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EDITORIAL

Medicines and the media: a journalist's view

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Index words: advertising, drug industry.

(Aust Prescr 2000;23:70–1)

Much research has examined how the promotional activities of the pharmaceutical industry influence medical practice. A recent review of 29 such studies suggests that the billions of dollars the industry spends on promotions directed at health professionals are not wasted.[1]

Far less attention has traditionally been paid to the impact of the industry's campaigns to influence media coverage of medicines. Yet, as every journalist working in the area knows, the industry invests significantly in public relations. Such campaigns are mostly aimed at promoting new products or new indications for old products, or at influencing health policy decisions, such as whether a product should be listed on the Pharmaceutical Benefits Scheme. Occasionally, such campaigns aim to highlight concerns about a rival product. Public relations practitioners can also assist with 'crisis management'; this might include training companies and their contacts in how to deal with the media about a potential or actual 'crisis', such as the publication of a negative study or a product contamination.

Public relations strategies can include sponsoring journalists to attend conferences, the mass dissemination of media releases, and working with opinion leaders such as medical specialists to ensure journalists are briefed on particular topics. Many campaigns involve professional and consumer groups; one company is reported to have established a web site to encourage patients to lobby health authorities over funding.[2] Using 'third parties' to spread the message may help circumvent industry codes of conduct governing relations with the media, as well as increase the credibility of the message with the media and its audiences. A similar effect can also be achieved by running campaigns to raise public awareness about particular diseases or conditions – so-called 'disease mongering' – which may help create demand for new or existing treatments, even if they are not named in the campaign.

Many journalists believe that medicines receive a surprisingly good run in the media, given that journalists generally perceive their role as critics rather than promoters. The enormous costs of pharmaceuticals – not just in dollar terms, but also in adverse effects – generally receive far less attention than their perceived benefits. Why this happens is probably a reflection of what is 'newsworthy', the constraints under which journalists work, and the authority of doctors, scientists and other 'experts'. It probably also illustrates the seductiveness of technological fixes to health problems.

In other words, a story about a 'breakthrough' new treatment is more likely to grab a larger audience (and a more prominent space in the newspaper or broadcast) than a more sober analysis. Journalists and media managers often do not have the time or skills to critically evaluate claims about medical treatments and technologies. If a professor makes a statement in a media release, many journalists will assume that this is the 'truth', not recognising that other experts may present alternative views or 'truths'.

If direct-to-consumer advertising is introduced in Australia, this will provide fertile ground for research examining its impact on editorial coverage of medicines. It might encourage even more extensive and positive reporting for two reasons: the media would be more aware of new developments, and the separation between advertising and editorial is not always honoured.

That media coverage of medicines is so often uncritical is cause for concern, given the media's powerful role in influencing the attitudes and behaviour, not just of the general public, but also of health professionals, policy makers and politicians. A study evaluating the scientific quality of health care reports in five major Norwegian newspapers found that

In this issue...

The media are usually the first to tell the public about new drugs. While this may inform consumers, leading medical writer Melissa Sweet reminds us that the reports are often uncritical. The internet is also a source of drug information, but Joel Lexchin tells us it can also be a source of misinformation.

Two popular topics in the media and on the internet are alternative medicine and sport. Anna Drew puts *Serenoa repens* in perspective, and Peter Fricker informs us that some alternative medicines may contain substances which are banned in sport. The issue of drugs in sport is certain to be widely discussed during next month's Olympic Games in Sydney.

Some internet sites promote cures for cancer. In contrast to these unproven cures, chemotherapy has an established role, even in elderly patients. Ian Olver explains why older people can benefit from treatment and Snow Partridge reveals how chemotherapy helped him.

it was difficult for readers to distinguish opinions from facts. There was rarely any indication of the validity of any underlying evidence or the size of the purported effects or risks.[3] It is a safe bet that this is a problem which extends beyond Norway's borders.

However, moves are afoot to place media reporting of health issues under greater scrutiny. Researchers in Norway have developed explicit criteria to assess the scientific quality of media reports on health issues. They are now conducting a randomised trial to assess the impact of inviting journalists to attend a workshop on evidence-based health care reporting. Les Irwig, professor of epidemiology at the University of Sydney, has also run workshops for journalists, aimed at promoting evidence-based reporting of health issues. An Australian journalist, Ray Moynihan, is involved in an international collaboration to develop tools for assessing media coverage of medicines, which has published a study based on an analysis of five years of media coverage of medicines in the USA.[4]

In the meantime, journalists could take simple steps to help their audiences better evaluate what they are being told about medicines. If a story originates from a public relations campaign, this should be explicitly stated – especially if the story is being told through a third-party source and its origins are unclear. However, some journalists and news managers may dislike this suggestion, as it may reduce a story's chance of 'getting a good run'. Some media outlets have previously failed to declare when a story has resulted from a vested interest sponsoring a journalist's travel or providing other incentives. This may occur less often in the future as the radio industry's recent 'cash-for-comment' controversy seems to have prompted greater awareness of ethical issues in the media.

