formulations of mesalazine available in Australia are Salofalk and Mesasal which are delayed-release preparations of mesalazine coated with a resin that dissolves at a pH greater than six (the approximate pH of the ileum/colon). In contrast, Asacol consists of 400 mg of mesalazine destined for release in the terminal ileum or colon as its resin coating dissolves at a pH greater than seven.

Mesalazine products with different coatings are not therapeutically equivalent and are not interchangeable. The results of the Abacus Investigator Group studies therefore cannot be generalised to all mesalazine preparations, including the oral preparations available in Australia. Such generalisations would be misleading.

The comment also claims that 'mesalazine is absorbed, but is rapidly metabolised and excreted in the urine'. However, like balsalazide, very little mesalazine is systemically absorbed after being orally administered. The active drug is believed to act topically on the intestine and the main route of elimination is the faeces.[6]

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Suicide and antidepressants in children

Editor, –The editorial 'Suicide and antidepressants in children' (Aust Prescr 2005;28:110–11) is potentially misleading. It stated that there was a 'small but significant increase in suicide risk'. This is not so.

Analysis of the UK General Practice Research Database found no suicides among the 6976 people aged 10–19 years who had been prescribed one of two selective serotonin reuptake inhibitors (SSRIs) or two tricyclic antidepressants between 1993 and 1999; however, 15 people in that age group who died by suicide had not received an antidepressant.[1] Similarly, a toxicological review of 14 857 suicides between 1992 and 2000 in Sweden detected no SSRIs in the 52 suicides under 15 years of age. In the 15–19 years age group those taking SSRIs had a lower relative risk of dying by suicide than those taking other antidepressants.[2]

Clinicians with responsibility for children and adolescents can be reassured by these data, and by the American Academy of Child and Adolescent Psychiatry and the American Psychiatric Association guidelines[3] which have been endorsed by over a dozen United States organisations comprising a 'national coalition of concerned parents, providers, and professional associations'. Similar guidance has been provided by the Australian/Australasian Colleges of General Practitioners, Physicians and Psychiatrists.[4]

In view of the strong association between child and adolescent mood disorders and suicide[5], it does not appear prudent to withhold antidepressant medication in young people with severe depression if non-pharmacological measures are ineffective.

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Professor Goldney has received honoraria and research grants from a number of pharmaceutical companies for presentations and research on depression.

Dr Jon N. Jureidini and Professor Anne L. Tonkin, authors of the article, comment:

Analysis by the US Food and Drug Administration (FDA) shows a statistically significant doubling (from 2 to 4%) in suicidal thinking and acts in randomised controlled trials. It is true that increased suicidal thinking and acts need not lead to completed suicide, but Professor Goldney seems unduly reassured by the fact that none of the 4000 individuals in those trials completed suicide. Based on 2003 Australian figures of 1.2 completed suicides/100 000 in people under 18 years old[1], a cohort 100 times greater is required to expect to see a single completed suicide in the time frame of these trials. While Professor Goldney is reassured by apparently favourable associations between antidepressant use and completed suicide, the data are inconclusive.[2]

In appealing to authority, Professor Goldney prefers the American Psychiatric Association and Academy of Child and Adolescent Psychiatry to the findings of US and British regulatory authorities cited in our paper. Inaccurate claims made by these organisations include 'a large number of clinical research trials … have clearly demonstrated the effectiveness' of antidepressant medications for children and adolescents with depression.[3] It seems that these organisations are subject to wishful thinking that things cannot be as bad for antidepressants as the evidence suggests.[4] Further, unlike Professor Goldney, the report of the various professional colleges[5] does not provide information about potential conflicts of interest.

General practitioners who find non-pharmacological means ineffective should be consulting with colleagues expert in child and adolescent mental health rather than prescribing unproven, potentially dangerous drugs.

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Thyroxine stability and formulation: why the secrecy?

Editor, – In May 2004 Australian pharmacists were instructed that thyroxine tablets should be stored refrigerated, before and after dispensing. This uniquely Australian directive, which carried the imprimatur of Sigma, the sole supplier of thyroxine tablets in Australia, and the Therapeutic Goods Administration, appears to have been ill-considered.[1] Dampness should be avoided during storage of thyroxine[2]; repeated daily opening of a refrigerated glass bottle over many months can make the tablets damp, with loss of potency.[1] Sigma has now conceded that tablets in current use from unsealed bottles should not be refrigerated[1], although pharmacists generally are unaware of this change.

In letters to doctors and pharmacists during 2005, Sigma foreshadowed a change in formulation so that thyroxine tablets will be presented in five bottles of 40 tablets, with a recommendation to refrigerate the unopened bottles, but not the bottle in current use. In support of this change, Sigma refers to 'new stability data'. However, Sigma has refused to present these data for professional scrutiny, except under terms of a confidentiality agreement that precludes discussion or peer review.

The reasons for seeking public disclosure of these 'new stability data' have been set out in detail.[3] The health of about 200 000 Australians depends on thyroid hormone replacement. They, and those who accept responsibility for prescribing this medication, have a right to know the details of the sole preparation that is available. If storage temperature is a key factor in maximising the tenuous shelf-life of thyroxine, our local data might be important in addressing the broader problems of stability, potency and bioavailability of thyroxine.[4,5]

If we cannot achieve a culture of open disclosure between the pharmaceutical industry and consumers for a medication as straightforward as thyroxine, what chance do we have with medications that are shrouded in commercial confidentiality, contentious trial data, patent law and unexpected or contentious adverse effects? Do we really care whether there is an ethos of evidence-based medicine in the manufacturing, regulatory and dispensing arms of pharmaceutical practice? If so, the 'new stability data' should be made known. Only in that way can consumers establish whether the modified formulation is necessary, or whether it is being introduced as a face-saving initiative.

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The international influence of *Australian Prescriber*

Editor, – I enjoyed reading the commemorative issue of *Australian Prescriber* (*Australian Prescriber* – the first 30 years, Aust Prescr 2005;28:120–2). I did not know of the 'near death' or even the year the journal disappeared. It just goes to show the struggle we have in trying to provide unbiased drug information in the face of enormous biased commercial interest.

One important fact missing from the article was the role of *Australian Prescriber* in the Asia-Pacific region. We in drug regulation and as teachers of clinical pharmacology in medical schools really appreciate copies of *Australian Prescriber*. The articles are avidly read by medical students (especially when prompted that examination questions may be based on them) and even by drug regulators in the region. For example, when evaluating a new chemical entity submitted for registration, reviews of the drug evaluation by *Australian Prescriber* are included in the dossier and provide a very important supportive tool for the regulators.

I would therefore like to add the congratulations of many people in the region to the *Australian Prescriber* on its 30 years. We hope that the journal will continue to be an independent source of information for our region for many more years.

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Managing hepatitis C in the community

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Summary

Infection with hepatitis C can lead to chronic hepatitis and cirrhosis of the liver, however this progression is not inevitable. Health professionals need to consider who may be at risk of the disease as the infection can be asymptomatic. If hepatitis C is diagnosed and the patient is found to have significant liver damage, treatment with ribavirin and injectable peginterferon alfa is indicated. These drugs can produce a sustained response in up to 90% of patients depending on the viral genotype. During treatment it is important to reduce other stresses on the liver such as a high alcohol consumption.

Key words: antiviral drugs, liver.

(Aust Prescr 2006;29:36–9)

Introduction

Hepatitis C is a worldwide problem and in Australia over 280 000 people are estimated to have been infected by the hepatitis C virus. Not everyone infected with the virus requires drug treatment, but those that do may be untreated, despite the fact that combination antiviral therapy can achieve a sustained response in up to 90% of those infected with particular genotypes of the virus. This significant disparity between the number of infected individuals and the number treated exists despite a significant effort being directed towards improving the management of hepatitis C in the community.[1,2,3,4,5,6]

While many people have asymptomatic infection, a significant minority (15–20% over the course of 30 years) will progress through chronic hepatitis to cirrhosis and complications of cirrhosis, namely liver failure and hepatocellular carcinoma. Hepatitis C is currently the most common indication for liver transplantation in Australia and many other Western countries. This situation is unlikely to change in the immediate future.

Diagnosing hepatitis C

The majority of patients who contract hepatitis C are asymptomatic and unaware that they have the virus and that they can transmit the virus to others. Certain groups of people are at increased risk of being exposed to the virus and practitioners should discuss hepatitis C testing with these groups (see box).

It is important to routinely ask all patients questions about the possibility of blood-to-blood contact and possible blood-borne virus exposure to allow an appropriate assessment of the need for testing for blood-borne viruses. Before testing, the meaning, implications, natural history, treatment options and notification requirements of a positive result need to be discussed.

Laboratory tests (Fig. 1)

The most appropriate test for screening for hepatitis C is the hepatitis C antibody test. A positive hepatitis C antibody result with abnormal liver function tests gives a greater than 80% likelihood that the patient has been infected. This can be confirmed with a test for viral RNA. If the patient is considering treatment, a hepatitis C genotype and viral load can be ordered before commencing therapy. In Australia, 55% of patients are infected with genotype 1 and 35% with genotype 3.

After the diagnosis

Once a patient has been identified as hepatitis C RNA positive with abnormal liver function tests, discuss the possibility that they may have significant liver problems and may need to consider antiviral therapy. Patients diagnosed with hepatitis C require a detailed history of drug use including their alcohol consumption. Other causes of abnormal liver function tests need to be explored and these include non-alcoholic fatty liver disease, medication-induced liver dysfunction and genetic disorders such as haemochromatosis and alpha$_1$ antitrypsin deficiency. Patients need to be given advice on their alcohol intake if it is above recommended safe drinking levels and patients need to be advised on managing obesity and regulating blood lipids.

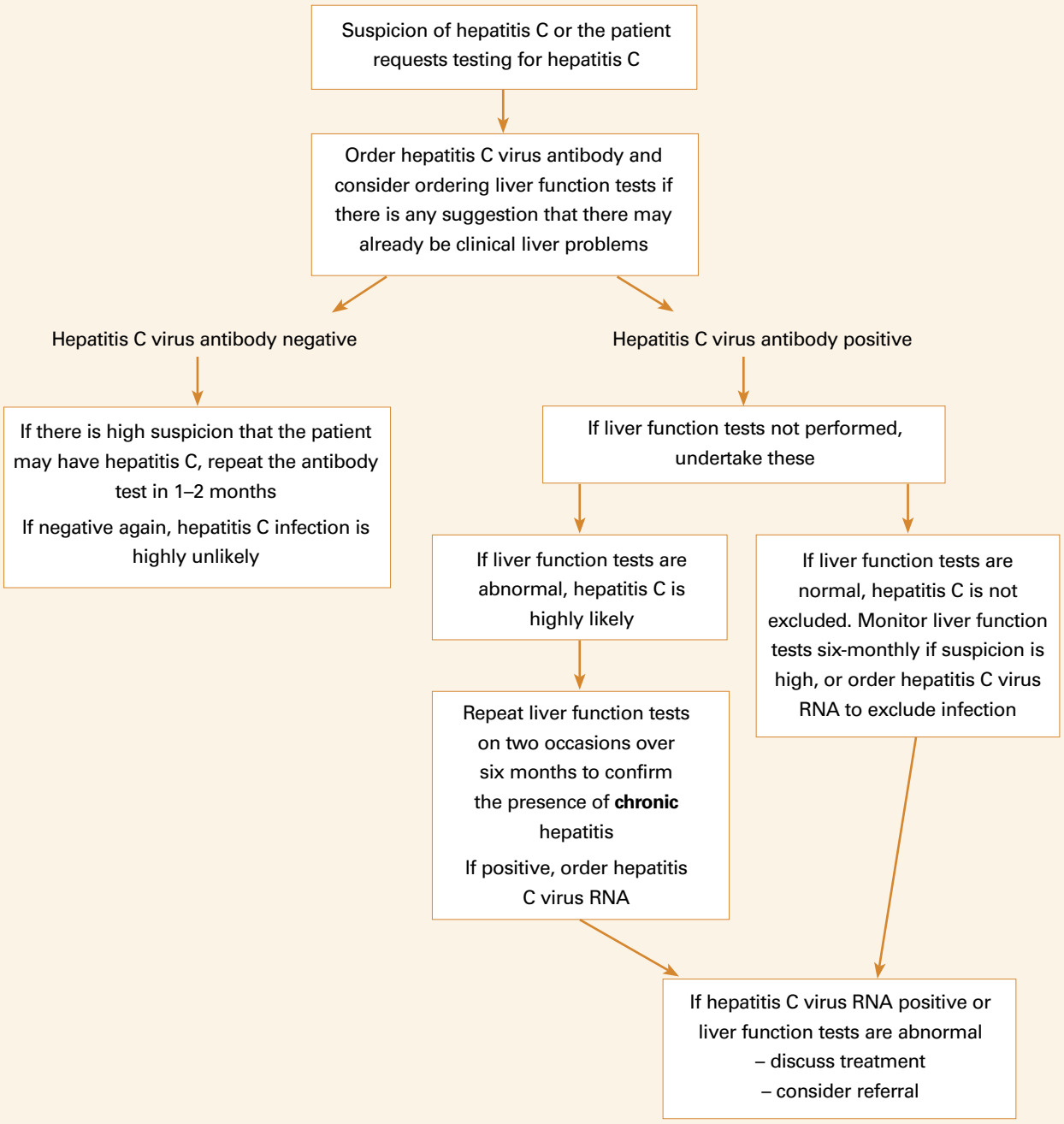
Consider discussing and testing for hepatitis C in these groups

People who have:

- received a blood product in Australia before 1990
- received blood products in other countries
- ever injected drugs
- ever been in a corrections facility
- been born in countries with a high prevalence of hepatitis C
- a partner with hepatitis C
- had multiple sexual partners[4]
- tattooing and body piercing

Fig. 1

Pathway for testing for hepatitis C



Risk factors for more progressive disease include being male, overweight, consuming alcohol regularly and being infected at an age greater than 45 years. Conversely, females infected at a young age who do not drink and who are of average body weight may have a very slow progression of their liver disease over 20–30 years.[7]

Discuss what treatments offer

Treatment options should be discussed with all patients with chronic hepatitis C. Patients with normal liver function tests and no signs of liver disease may decide not to undergo treatment and this decision should be supported. Many patients can be assured that this deferring of treatment is appropriate as liver disease progresses slowly in the majority of patients. They can be observed with six-monthly liver function tests. A small number of patients with normal liver function tests still choose to have therapy to eliminate the risk of infecting others and this indication is now subsidised by the Pharmaceutical Benefits Scheme (PBS).

The combination of injectable pegylated interferon alfa-2a or -b and oral ribavirin can provide sustained response rates of 45–90% in patients with hepatitis C (Table 1). A sustained viral

Fig. 2

Pathway for referral for treatment to liver clinic

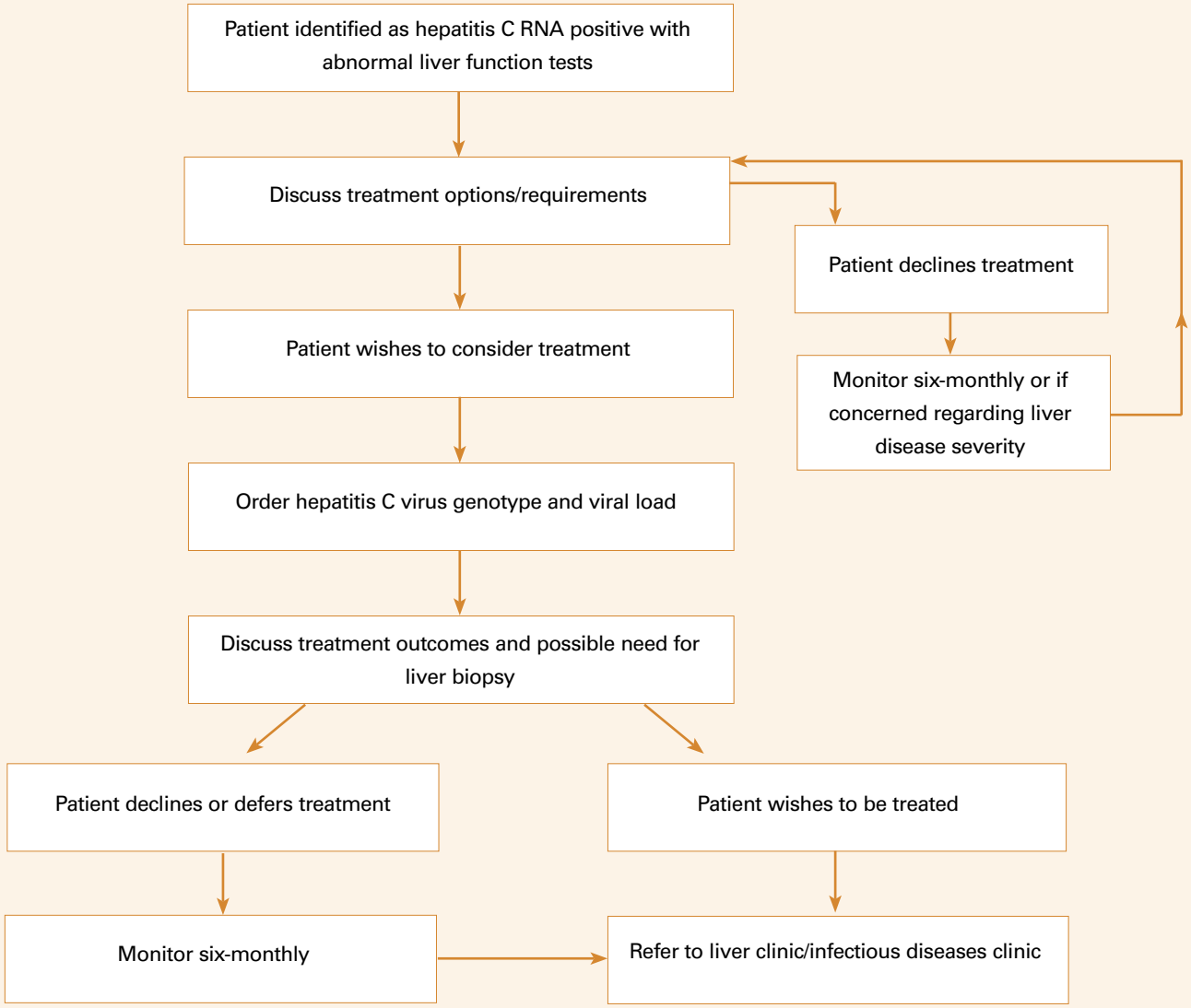


Table 1

Outcomes of combination therapy (pegylated interferon and ribavirin)