Many media professionals would bristle at suggestions that they should have a role in health promotion. They are more likely to respond to interventions aimed at improving journalistic skills in areas such as critical analysis.

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Melissa Sweet is a freelance journalist specialising in health. She writes for The Bulletin magazine and has a regular column in Australian Doctor on media issues.

Valedictory

Peter Fletcher

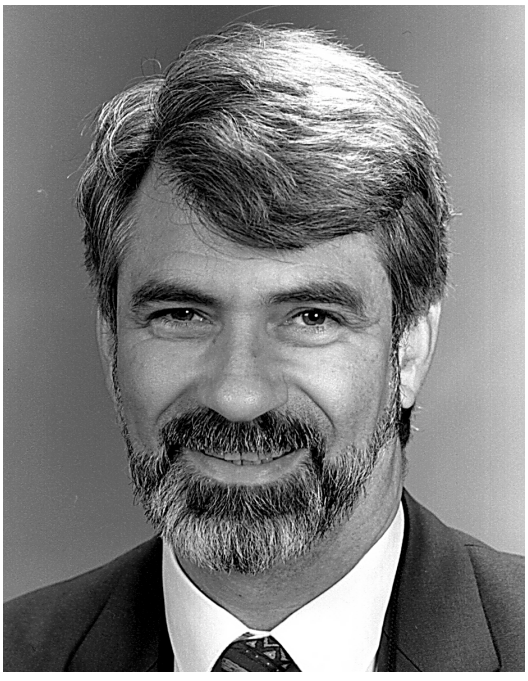
The Executive Editorial Board of *Australian Prescriber* has said farewell to its long-standing chairman Professor Peter Fletcher.

Professor Fletcher joined the Editorial Board in 1985. He took over the chair in 1990, becoming the first full-time clinician to hold the position. Under his guidance the influence and readership of the journal have expanded enormously. Professor Fletcher has particularly encouraged the development of the electronic version of *Australian Prescriber*.

The Editorial Board has enjoyed Professor Fletcher's avuncular style of leadership. This has led to very productive meetings and the successful resolution of many difficult issues.

Although he is leaving the Editorial Board, Professor Fletcher will not have a lot of extra time on his hands. He is taking on the task of helping to organise the 14th World Congress of Cardiology in Sydney, 2002.

We wish him success in this project and in his continuing role as the Professor of Cardiovascular Medicine at the University of Newcastle.



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.

Fungal toenails and terbinafine

Editor, – Professor Kamien recently wrote (Aust Prescr 1999;22:135) about the high cost of using terbinafine in people with suspected tinea of the toenails who are negative on microscopy or culture but who wish to purchase the drug privately. The cost of the treatment can be halved by using terbinafine 250 mg twice a day for one week in every four week cycle.[1,2] This is continued for a total period of 12–16 weeks, i.e. three or four weeks of treatment over three or four months.

The regimen is apparently as effective as the current 250 mg a day for the same period, and effectively cuts the cost of the treatment down by a half.

K. Dallimore
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Perioperative management of anticoagulation

Editor, – The article 'The perioperative management of anticoagulation' (Aust Prescr 2000;23:13–6) discusses surgical procedures in patients who for one reason or another are on long-term warfarin. Whilst there may be some indications for warfarin that can be stopped for a few days without risk, there are others in which the warfarin must be ceased and heparin begun so the operation can take place. The patient then requires to be put back on warfarin at a suitable time, a process which is not easy and takes several days, often as an inpatient.

When Professor Hughes from Wales was in Australia many years ago he mentioned to me that he had performed certain operations without stopping the warfarin. Since then I have done a number of perianal procedures, hernias and even a laparotomy without stopping the warfarin and in only one hernia was there a significant haematoma. It is important of course to check that the INR is in therapeutic range before operating on patients on warfarin, and haemostasis must be meticulous, while careful observation of the patient postoperatively is also essential.