Genotypes 2 and 3	
Duration of therapy	6 months
Expected sustained viral response*	70–90%
Genotypes 1 and 4	
Duration of therapy	12 months
Expected sustained viral response*	40–50%

* there is no hepatitis C RNA in the serum six months after completing treatment

response is defined as the absence of hepatitis C RNA in serum and liver six months after cessation of therapy. Relapse within six months of stopping therapy occurs in 10–20% of those with genotype 2 and 3 infection and in 50–55% of those with genotype 1 and 4 infection. While 5% of patients may relapse in the period between six and 12 months after ceasing therapy, those that remain hepatitis C RNA negative at 12 months can expect their sustained response to be maintained for years with the longest follow-up now extending for greater than 15 years.

Who should be referred for hepatitis C antiviral therapy? (Fig. 2)

All patients with signs of liver disease of any severity and those who wish to consider treatment should be referred to a liver clinic. Now that liver biopsy is no longer required to access

PBS-subsidised treatment, it is probable that a greater number of patients will request referral to consider antiviral therapy. Many patients with signs of significant liver disease will still be recommended to undergo a liver biopsy as the presence of cirrhosis can modify the approach to the use of interferon and ribavirin.

Will most patients with hepatitis C decide to undergo treatment?

At present some patients, having been given advice about their liver function and the treatment outcome, decide to defer treatment. This is a reasonable decision for many patients, particularly those who have a genotype 1 or 4 infection which responds less well to current therapies. However, if a patient has clear clinical signs or biochemical evidence of significant liver disease, this decision should be questioned. If necessary these patients can be referred for further discussion with a second clinician with an interest in hepatitis C to ensure that they are receiving at least two opinions on whether to defer treatment or not.

Adverse reactions to treatment

Some patients tolerate therapy well and develop few adverse effects from their course of therapy. A significant percentage do develop troublesome adverse effects which include mood swings, irritability, headaches, insomnia, flu-like symptoms, dry skin, myalgia, arthralgia and thinning of the hair. Treatment can cause exacerbation of epilepsy, diabetes and psoriasis.

A small percentage of patients develop serious adverse effects which include anaemia, thrombocytopenia, leucopenia, depression and psychosis. Sudden haemolytic anaemia can precipitate cardiovascular symptoms in those who have previously not had evidence of clinical ischaemic heart disease. In older patients it is wise to explore their family history of coronary artery disease and to perform an ECG if there is any suggestion that they may have asymptomatic coronary artery disease.

Follow-up

The care of patients is often shared between the liver unit and general practitioners. To assist general practitioners with monitoring their patients, liver units in Australia will normally provide a protocol for testing. Patients should be tested for liver function, full blood count and thyroid function second monthly and if there is concern other investigations may be ordered.

Conclusion

Hepatitis C itself is often not going to cause severe liver disease. It is the combination of the viral infection plus factors such as alcohol excess, obesity, diabetes and haemochromatosis that leads to more severe liver disease. Addressing the secondary factors will lead to significant changes in liver function thus allowing a decision on requirements for antiviral therapy to be made in a more rational way.

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Conflict of interest: none declared

See also **Dental notes** page 52

Patient support organisation

Australian Hepatitis Council

The states and territories have independent Hepatitis Councils which provide information, support, referral and counselling about hepatitis C. The Australian Hepatitis Council website contains many resources, fact sheets and links.

Website: www.hepatitisaustralia.com

Self-test questions

The following statements are either true or false (answers on page 55)

1. Most patients with hepatitis C will develop cirrhosis within 20 years.
2. A patient's lifestyle may affect the response to treatment for hepatitis C.

Meals and medicines

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Summary

Food and its constituents may have a significant effect on both the rate and extent of absorption of drugs after oral administration. Understanding the effect of meals on medicines enables health professionals to advise patients about taking medicines with or without food. Co-administration of drugs with food generally delays drug absorption. However, meals may have a variable effect on the extent of absorption – depending on the characteristics of the meal, the drug and its formulation. Some drugs have strict guidelines about when they should be taken in relation to meals. Generally, patients should be advised to take their medicines consistently at the same time with respect to meals.

Key words: bioavailability, drug interactions, food.

(Aust Prescr 2006;29:40–2)

Introduction

Understanding the possible clinical implications of taking medicines with or without a meal is important for achieving quality use of medicines. Although the effect of food is not clinically important for many drugs, there are food–drug interactions which may have adverse consequences. Often these interactions can be avoided by advising the patient to take their medicines at the same time with respect to meals.

The effect of food on absorption

The formulation of a drug influences its absorption. Food can affect both the rate and extent of absorption (Table 1).

Rate of absorption

Meals slow down gastric emptying and this can delay drug absorption. The composition of the meal influences the rate of gastric emptying – high fat meals lead to delayed gastric emptying. A delay in the drug reaching the small intestine can delay its subsequent absorption into the systemic circulation. Based on these observations, oral administration of a medicine under fasting conditions is often recommended when rapid absorption (and hence rapid onset of therapeutic effect) is needed. For most medicines, especially those used for chronic conditions, a delay in the onset of absorption is of no clinical consequence as long as the amount of drug absorbed is unaffected.

Extent of absorption

Food has the potential to either increase or decrease the extent of drug absorption. Understanding food–drug interaction mechanisms enables the clinician to provide appropriate advice to patients about taking medicines with respect to the timing and composition of meals.

The effect of food depends on the physicochemical and pharmacokinetic characteristics of the drugs.[1] The clinical significance of the effect will in turn depend on the pharmacodynamic characteristics of the drug. For example, the poorly water soluble antiretroviral drug saquinavir should be taken with food to allow bile enhancement of its dissolution which then facilitates absorption. The extent of absorption is more than doubled by taking saquinavir after a full cooked breakfast. Taking saquinavir on an empty stomach reduces its bioavailability and could lead to therapeutic failure.[1]

Delayed gastric emptying after a meal and the associated gastric acid secretions can reduce the bioavailability of some medicines that are acid labile. The constituents of a meal may also specifically interact with drugs (Table 2). Calcium and other cations in food can form insoluble chelates with some medicines preventing their optimal absorption. Bisphosphonates are therefore recommended to be taken with plain water to prevent the formation of chelates which significantly reduce bioavailability.

Grapefruit juice: an important example

Co-ingestion of grapefruit juice and certain drugs (Table 3) significantly increases their bioavailability because the constituents of the juice inhibit pre-systemic drug metabolism or transport. This increase in bioavailability can lead to excessive beneficial or adverse effects.[2] The effects of grapefruit juice are complex and have been widely studied.[3,4]

A single glass of grapefruit juice is enough to increase the bioavailability of some drugs. If the juice is drunk over several days the effects are long-lasting[3,4], so simply separating the dose of medicine and the ingestion of grapefruit juice does not prevent the interaction. For this reason grapefruit juice ingestion should be avoided completely with certain drugs, for example cyclosporin.

Could grapefruit juice be routinely used to enhance the bioavailability of some medicines? The answer would appear to be no because the effect of grapefruit juice on drug absorption is highly variable. It depends on the constituents of the juice, how it is prepared and varies with brands and batches.

Table 1

Mechanisms of food–drug interactions [1]

Mechanism	Medicines or class	Implication	Actions *
Poor acid stability	azithromycin† ampicillin† erythromycin (some salts)† isoniazid phenoxymethylpenicillin	Exposure to acid and prolonged gastric residence leads to chemical degradation and reduced bioavailability with risk of therapeutic failure	Take on an empty stomach († or at a consistent time with respect to meals)
Chelation	bisphosphonates ciprofloxacin norfloxacin penicillamine	Reduced therapeutic effect	Take on an empty stomach († or at a consistent time with respect to meals)
Acid dependency	amprenavir itraconazole (capsules) ketoconazole	Reliable absorption depends on acid environment	Take with meals or at a consistent time with respect to meals
Bile acid or fat enhanced drug dissolution	acitretin carbamazepine griseofulvin isotretinoin halofantrine mefloquine saquinavir tacrolimus	Enhanced bioavailability	Take with meals or at a consistent time with respect to meals
Physical binding/adsorption	digoxin	Digoxin may bind to fibre reducing its bioavailability	Avoid concurrent ingestion with fibre or take digoxin at consistent time with respect to meals
Reduced gastric emptying	most medicines	Reduced rate of absorption	Take at a consistent time with respect to meals

* Note: Taking a medicine with a meal implies taking the dose within 30 minutes of a meal. Taking a medicine on an empty stomach implies taking the dose one hour before or two hours after a meal.

Table 2

The effect of specific dietary components on selected drugs [1]

Specific foods	Medicine (class)	Advice on meals and implications
Vitamin K rich foods	warfarin	Dietary intake of vitamin K rich foods should be consistent to avoid fluctuation in INR. Abstinence is not required.
Potassium rich foods and supplements	ACE inhibitors, potassium sparing diuretics, and angiotensin receptor antagonists	Foods and accompaniments high in potassium should be ingested in moderation to avoid the risk of hyperkalaemia
High protein meal	levodopa	Reduce the cerebral uptake (not bioavailability) of levodopa and potentially reduce clinical efficacy
Tyramine rich foods	monoamine oxidase inhibitors	Significant risk of hypertensive crisis
Calcium rich foods	tetracycline quinolones	Co-administration of calcium rich foods and supplements results in chelation and reduced drug absorption with a risk of therapeutic failure

Table 3

Drugs affected by oral co-ingestion of grapefruit juice [3,4]

Advice to patients	Drug
Avoid co-ingestion of grapefruit juice due to risk of unwanted effects	amiodarone atorvastatin cyclosporin diazepam felodipine midazolam nifedipine saquinavir sildenafil simvastatin verapamil
Co-ingestion of grapefruit juice may be acceptable with appropriate monitoring and awareness	amlodipine diltiazem ethinyloestradiol pravastatin prednisolone/prednisone theophylline

Grapefruit juice is not 'pharmaceutical grade' or consistently of the same 'quality', so co-administration with a drug would lead to a variable response.

Studying the effect of food

The product information approved by the Therapeutic Goods Administration is the main source of information about the possible effects of food on drug absorption. This information is generally derived from a 'food effect study' that is conducted during drug development. Typically, this involves a randomised cross-over single dose pharmacokinetic study in healthy people. They take the drug of interest after an overnight fast and also after a standard high fat breakfast. This design is meant to examine the effect of food under 'extreme' conditions. Unfortunately, a volunteer eating a high fat meal does not necessarily reflect the circumstances of the patients who will take the drug. Dosing recommendations with respect to food derived from these studies may therefore not provide the best guide to the actual impact of food on drug absorption.

Taking medicines with meals to help adherence, tolerability and efficacy

Prescribing a drug regimen that fits in with the patient's daily routine (which is usually centred around mealtimes) can enhance the patient's adherence to treatment. This leads to the general recommendation that patients should take their medicines at prescribed and consistent times relative to their meals. This is despite the fact that the absorption of some medicines may be significantly reduced when taken with food, for example atorvastatin and thyroxine. Patients should also be informed if particular foods can interfere with their treatment (Table 2).

Some medicines (for example non-steroidal anti-inflammatory drugs and metformin) are taken with food to minimise the risk of gastrointestinal adverse effects. Repaglinide and the sulfonylureas should be taken before a meal to avoid the risk of significant hypoglycaemia. In the case of repaglinide, if a meal is skipped then the drug dose should also be skipped. Similarly, taking acarbose with meals is essential to ensure its maximum efficacy in delaying the intestinal absorption of carbohydrates.

Conclusion

Meals may have variable and often unpredictable effects on drugs via a range of mechanisms. By understanding and appreciating the clinical consequences of these effects health professionals can provide advice about the appropriateness of ingesting medicines with respect to the times and the composition of meals. The provision of timely and appropriate advice about the possible effects of meals on medicines and the importance (or lack) of the timing of meals and medicines is an important issue impacting on the quality use of medicines.

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Associate Professor McLachlan and Associate Professor Ramzan have acted as consultants to the pharmaceutical industry and are members of the Pharmaceutical Subcommittee of the Australian Drug Evaluation Committee (ADEC).

Self-test questions

The following statements are either true or false (answers on page 55)

3. Taking bisphosponates with milk increases their bioavailability.
4. The bioavailability of some drugs is increased by a high fat meal.

Weight management

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Summary

Obesity treatment is effective and moderate weight losses can be maintained for 4–5 years. Even small weight losses are effective in preventing diabetes, improving the control of diabetes and improving the cardiovascular risk profile. They also improve mobility, sleep apnoea and general well-being. There is a place for pharmacotherapy but drugs must be used in conjunction with a behavioural change (lifestyle) program. Pharmacotherapy (currently orlistat and sibutramine are available) used for 2–4 years can help to maintain weight loss, but the ideal duration of such therapy is uncertain. When pharmacotherapy is ceased some weight will be regained. This regain generally results in the weight increasing to the weight that would have been achieved by effective lifestyle programs. Other therapies such as very low calorie diets and obesity surgery also produce long-term successful weight loss.

Key words: obesity, orlistat, sibutramine.

(Aust Prescr 2006;29:43–7)

Introduction

In the six years since an article on 'Obesity management' appeared in *Australian Prescriber*, a great deal has changed. Obesity is now recognised as a major health and social issue. The importance of obesity in the production of disease is acknowledged in the technical report of the World Health Organization (WHO)[1] and the more recent clinical practice guidelines produced by the National Health and Medical Research Council.[2,3] An important advance is the recognition that small weight losses (5 kg or so) can have major effects on cardiovascular risk factors and the incidence of diabetes. In addition, there are more effective weight management programs, and a greater understanding of many aspects of obesity (including genes and obesity, the effects of obesity and the role of adipose tissue).

Aetiology

For obesity to occur there must be either an increase in energy intake over our body's needs, a decrease in energy expenditure, or both. In Australia there is an abundance of relatively cheap food and there is a decline in exercise and the activity of daily living (due to increased use of technology, 'less time', safety fears and changes to our living environment). Genetic causes are very rare.

Adipose tissue

Adipose tissue is now known to have many functions other than energy (triglyceride) storage. It is an active endocrine organ[4] secreting leptin, adiponectin and resistin among other hormones. Most of these (with the exception of adiponectin) increase as the adipose tissue mass increases. The major site of secretion (with the exception of leptin) is the visceral or abdominal adipose tissue.

In humans leptin appears to have a role in protection from starvation, but the role of resistin is being debated. Adiponectin is an 'insulin sensitising' hormone and its absence may be important in the production of diabetes mellitus. Certainly people with genetic defects of adiponectin synthesis develop diabetes.

Adipose tissue also produces cytokines and pro-inflammatory factors that may contribute to atherosclerosis and vascular disease. A reduction in adipose tissue should be a major aim in our management of cardiovascular disease. The benefit of weight loss and maintenance therefore needs to be emphasised.

Prevalence of obesity

The recent AUSDIAB study[5] found that approximately 20% of Australian adults were obese (BMI* greater than 30), with slightly more women than men being obese. Two in three Australian adult males are overweight or obese, as are approximately 50% of females. In children the prevalence of overweight and obesity has doubled over the last 10–15 years, so now 5–6% are obese and 14–18% overweight.[6]

The increase in prevalence is worldwide and because of increasing obesity we may for the first time for a thousand years be facing a decrease in our life expectancy.[7]

Risks associated with obesity

Obesity increases mortality and is associated with both metabolic disease (diabetes, hypertension, dyslipidaemia and coronary heart disease) and mechanical disease (osteoarthritis and obstructive sleep apnoea). We now know that obesity is a risk factor for certain cancers (breast, uterus, prostate, bowel, kidney and pancreas).

* Body mass index: weight (kg)/height (m)^2

While there are no good studies of the effect of intentional weight loss on mortality, an early study gave encouraging results.[8] A number of long-term trials are now studying the effect of 'lifestyle modification' programs, with or without pharmacotherapy. Minor weight losses can have major effects on fertility and such weight loss improves the effectiveness of *in vitro* fertilisation programs.

Assessment of obesity

The BMI remains the simplest clinical measure of adiposity, although it has limitations at the extremes of age and in very muscular patients. There is now an international standard of BMI for age, for use in children and adolescents. There is considerable discussion about whether the BMI cutpoints for overweight and obesity used for Caucasians are appropriate for those of Asian origin or Indigenous Australians as there is some evidence that they may have a greater risk of disease at lower BMIs.[9] The WHO has produced a series of cutpoints[10] to help with this conundrum, but whether they need lower BMIs needs to be determined in a definitive study.

What is not in dispute is the need to measure central (abdominal or visceral) adiposity in clinical assessment. Abdominal adiposity is strongly associated with metabolic disease (which includes type 2 diabetes, dyslipidaemia, hypertension and cardiovascular disease) and the simplest measure of it is the waist (really abdominal) circumference. Men at high risk have waists measuring more than 102 cm and women at high risk have waistlines greater than 88 cm. Risk increases at waists of 94 cm in men and 80 cm in women. There is also accumulating evidence that these measurements are too great for Asians, so measures of 90 cm for men and 80 cm for women have been suggested as markers of high risk. Other measures of central adiposity include the waist:hip ratio, but there is argument about whether this ratio is the best assessment for epidemiological studies.