There would appear to be considerable merit in certain cases, in experienced hands, for keeping the patient on oral anticoagulant for selected surgical procedures.

Kevin Orr
Surgeon
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Dr Andrew Grigg, one of the authors of the article, comments:

Unfortunately there are few prospective studies which address the issue of what constitutes a 'safe' INR for various surgical procedures. A study performed almost 40 years ago[1] randomised 60 patients undergoing cholecystectomy or gastric resection to either no anticoagulation or anticoagulation to achieve a thrombotest concentration of 15–20% of normal, equating to an INR of 1.6–2.1. There was no overall significant difference in operative, 24 hour or 72 hour blood loss between the two groups; four of 30 patients in the treated group had blood loss exceeding 1500 mL in the first 24 hours compared with one of 30 in the control group.

I put this issue to Professor Jack Hirsh, co-author of a review article on management of anticoagulation before and after elective surgery.[2] His reply was, 'If a surgeon chooses to do so, it would be reasonable to continue warfarin at an INR of about 1.5 during surgery. However, I know of no hard data supporting the safety of this approach.'

The paucity of data gives the opportunity for surgeons and haematologists to collaborate in a prospective study so that anecdotal experience could be replaced by evidence-based medicine.

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Drug-induced neuropathy

Editor, – While a short article cannot be encyclopaedic, 'The use of anticonvulsants for neuropathic pain' (Aust Prescr 1999;22:140–1) omits to mention prescribed drugs in the potential causes of peripheral neuropathy. Exclusion of a pharmacological cause should be one of the earliest steps in the management of this disorder, although in some cases symptoms continue to worsen for some time after ceasing the culprit drug.

The association with certain antineoplastic drugs is well known, but there are many other medications that may cause neuropathy, including commonly prescribed drugs such as metronidazole, nitrofurantoin, isoniazid and dapsone, as well as some anti-HIV drugs. Phenytoin and pyridoxine, which may be used in the treatment of neuropathy, may themselves, albeit rarely, cause the condition.

These patients are often desperate for relief of symptoms, and there is a natural desire on the part of their doctors to 'do something'. As the author points out this can be unhelpful or harmful.

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Click, click the internet and prescription drugs

Joel Lexchin, Staff Emergency Physician, University Health Network, Toronto, and Associate Professor, Department of Family and Community Medicine, University of Toronto, Canada

SYNOPSIS

The internet exposes doctors and consumers to advertisements for prescription drugs. The commercial nature of a web site may not be obvious, and key pieces of information may be missed amidst the multiple pages on a web site. Developing standards to deal with internet advertising will be difficult because web sites can be based and accessed from anywhere in the world. Drugs can even be ordered over the internet without any contact with a doctor and before the drug is approved by regulatory authorities. The creation of virtual pharmacies may be helpful to some people, but they will also not be able to duplicate some of the traditionally important functions of the person-to-person interaction.

Index words: advertising, consumer information, drug industry, regulation.

(Aust Prescr 2000;23:73–4)

Introduction

Need information about prescription drugs? Click, click – there it is. Want to order a drug from the privacy of your own home without seeing a doctor? Click, click – it's on its way. Those are the promises, or threats, of the internet.

Information or advertising?

Consumers want, and deserve, more information about the drugs that they use. The question is what kind of information are they going to get when they connect to the internet. Drug companies are eager to provide information on web sites, especially since, in most areas of the world, they are forbidden from advertising prescription drugs directly to the public. Before we advise our patients to rush home and turn on their computers, there are a few caveats to consider.

Will consumers even know that they are looking at advertising when they click on a web site? It is clear when you see an advert in a magazine or on television what you are looking at (with the exception of advertorials). Web sites are more confusing; the entire page can rarely be seen on the screen at one time. Unless you scroll to see the whole page, you might not even know that you are looking at an advertisement.

Another difference between the internet and printed information is the ease of finding the information that you want, or at least recognising that it is missing. When you see a page of print you can scan it quickly to find safety or dosing information if that is what you are interested in. Since electronic sites can potentially be endlessly expandable and thereby offer huge volumes of information you may have to go through a number of screens of material before you find what you want. If directions on the web site are not clear, some consumers may simply give up and see only the first few pages with the bold colours and imaginative graphics and never find the key piece of information they are seeking. Consider the Café Herpé web site set up by SmithKline Beecham, makers of Famvir (famciclovir).[1] The material on the main pages is useful and objective but it is not complete. It is not until you get past the designer pages to the pages of pure print and read closely that you discover that famciclovir does not cure herpes labialis or stop transmission. Just as in any form of advertising, companies will present the information that they want consumers to have in the most prominent way and the other information, while there, will take some work to find.