Weight management strategies

It is important to spend time with the patient and to approach the issue of weight holistically. Several things need to be emphasised at the outset:

- current management strategies are effective and it has been possible to maintain weight losses for four years (or even longer with surgery)
- modest weight losses of the order of 5–10% of body weight produce significant benefit with cardiovascular risk reduction, control of diabetes, improvements in sleep apnoea and in mobility, increased fertility and improved quality of life
- relatively small weight losses can reduce the incidence of diabetes in those at high risk.

A behaviour change program, to alter eating patterns and increase activity, is the basis on which all weight loss and maintenance therapies are built. A daily reduction in energy intake of 500–600 kcal aids weight loss (one calorie is equal to 4.18 joules). This can be achieved by reducing intake, preferably by reducing saturated fat while increasing the intake of fibre and carbohydrates with a low glycaemic index (GI). Protein intake may also be increased if desired. Those who maintain weight loss over the long term do so with a reduction in fat intake. Other diets such as the low GI diet and the low carbohydrate-high protein diet (e.g. Atkins, Zone) are certainly effective, but mainly appear to work by increasing satiety and/or reducing intake. The CSIRO Total Wellbeing diet combines an increase in protein with lower carbohydrate intake. The diet prescribed for weight loss should be acceptable to the patient, based on their habitual type of diet and, with a number of small changes, resulting in a reduced energy intake.

Activity should be increased. This can start with strategies to increase incidental activity (daily activities such as walking up stairs, to the railway station or to work) but can include a specific exercise program. The use of tools such as a pedometer may help and certainly it appears that prescribing exercise is important.

When behaviour changes are suggested it is important to follow up that they have been implemented and to then make further small changes or investigate why there are difficulties with the prescribed changes. Simultaneously, consider the patient's habits and any individual problems that may be contributing to the patient's weight problem. Proper medical management of problems, such as reduced mobility due to arthritis, and sleep apnoea, must be included in any 'lifestyle intervention' program.

Despite the ingrained pessimism in the Australian medical community these programs are effective. Several lifestyle interventions have been found to be beneficial in communities as diverse as the USA, Finland and China. It is possible to induce and maintain weight loss of the order of 4–5 kg for four years which is clinically significant. For example, it reduces the incidence of diabetes by 58% in high-risk groups.[11] This approach is far more effective and does not cost much more than a pharmacological approach (the use of metformin, a cheap drug) in the same groups to prevent diabetes.[12] The greater the weight loss, the greater the reduction in incidence of diabetes. With the addition of orlistat to a lifestyle program, the maintained weight loss is 6.7 kg at four years with a reduction in the incidence of diabetes in those at risk of 37% compared with the placebo group.[13] In the Diabetes Prevention Program the lifestyle intervention produced a weight loss of 4.6 kg and a reduction in incidence of diabetes of 58% compared to the control group. Comparison of these studies would suggest that a weight loss of 6.7 kg would produce a reduction of diabetes incidence of some 80% in those at high risk.

Adjunctive therapy is considered when patients with a BMI greater than 27 do not achieve weight loss with lifestyle

changes or have additional medical reasons such as diabetes, cardiovascular risk, sleep apnoea or arthritis. This includes pharmacotherapy, the use of meal replacements, very low calorie (energy) diets and surgery for obesity in those with BMI greater than 35 and comorbidities.

It is difficult to quantify the proportion of patients needing adjunctive therapy. It depends on the enthusiasm with which the lifestyle program is administered and encouraged, the degree of obesity-related complications and metabolic disease. It is likely that 25–30% of obese people may need adjunctive therapy.

Pharmacotherapy

Currently orlistat and sibutramine are available to treat obesity. They must be used in association with a continuing weight loss and maintenance program. These drugs have different mechanisms of action, but both can add to the weight loss achieved with a lifestyle program. They also have additional benefits in cardiovascular risk reduction, the control of diabetes and other disorders.

Check weight loss in the first six weeks to three months. Patients who lose weight early in treatment will be those who obtain long-term benefit. Weight tends to be lost in the first six months of a program and then a weight maintenance phase is entered. There is usually inexorable weight gain (1–2 kg per year) in those who are obese (and not on active treatment) so maintaining their weight is a major and continuing benefit. There are always adverse effects, but these are minimal when the drugs are used appropriately.

If no weight is lost in the first six weeks to two months of the program then the dose of the drug should be increased (sibutramine). If less than 5% of initial body weight is lost by six months then consideration should be given to stopping pharmacotherapy. At the moment it is clear that continuing therapy, once adequate weight loss has been achieved, helps maintain weight loss for 2–4 years.[14,15] Careful consideration should be given to withdrawing active medication after 1–4 years of therapy (if weight loss is maintained) but the patients must be supported with an ongoing lifestyle program. As the available data show that weight regain does occur, there is still debate about the correct procedure for withdrawing drug treatment. Perhaps the most pragmatic approach, after successful weight loss and maintenance for 12–24 months, is to withdraw the drugs and to observe. If weight is regained then consider reinstating drug therapy.

Sibutramine and orlistat are of use in helping obese adolescents maintain or lose weight. There are no available data about their use in children.

Another drug which has been shown to be effective is topiramate. This is effective at maintaining and producing further weight loss after treatment with very low calorie diets[16], but the adverse effect profile is troublesome. A new drug, rimonabant, a blocker of the endocannabinoid system, is being assessed in trials.

Orlistat

Orlistat is an intestinal lipase inhibitor which acts in the gut to reduce fat absorption. The patient must eat a low fat diet, otherwise they will develop diarrhoea and/or fat leakage. The usual dose is 120 mg three times a day immediately before meals. In Australia, orlistat is available over the counter.

Efficacy

In many clinical trials orlistat has been effective in producing extra weight loss (an extra 70–100%) over a standard lifestyle program. The weight loss is approximately 5 kg with placebo and 9.6 kg with orlistat.[14] Patients who lose 4–6 kg in the first three months will go on to lose more weight and can maintain this loss. Weight loss has been maintained in studies of two and four years' duration. Orlistat has been shown to be effective in general practice and in patients with diabetes.

In addition to weight loss, there are reductions in total and LDL cholesterol (particularly because of the mechanism of action), blood pressure and glycated haemoglobin.[17] After the initial weight loss phase, there is a 5–10% increase in HDL cholesterol. In patients with the metabolic syndrome[18] there is a significant reduction and improvement in all aspects of the syndrome. There is an improvement in many aspects of glucose metabolism (glucose concentrations, insulin sensitivity, hepatic glucose output) in patients taking orlistat.[19] This appears to be due to the mechanism of action of the drug, by reducing fat intake and the effects of lower concentrations of circulating free fatty acid on insulin resistance. In a study of patients with multiple comorbidities, no reduction in absolute five- and ten-year cardiovascular risk was found, but there were significant reductions in individual risk factors and in medication use for the associated comorbidities (diabetes, hypertension, dyslipidaemia).[20]

Safety

The adverse effects of orlistat are mainly gastrointestinal and can be controlled by adhering to a low fat diet. These adverse effects can be a learning experience for the patient. If they avoid the foods associated with an episode of diarrhoea or fat leakage then they will be changing to a more appropriate, healthier diet.

The absorption of fat soluble vitamins is a concern, but in all the trials, although there is a reduction in vitamin concentrations, they remain in the normal range. If long-term use is contemplated it may be prudent to supplement these vitamins (supplement given at night before bed). There have been a few reports of idiosyncratic hypertension associated with orlistat, but this does not appear to be a major problem. It is appropriate to check the concentrations of fat soluble immunosuppressive

drugs such as cyclosporin when orlistat is used to reduce weight in patients who have had a transplant. Otherwise, there appear to be no interactions between orlistat and the major drug classes.

Sibutramine

Sibutramine is both a selective serotonin reuptake inhibitor (SSRI) and a selective noradrenaline reuptake inhibitor. It has central and peripheral effects. It enhances satiety and reduces the desire to eat (the amount eaten at each meal is reduced by 10%). It also acts peripherally by preventing the usual fall in resting metabolic rate that occurs with weight loss. The initial dose is 10 mg daily. Blood pressure and pulse should be monitored. If there is not a weight loss of 1.5 kg or more in the first 4–6 weeks of treatment, the dose should be increased to 15 mg daily providing that the blood pressure is unchanged. Patients with diabetes tend to need the higher dose.

Efficacy

Sibutramine has the same degree of effectiveness as orlistat in the extra weight loss it produces over the usual lifestyle program. The amount of weight loss with sibutramine treatment is approximately 10 kg (about double that obtained with placebo) and it has been shown to aid weight maintenance for up to two years.[15] Cardiovascular risk factors reduce in proportion to the degree of weight loss. There is an increase in HDL cholesterol (20–25%) which is independent of the degree of loss and is related to sibutramine treatment itself (those in the STORM trial who were treated with sibutramine initially and then switched to placebo also maintained an increased HDL cholesterol).[15] Sibutramine works in patients with diabetes, reducing the glycated haemoglobin in proportion to weight loss.[21]

Safety

The adverse reactions include dry mouth, tiredness and some gastrointestinal effects. The selective noradrenaline reuptake inhibitor effect can increase the pulse rate (usually 2–3 beats per minute), and some patients may experience palpitations. With weight loss blood pressure does reduce, but the reduction is probably not in proportion to the degree of weight loss. Monitor the blood pressure as some patients may have a small rise in pressure. While sibutramine currently should not be used in those with cardiovascular disease or hypertension, a trial is investigating the effects of weight loss with a lifestyle program and sibutramine on cardiovascular outcomes.

There is a theoretical risk of serotonin syndrome. There is not yet evidence that this is a problem at therapeutic doses, but sibutramine should not be used in conjunction with antidepressants, particularly other SSRIs and monoamine oxidase inhibitors.

Very low calorie diets and meal replacements

These strategies can be effective in producing and maintaining weight loss.[22,23,24] Meal replacements, used consistently for a few months and then intermittently, can produce and maintain weight loss for more than four years, with associated reductions in risk factors. Very low calorie diets are also effective. They may be used to initiate weight loss (a defined management protocol is necessary) and then pharmacotherapy can assist in maintaining the loss.

Obesity (bariatric) surgery

Surgery is the most effective treatment for obesity. The results of the Swedish Obese Study[25] and from units in other parts of the world[26] have shown that significant weight loss (greater than 20 kg) can be produced and maintained. Any surgical procedure for obesity, to be effective long term, must be coupled with an ongoing weight loss and maintenance (lifestyle) program. Such a combined approach (appropriate patient selection, then surgery plus ongoing weight maintenance program) is essential for efficacy. The newer techniques, particularly with the inflatable gastric band, are much less invasive (performed laparoscopically), and gastric banding is easily reversible.

Prevention

It is better to prevent obesity than to treat it. As well as individuals being educated about, and changing, their eating, activity and habits, it is essential that the community and government at all levels investigate ways of changing our environment so it becomes easier to maintain a healthy weight.

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Professor Caterson has performed clinical trials on obesity for Servier Laboratories, 3M Pharmaceuticals, Roche Products and SanofiAventis. He has provided advice on obesity for Roche Products, Abbott Laboratories and SanofiAventis.

Professor Caterson has consulted with several other pharmaceutical companies, and acted on advisory boards as well as for government. He holds no shares in any pharmaceutical company.

Self-test questions

The following statements are either true or false (answers on page 55)

5. Sibutramine should not be used in patients with hypertension.
6. There is unlikely to be a long-term benefit for obese patients if they do not lose weight during the first three months of drug therapy.

Abnormal Laboratory Results

The second edition of Abnormal Laboratory Results, which contains articles from *Australian Prescriber*'s Abnormal Laboratory Results series, is now available. Edited by Professor Geoffrey Kellerman, it is available for $44.95 from McGraw-Hill, phone (02) 9900 1836.

Biochemical tests for abnormalities in pregnancy

Huy A. Tran, Head and Associate Professor, Department of Clinical Chemistry, Hunter Area Pathology Service, John Hunter Hospital, Newcastle University, Newcastle, New South Wales

Summary

Pregnancy induces major physiological, hormonal and biochemical changes to achieve an optimal outcome for the baby and its mother. When the pregnancy deviates from its normal course, there are many biochemical markers which can be used to assess these abnormalities. As biochemistry is only one part of obstetric care, results should be interpreted in conjunction with clinical and medical imaging data. Imaging is especially important and can be used to assess many placental and fetal abnormalities. Ultrasonography continues to improve and be refined in the early detection of fetal structural defects. It has equalled, if not superseded, biochemical testing in many aspects of obstetric care.

Key words: alpha fetoprotein, human chorionic gonadotrophin.

(Aust Prescr 2006;29:48–51)

Introduction

Biochemical markers are used to assess maternal, placental and fetal health. They help to diagnose and monitor maternal conditions such as gestational diabetes and pre-eclampsia, trophoblastic disease and fetal chromosomal abnormalities such as Down's syndrome (Table 1). These biochemical and hormonal tests constitute only one aspect of obstetric care. They should be used together with clinical findings and imaging, particularly ultrasonography.

Biochemical assessment of maternal health

Common problems in pregnancy include gestational diabetes and pre-eclampsia.

Diabetes

The prevalence of gestational diabetes mellitus ranges from 1 to 14% depending on the populations studied.[1] In Australia, the prevalence ranges from 5.5 to 8.8%.[2] Screening for gestational diabetes mellitus in Australia is strongly advocated at 26–28 weeks of gestation. This enables early intervention which results in significant improvements in both fetal and maternal outcomes.[3]

Occasionally, the serum glucose is unexpectedly found to be in the diabetic range in the first trimester. By definition, this is gestational diabetes mellitus, but does not distinguish between diabetes that may have preceded or occurred at the same time as pregnancy. The diagnosis can be confirmed by further tests of fasting glucose concentration or a 75 g oral glucose tolerance test. These patients should be reassessed in the postpartum period for evidence of diabetes. The woman's glycated haemoglobin (HbA1c) should be maintained in the normal range or as near normal as possible to ensure optimal fetal outcome.

Pre-eclampsia

Pre-eclampsia occurs typically in the third trimester and affects 4–8% of pregnancies.[4] It constitutes a triad of pregnancy-associated hypertension (that is, there is no pre-existing hypertension), marked proteinuria (greater than 300 mg daily) and pathological oedema. It is thus critical that urinary dipstick testing for protein, which can be fully quantitated if required, is performed at each antenatal visit together with blood pressure measurement and careful examination for oedema. Other findings include rises in serum uric acid (which can antedate the onset of hypertension), urea and creatinine. Low haemoglobin and platelet concentrations are informative if the patient is suspected to have the severe form of pre-eclampsia – haemolysis-elevated liver enzymes-low platelets (HELLP). In the absence of pre-existing pathology, these biochemical parameters should return to normal after delivery.

Biochemical assessment of placental health

Ultrasonography has added another dimension to first trimester obstetric care to such an extent that many traditional biochemical tests have been rendered redundant. Maternal serum human placental lactogen and serum or urinary oestriol concentrations which were previously used extensively in the assessment of placental function, are rarely used nowadays.

Human chorionic gonadotrophin (HCG)

As pregnancy progresses, the patient's hormonal profile continues to evolve with steadily rising concentrations of progesterone and oestrogen. These continue to rise well into the first trimester while concentrations of luteinising hormone and follicle stimulating hormone are low or suppressed. To maintain

Table 1

Biochemical tests for common maternal, placental and fetal conditions

	Condition	Test
Maternal	Gestational diabetes	Glucose screening tests at 24–28 weeks: 50 g challenge test **or** 2-hour 75 g oral glucose tolerance test
	Pre-eclampsia*	1. Urinary protein (by dipstick testing or formal quantitation) 2. Serum uric acid 3. Renal function tests 4. Full blood count (for Hb concentration and platelet count)
Placental	Trophoblastic disease* (hydatidiform mole or choriocarcinoma)	1. HCG 2. Free β-HCG 3. Urinary HCG when indicated
Fetal	Down's syndrome*	Maternal serum alpha fetoprotein, HCG, pregnancy-associated plasma protein-A, and transnuchal ultrasound between 11 and 13 weeks gestation Maternal serum alpha fetoprotein, HCG, pregnancy-associated plasma protein-A, and serum unconjugated oestriol in various combinations between 15 and 18 weeks gestation
	Neural tube defects	1. Maternal serum alpha fetoprotein **or** 2. Amniotic fluid alpha fetoprotein (less common)

* potential use of fetal DNA in maternal circulation
HCG human chorionic gonadotrophin

progesterone production from the corpus luteum in order to keep the pregnancy viable in its early stage, the placenta starts to secrete HCG. The serum HCG concentration is therefore the test of choice for confirming pregnancy.

Physiologically, serum HCG arising from trophoblastic activity is elevated as early as the eighth day after implantation. Concentrations double every 2–3 days and peak at approximately 10 weeks. They then decline and plateau out at a lower concentration until parturition (Fig. 1).

In addition to confirming pregnancy, serum HCG can be used as a marker to assess various abnormalities in the first trimester. A failure to rise at the appropriate rate suggests the impending loss of the pregnancy from spontaneous miscarriage or an unviable/ectopic pregnancy. A markedly elevated serum HCG suggests the presence of multiple pregnancies, especially with assisted fertilisation, or the presence of gestational trophoblastic disease including chorionic carcinoma and hydatidiform mole. A hydatidiform mole typically appears as a 'snow storm' on ultrasound. Confirmatory biochemical tests should include the **free** β-HCG concentration because this form of HCG is secreted in disproportionately high amounts.[5]

HCG can be used to assess the effectiveness of therapy and monitor for recurrence following surgery for gestational trophoblastic disease. A rapid decline or the disappearance of serum HCG is to be expected after successful surgery. False positive results at low HCG concentrations have been reported and have led to unnecessary surgery.[6] It is therefore important that when the HCG concentration is contrary to the clinical assessment, parallel **urinary** HCG concentrations should be analysed. (If the serum concentration of HCG is low but detectable in a clinically cured patient, the absence of urinary HCG raises the suspicion of a false positive serum result. If HCG is also present in the urine a residual tumour is more likely.) In these complex situations, ongoing communication with the laboratory is critical to the care and outcome for patients.