Regulation

The answer to concerns about the internet is that the contents of web sites should be regulated. At present, drug advertising on the internet is so new that there are few standards. The fact that any web page can be accessed from anywhere in the world is going to add an entirely new dimension to the problems of deciding on standards. If a company in the USA sets up a web site, anyone in Australia with a computer can see that web site. What happens if the information on that site does not conform to the Australian standards recently launched by the Australian Pharmaceutical Manufacturers Association?[2] You can argue that we already have to deal with that problem since American magazines with direct-to-consumer advertising are read in Australia, but people at least know that they are reading an American magazine with information geared to an American audience. Who knows where the web site is based? Will the company go to the expense of maintaining a purely Australian web site for the same product? If they do not like the Australian standards why spend the money, since the company will not be losing any of its potential audience: a web site based at the North Pole can be accessed just as easily as one operated from Sydney. There is no regulatory mechanism for web sites to be inspected before going on-line. As with other forms of advertising on the internet the only regulation is self-regulation.

How do we apply sanctions if there is only a single worldwide web site for any given product? Is it fair to punish an Australian subsidiary because the American company's web site lists

indications that have not been approved in Australia or omits safety information that is required by the Therapeutic Goods Administration?

Besides the concerns listed above, a public meeting in September 1996, convened by the United States Food and Drug Administration, brought forward others:

- distinguishing between advertisements aimed at consumers and health professionals can be difficult
- pharmaceutical companies' home pages may be linked to other sites giving out information on unapproved use of drugs
- conditions of company sponsorship of 'chat rooms' and 'newsgroups' are unclear.[3]

World Health Organization

In September 1997, the World Health Organization (WHO) convened a working group as a follow-up to a resolution passed at the 50th World Health Assembly.[4] The working group made recommendations for ways in which WHO, national drug regulators, the industry and consumers could act to improve the standard of information available on the internet. The meeting stressed that both regulatory standards and voluntary codes should aim to ensure that all internet promotional activities complied with the WHO Ethical Criteria.[5] Some specific recommendations for the pharmaceutical industry included:

- disclosure of web site ownership or financial support
- statements about who the intended audience is and the purpose of the information
- provision of accurate, balanced information, including information on dangers and adverse effects
- careful selection of internet linkages.[6,7]

Internet prescribing

Trying to come up with acceptable standards to govern internet advertising is something like trying to find your way around a new city without a map. If we are going to need a road map to deal with advertising, then we are going to have to build the roads when it comes to prescribing and accessing drugs over the internet.

Months before sildenafil was available in the UK, people there were able to order it through web sites and have it mailed to them. No prescription was required, no examination by a doctor, just a credit card to pay for the product. These web sites were not operated in the UK so the authorities there had no power over them. Intercepting the drugs in the mail on a large scale was just not possible.

An American survey found 77 web sites which offered sildenafil without the need to see a doctor. Less than half the sites asked if the consumer had erectile dysfunction and only 55% included information about contraindications. Only 18% required the consumers to verify that they understood the adverse effects.[8]

In the USA people can click onto a web site, fill out a questionnaire about their health problem, have the questionnaire evaluated by a doctor halfway across the country who never sees them and who is not even registered to practise medicine in the same State, and then have the prescription mailed to them from a third point in the country. So far the authorities in the USA appear to be virtually helpless to deal with this phenomenon.

The situation in Australia may never get as bad as in the USA, but the existence of 'virtual pharmacies' is not hard to imagine. Doctors e-mail a prescription to a web site address and the prescription is then mailed or otherwise delivered to our patients' homes. In some ways this may prove to be an advantage. An e-mailed prescription is always going to be legible. Not having to physically take the prescription to a pharmacy may be convenient for some people, especially the elderly who find it difficult to get around or in rural areas where the nearest pharmacy may be a long way away.

What about the traditional role of the pharmacist in giving advice to people? The virtual pharmacy can offer an on-line pharmacist to answer questions and some people may find it easier to 'talk' to someone via computer than face-to-face. On the other hand, on-line pharmacists are going to miss all the non-verbal clues that provide an essential element of communication. How do you show an on-line pharmacist the rash that you think may have been caused by the drug you are taking?

Conclusion

The internet can give consumers access to information about medicines. There are, however, no controls on the quality of this information. The internet also allows the consumer to bypass the advice of their doctors and pharmacists.

Click, click – there are the problems; click, click – where are the solutions?

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Self-test questions

The following statements are either true or false (answers on page 87)

1. Patients cannot obtain prescription-only drugs over the internet without consulting a doctor.
2. The Therapeutic Goods Administration inspects the web sites of Australian pharmaceutical companies before the information is displayed to the public.

Click, click the internet and prescription drugs – a consumer perspective

Debra O'Connor, Consumer Representative, General Practice Computing Group; and Matthew Blackmore, Executive Director, Consumers' Health Forum

Joel Lexchin's article highlights two of the many risks for consumers in obtaining prescription medicines or drug information from the internet. The first risk is the blurring of promotional information with balanced objective information on suppliers' web sites. This can mislead consumers and expose them to the second major risk, internet supply of prescription medicines with no or limited 'virtual' medical advice.

If advertising is not seen for what it is, consumers will be hard pressed to distinguish it from balanced information. It is always difficult to know if information on the internet is balanced. Given recent Australian experience in other arenas (Crimenet, internet gambling) regulation of the internet is unlikely.

Consumers need to know how to minimise the potential problems of obtaining information and medicines from the internet. Some consumer groups and other researchers have begun developing criteria to assist consumers to evaluate the health information they obtain from the internet. For many consumers, discussing the information they find on the internet with their doctor will be an important check.

The development and promotion of 'authoritative' web sites is equally important. At a national level, the development of 'HealthInsite'[1] as an internet 'portal' by the Department of Health and Aged Care, is a welcome development. HealthInsite 'endorses' sites so that consumers can be certain of the quality of the information. However, more resources will be needed to ensure that valuable information from the consumer movement is available through HealthInsite.

The article does not mention alternative therapies. This is an area where there is less stringent regulation. Misleading or insufficient information from suppliers may therefore present even greater challenges for consumers, particularly where health care providers may be unable to act as informed advisers.

Obtaining prescription medicines through the internet without the need to see a doctor can be a risk for consumers. However, doctors are not necessarily excluded from helping consumers to benefit from electronic commerce and may be able to assist consumers to minimise the risks. In Australia general practitioners are already using electronic prescribing and there are trials of electronically transferring prescriptions to a pharmacy. This could lead to 'virtual' pharmacies in future with potential benefits for consumers. People isolated by their age, illness or distance would not have to take their prescriptions to a pharmacy; the doctor could e-mail the prescription and the medicine could be delivered to the patient's home.

Purchasing medicines through the internet could also make it easier for consumers to shop around for cheaper medicines. This would be a welcome development for people with high medication costs due to chronic and complex conditions. Internet prescribing can also inform doctors and patients about medicines that are not available in Australia and allow them to consider all the options.

Consumers value effective face-to-face communications with trusted health professionals about treatment options and how to use their medicines appropriately. The reluctance of some health professionals to provide advice and consumer medicine information may have undermined consumers' perceptions of the value of that interaction. However, the internet is only a supplement to personal communications with health care providers and not a replacement.

REFERENCE

1. http://www.healthinsite.gov.au

Australian Prescriber on the internet

Readers of *Australian Prescriber* may wish to access the journal via the internet, as well as – or instead of – reading the paper copy. Overseas readers in particular are encouraged to read the internet version, to save postage costs.

If you have not already done so, visit the homepage at *www.australianprescriber.com* The web site contains all issues since 1994, index and search facilities, news, a feedback section for letters to the Editor, and a new issue notification service (see box).

Australian Prescriber was one of the first medical journals to make its full text available free to all readers on the internet. It is still free, and can be read and downloaded in HTML or PDF format (identical with the paper copy).

The *Australian Prescriber* site is linked to many other useful sites (see Links) and can be a valuable addition to the reader's desktop. Bookmark the homepage, or join the new issue notification service and link directly from the e-mail message to the home page.

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Drugs in sport

P.A. Fricker, Head of Sports Science and Sports Medicine, Australian Institute of Sport, and Chair of Sports Medicine, University of Canberra, Canberra

SYNOPSIS

Drugs in sport are a concern for medical practitioners because of the implicit risks to the health of the athlete. There are also ethical concerns about cheating by artificially enhancing athletic performance. The International Olympic Committee has prepared an Olympic Movement Anti-Doping Code.[1] This specifies prohibited substances, and prohibited methods of doping. Health professionals must be aware of the need to avoid giving 'banned' medications and the need to provide written notification when restricted substances are necessary. Sources of information about restricted substances include the Drugs in Sport Handbook[2] published by the Australian Sports Drug Agency.