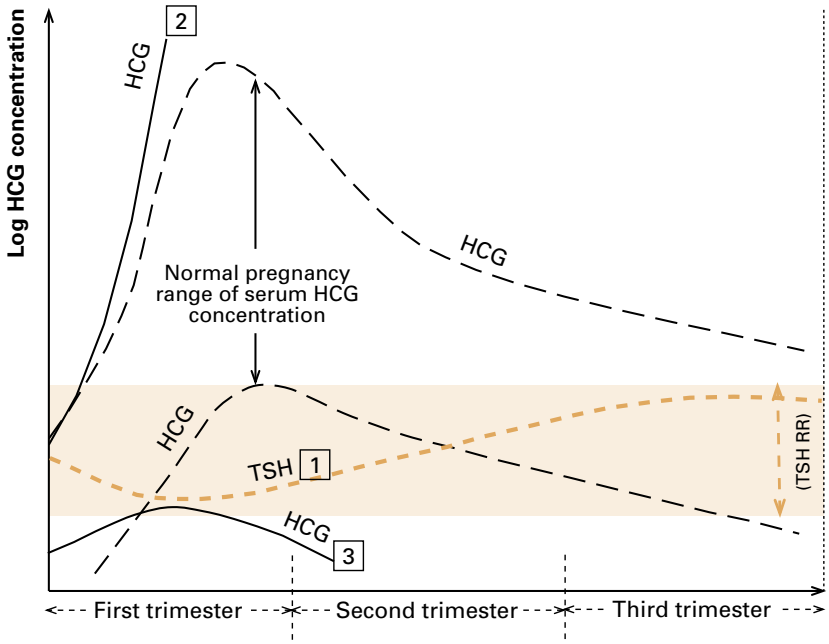
In the second trimester an elevated serum HCG concentration has been associated with a two- to threefold increased risk of fetal growth retardation.[7]

Biochemical assessment of fetal health

The major aim of fetal assessment is to ensure satisfactory growth *in utero*. There are many factors which can cause fetal

Fig.1

Human chorionic gonadotrophin (HCG) and thyroid stimulating hormone (TSH) concentrations



Note the broad reference intervals for HCG which peaks during the first trimester of pregnancy.

1 Represents the normal response of serum thyroid stimulating hormone (TSH) during pregnancy. The reference range (RR) for TSH is in the shaded area. Note the drop in TSH concentration in the first trimester corresponding with the peak HCG concentration. This is due to negative feedback on TSH secretion resulting from the stimulating effect of HCG on TSH receptors.

2 The high baseline HCG concentration with markedly shortened doubling time suggests multiple pregnancy or a trophoblastic tumour.

3 Failure of HCG to rise or double with time. This suggests the presence of an unviable or ectopic pregnancy or threatened miscarriage.

growth retardation. These range from poor maternal nutritional state to placental insufficiency and fetal abnormality. Similar to placental function, medical imaging is increasingly used to detect fetal abnormalities, thus reducing the utility of biochemical markers.

Alpha fetoprotein

Alpha fetoprotein is a fetal protein arising from the yolk sac and fetal liver. It can be detected in increasing concentrations in maternal serum until 32 weeks of normal gestation.

Neural tube defects

In neural tube defects such as spina bifida[8] and anencephaly, the concentration of alpha fetoprotein in the maternal serum is unusually high in the first trimester because cerebrospinal fluid leaks into the amniotic fluid. Other causes of elevated alpha fetoprotein, such as incorrect gestational date and multiple pregnancy, need to be excluded. As a marker of neural tube defects maternal serum alpha fetoprotein, ideally, should be measured between 15 and 18 weeks of gestation. Any suspicion of a neural tube defect can be further assessed with ultrasound, usually at 18–20 weeks. This scan also assesses for other fetal morphological abnormalities and placental placement.

Down's syndrome

Down's syndrome is one of the common causes of fetal growth retardation. It is the result of either partial or total trisomy of chromosome 21 and is a major obstetric concern, particularly in older women. Important biochemical markers include alpha fetoprotein, HCG, unconjugated oestriol, pregnancy-associated plasma protein-A, serum inhibin-A and free β-HCG. These markers are used in various combinations and together with ultrasound to increase the detection rate of Down's syndrome. It cannot be overemphasised that the gestational age must be correct in order for screening parameters to be accurate.

Between 11 and 13 weeks (that is late **first** trimester), serum

pregnancy-associated plasma protein-A, free β-HCG and ultrasound assessment of nuchal thickness (the physiological space between the back of the neck and the overlying skin of the fetus) are most commonly used in the assessment of Down's syndrome. Due to the changing concentrations of these markers in the normal pregnant population, the results are mathematically corrected for easy comparison. The nuchal thickness is increased in Down's syndrome and approximately 70% of cases will be detected by ultrasound in experienced centres. In combination with biochemical markers, the detection rate increases to 85–90%.[9,10] Abnormal results can be followed up with direct karyotyping using chorionic villous sampling, but this carries a 0.5–1.0% risk of pregnancy loss in the first trimester.

In the **second** trimester, screening for Down's syndrome traditionally employs the triple test of maternal serum HCG, serum unconjugated oestriol and alpha fetoprotein at 15–18 weeks of gestation. Some laboratories also measure serum pregnancy-associated plasma protein-A. The combination of these markers and maternal age delivers a 60–65% detection rate, but this includes the 5% of women who have a false positive result. Transnuchal thickness in the mid to late second trimester does not correlate well with Down's syndrome and does not add to the value of biochemical markers.[11]

The results of Down's syndrome screening in the first and second trimester are expressed as the proportion of affected pregnancies, for example 1 in 488 chance of having Down's syndrome. This is accomplished using a risk-assessment program that incorporates nuchal thickness (only in the first trimester), biochemistry results and maternal age.

Other approaches

Another biochemical method of assessing fetal health is the analysis of amniotic fluid. The measurement of bilirubin concentration in amniotic fluid is critical for assessing fetal intravascular haemolysis in the presence of Rhesus incompatability. The lecithin-to-sphingomyelin ratio in amniotic fluid can be used to assess fetal lung maturity in preterm labour but is rarely used these days due to the widespread availability of synthetic surfactant.

Recently, there has been a resurgence of interest using maternal growth hormone and insulin-like growth factor levels during the first and second trimester of pregnancy as predictors of fetal outcome, but these are yet to be of routine clinical use.[12]

Fetal DNA

A major advance in molecular biology has been the possible detection and isolation of fetal DNA in the maternal circulation.[13] This exciting discovery has opened up new horizons in the 'non-invasive' assessment of fetal-maternal health. High concentrations of fetal DNA in the maternal circulation have been found in Down's syndrome, pre-eclampsia, invasive placenta and preterm labour. This technique has also allowed for the prenatal non-invasive diagnosis of Rhesus D genotype, myotonic dystrophy and achondroplasia.[14]

Conclusion

Biochemical markers are important in the assessment of maternal, placental and fetal health. They remain critical in supporting and diagnosing many associated conditions despite the increasing quality and use of ultrasonography. As normal values continue to change with gestational age, these markers should be measured at the correct gestational age to enable accurate interpretation.

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Further reading

Joint HGSA/RANZCOG recommended 'Best practice' guidelines on antenatal screening for Down's syndrome and other fetal aneuploidy. 2004. http://www.ranzcog.edu.au/publications/collegestatements [cited 2006 Mar 8]

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 55)

7. Alpha fetoprotein is not found in maternal serum during the first trimester of a normal pregnancy.
8. Fetal growth retardation is best assessed by serial measurements of serum oestriol.

Dental notes

Prepared by Dr M. McCullough of the Australian Dental Association

Managing hepatitis C in the community (p.36)

The number of Australian adults living with hepatitis C is increasing and is not confined to any one section of the population. Dentists need to be aware that hepatitis C may be present in the saliva of infected patients. Our infection control practices therefore need to be exemplary to avoid spread of this, and other blood-borne viruses. Dentists are in a position to support medical advice that infected patients undergo antiviral treatment where appropriate and address secondary factors associated with liver disease in these patients.

Any dentists who carry a blood-borne virus have a professional and ethical responsibility to review the way they practise so as to ensure that they minimise the likelihood of infecting their patients. The Australian Dental Association offers advice and co-operation that should be sought.

Your questions to the PBAC

Adrenaline: shelf-life

I was very interested in 'Your questions to the PBAC: Adrenaline' (Aust Prescr 2005;28:90). In particular I wish to comment about the short expiry date of EpiPens.

About six or seven years ago I contacted the distributor of the EpiPen in Australia. I complained that sometimes I would purchase an EpiPen for my son and often it only had seven or eight months left before it expired.

Their explanation was that it was actually transported from the USA and by the time it arrived here many months of its 12-month shelf-life were gone.

On hearing this I checked out an old Martindale (26th edition) and I read that adrenaline in solution was very stable for a number of years. I wrote to the manufacturer of EpiPens in the USA with a photocopy of the extract out of Martindale but never received a reply.

Being a sceptic I just wonder whether it suits the manufacturer to overlook these details as obviously it would affect their sales substantially. Also I think it would be unlikely that a company would actively pursue ways of extending the expiry date!

At the time I was thinking about having the adrenaline stability checked out in an expired EpiPen, but did not have time to pursue this further.

Perhaps if the Pharmaceutical Benefits Advisory Committee (PBAC) did it on a more authoritative basis one might receive a reply.

Kevin Dallimore
Dermatologist
Perth

PBAC response:

The PBAC is aware of the short expiry date of EpiPen. However, the sponsor, CSL Limited, has advised recently that the most recent data from the manufacturer's stability program do not support an extension of shelf-life.

CSL Limited is currently implementing a number of changes to the distribution process. These aim to improve the shelf-life in Australia of EpiPen which is produced with a 20-month shelf-life by the US supplier, Dey Laboratories. The company advises that the following changes have been introduced to minimise the time lost between manufacture and patient in the distribution chain:

- EpiPen will now be produced with Australian packaging by Dey Laboratories to save on repacking time in Australia
- CSL will work with wholesalers and pharmacies to minimise the time stock spends on shelves

- CSL will not release EpiPen with a shelf-life of less than 13 months and in most cases it will be considerably more. Stock released since September 2005 will not expire for 17 months.

Letters explaining these changes were sent by CSL to doctors (general practitioners, immunologists, allergists, paediatricians and respiratory physicians), pharmacies and wholesalers.

New drugs

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

Anecortave acetate

Retaane (Alcon)

vials containing 15 mg/0.5 mL suspension

Approved indication: macular degeneration

Australian Medicines Handbook section 11.7

Most people with age-related macular degeneration have the non-exudative (dry) form. The exudative (wet) form is less common, but is more likely to cause blindness. Blood vessels grow through defects in the basement membrane of the retina then leak. This leakage causes loss of vision and scarring. The vessels can be treated with photocoagulation or, in patients with classical subfoveal choroidal neovascularisation, photodynamic therapy with verteporfin.

As the exudative form involves neovascularisation, it is possible which inhibiting angiogenesis will stop the disease progressing. Anecortave acetate is a molecule, structurally related to cortisol, which inhibits the proteases needed for blood vessel growth. Injecting the depot formulation through a cannula into the posterior juxtascleral area can stabilise the condition for several months. If indicated, the injection can be repeated six months later.

A clinical trial randomised 128 patients to receive anecortave (3 mg, 15 mg or 30 mg) or a placebo. Most of these patients with wet age-related macular degeneration had predominantly classic lesions. After six months there was a significant difference in the size of the lesions in patients given 15 mg anecortave. Although this difference was not statistically significant after 12 months, there was a significant difference in visual acuity. Patients given 15 mg anecortave were more likely to have stable vision and less likely to have severe loss of vision than patients given placebo. Efficacy seems greater in the patients with predominantly classic lesions.[1] The advantage of anecortave over placebo remained for those patients still in the study after 24 months.[2]

During the study approximately 41% of patients dropped out, mainly because of disease progression.[1] Adverse events reported during clinical trials include eye pain, hyperaemia, cataract, reduced intraocular pressure and ptosis.

The product information contains summary data from phase II trials comparing anecortave with verteporfin and photodynamic therapy. One trial gave patients anecortave or placebo 5–8 days after photodynamic therapy with verteporfin. Anecortave did not have a statistically significant advantage over placebo. The other trial has now been published. It randomised 263 patients with predominantly classic lessons to receive anecortave and 267 to receive photodynamic therapy with verteporfin. After 12 months, 45% of the anecortave group and 49% of the photodynamic therapy group had lost less than three lines of vision on the trial's visual acuity chart. Although the trial was designed to show that anecortave was not inferior, non-inferiority could not be confirmed.[3]

T T manufacturer provided some data

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Erlotinib

Tarceva (Roche)

25 mg, 100 mg and 150 mg tablets

Approved indication: non-small cell lung cancer

Australian Medicines Handbook section 14.3.9

In some cancers there is overexpression of epidermal growth factor receptors. These receptors are linked to tyrosine kinase and increased tyrosine kinase activity is associated with angiogenesis and tumour progression. This enzyme is therefore a target for drug therapy (see 'Angiogenesis inhibitors in cancer' Aust Prescr 2006;29:9–15).

Erlotinib inhibits the tyrosine kinase associated with epidermal growth factor receptors. It is uncertain what effect it has on other tyrosine kinase enzymes.

As epidermal growth factor receptors are present in some lung cancer cells, erlotinib has been studied in patients whose cancers have progressed despite chemotherapy. In one trial seven of 57 patients who took erlotinib daily had a complete or partial response.[1] Erlotinib was then used in a double-blind placebo-controlled study of 731 patients with stage IIIB or IV non-small cell lung cancer which had previously been treated with chemotherapy. Less than 1% of the placebo group responded compared with 8.9% of the erlotinib group. Although erlotinib improved survival, the patients only lived for a median of 6.7 months while those in the placebo group survived for 4.7 months.[2]

During the double-blind trial 76% of the patients given erlotinib developed a rash. This required some people to reduce their dose. Other adverse effects with a frequency greater than placebo included stomatitis, infection, diarrhoea, anorexia and ocular toxicity.[2]

The bioavailability of erlotinib is greatly increased by food so the tablets should be taken at least one hour before or two hours after meals. Erlotinib is metabolised mainly by cytochrome P450 3A4 so there is a potential for interactions with drugs that inhibit or induce this enzyme. Caution is needed if the patient is taking warfarin. The half-life of erlotinib is 36 hours, but its clearance may be increased in smokers. No pharmacokinetic data are available on the use of erlotinib in patients with liver metastases.

The role of erlotinib still requires clarification. There is a possibility that patients who develop a rash survive longer[1] and there is debate about the efficacy of erlotinib in patients whose tumours do not overexpress epidermal growth factor receptors. There is no benefit in giving erlotinib with chemotherapy so its use is restricted to patients whose locally advanced or metastatic non-small cell lung cancer progresses after chemotherapy. Whether erlotinib has an overall advantage over gefitinib, another tyrosine kinase inhibitor with the same indication, is currently uncertain.

T T T manufacturer provided all requested information

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Lanthanum carbonate hydrate

Fosrenol (Orphan)

500 mg, 750 mg and 1000 mg chewable tablets

Approved indication: hyperphosphataemia in chronic renal failure

Australian Medicines Handbook section 7.7

Patients being treated with continuous ambulatory peritoneal dialysis or haemodialysis for chronic renal failure are at risk of hyperphosphataemia. High phosphorus concentrations are associated with increased mortality. To try and control hyperphosphataemia patients may be given binding agents such as calcium carbonate. These bind to phosphate in the gut to reduce its absorption.

Lanthanum is a rare earth element which can bind phosphate. The tablets of lanthanum carbonate hydrate dissociate in the acid environment of the upper gastrointestinal tract to release lanthanum ions. These ions bind with dietary phosphate to form lanthanum phosphate. As this compound is insoluble, phosphate absorption is reduced. The dose is adjusted every 2–3 weeks until the serum phosphate concentration is controlled. Most patients will require a total daily dose of 1500–3000 mg. The tablets are chewed three times a day with meals.

A six-week double-blind study compared lanthanum to placebo in 145 patients with end-stage renal disease and a serum phosphorus of at least 1.8 mmol/L. There was a dose-related reduction in serum phosphorus within two weeks of starting therapy.[1]

Another placebo-controlled trial enrolled 163 patients having haemodialysis. After a washout period and a dose-titration period, 94 patients were entered into a double-blind phase. This maintenance phase lasted for four weeks. At the end of this phase the serum phosphorus concentration in patients given placebo was similar to the concentration at the end of the washout period. The patients who continued lanthanum during the maintenance phase retained control of their phosphorus concentrations. At the end of the study their mean concentration was 1.92 mmol/L compared with 2.53 mmol/L in the placebo group.[2]

Comparative studies with other phosphate binders are limited. One study compared the effects of lanthanum carbonate and calcium carbonate on the development of renal osteodystrophy in 98 patients.[3] After one year 15% of the patients given lanthanum had normal bone histology compared with only 3% of the patients given calcium carbonate. Both binders controlled the phosphorus concentration.

Lanthanum is less likely to cause hypercalcaemia than calcium-based binders, but it may have more gastrointestinal adverse effects such as diarrhoea, nausea and vomiting. Although only a little lanthanum is absorbed it is distributed into bone.

Lanthanum is only slowly released (half-life greater than 26 weeks) and its long-term effects are unknown. Patients should not take lanthanum for more than two years.

Although lanthanum probably has advantages over calcium-based binders, so may sevelamer hydrochloride, another recently approved phosphate binder. There appear to be no published comparative trials of lanthanum and sevelamer. These drugs are more expensive than calcium carbonate and it is uncertain if their benefits outweigh their higher price.

T T manufacturer provided some data

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The T-score (T) is explained in 'Two-way transparency', Aust Prescr 2005;28:103.

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

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

Answers to self-test questions

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

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