Index words: anabolic steroids, stimulants, growth hormone, doping.

(Aust Prescr 2000;23:76–8)

Introduction

'Drugs in sport' receives daily attention in the media, the medical literature and in conversations across the country. In the twelve months 1998–99, the Australian Sports Drugs Agency (ASDA) conducted 4801 dope tests across 52 sports and events. Positive tests were recorded for drugs such as clenbuterol (a beta-agonist with anabolic properties), nandrolone and stanozolol (anabolic steroids), frusemide, pseudoephedrine, prolintane (a stimulant used in the treatment of attention deficit hyperactivity disorder) and cannabis. Sporting organisations imposed sanctions on the offenders ranging from 'warning' to 'life ban'.

The problem of using performance enhancing agents is not new. Anecdotal reports go back to ancient Greece when meat and wine were prescribed for better performance in the marathon. A death from stimulant (amphetamine) abuse by a cyclist was reported in 1960.[1,3] Cycling has more recently brought to light the problem of erythropoietin (EPO) abuse and this is the focus of research (using red cell markers) at the Australian Institute of Sport in Canberra and the Australian Sports Drugs Testing Laboratory in Sydney. Similarly, swimmers were recently caught with human growth hormone (HGH), and the International Olympic Committee (IOC) has now funded an international study on the detection of HGH abuse by athletes.

The use of drugs such as DHEA (dehydroepiandrosterone), which is banned by the IOC, and supplements such as creatine and hydroxymethylbutyrate (HMB), which are not banned, add to the ever increasing complexity of performance enhancement in sport. This is a concern for the treating practitioner who may be asked to assist an athlete.

Doping

Doping is the application of chemical substances with the deliberate intention or effect of altering performance.[4] It is opposed by the IOC and its member bodies and affiliates on ethical grounds (doping is cheating) and because doping poses a risk to the health of the athlete.

The IOC has produced a schedule which is updated annually and outlines the major classes of prohibited substances, prohibited methods of doping, and classes of drugs subject to certain restrictions (see Table 1). The prohibited substances include stimulants (e.g. ephedrine and amphetamine), narcotics, anabolic agents (e.g. testosterone and its related compounds, including nandrolone and DHEA), diuretics, hormones (including HGH and EPO) and hormone analogues.

The difficulty for medical practitioners is recognising prohibited substances in common usage and ensuring that their patients who are athletes do not inadvertently test positive to a dope test. By far the largest cause of 'inadvertent positives' is pseudoephedrine, which is available in many over-the-counter preparations.

Doctors and pharmacists can readily check any medication, to see whether or not it is permitted, by referring to the bimonthly

Table 1

International Olympic Committee guide to classes of prohibited substances and methods of doping

Prohibited classes of substances
A. Stimulants
B. Opioid analgesics
C. Anabolic agents
D. Diuretics
E. Peptide hormones, mimetics and analogues
Prohibited methods
A. Blood doping
B. Pharmacological, chemical and physical manipulation
Classes of drugs subject to restrictions
A. Alcohol
B. Cannabinoids
C. Local anaesthetics
D. Corticosteroids
E. Beta blockers

issue of MIMS. Against each entry is a symbol which indicates if the drug can be used in sport or if certain restrictions apply. There is no symbol for those substances which are totally banned. More information is available from ASDA or national sporting organisations.

Prohibited substances

Caffeine

Routine urine screening includes caffeine assay. A concentration above 12 microgram/mL is deemed a positive dope test. There are no acceptable excuses and athletes must be warned that caffeine excretion can vary from individual to individual. Approximately six cups of brewed or percolated coffee (drunk rather rapidly) or 6–8 cans of a cola soft drink may put the athlete at risk of a positive test.

Anabolic agents

The abuse of anabolic agents such as testosterone and its analogues, and of HGH and human chorionic gonadotrophin (HCG), is unfortunately endemic. Black market availability is widespread and athletes in sports which involve lifting, throwing, jumping and sprinting are particularly likely to be tempted. The dangers of anabolic androgenic steroids lie in their hepatotoxicity (in the 17 alpha-alkyl substituted forms), with resultant hepatitis, peliosis hepatis and risk of tumour. They can also virilise and produce permanent sequelae such as deepening of the voice, gonadal atrophy and clitoral hypertrophy.[5] Some beta-agonists including clenbuterol and fenoterol are anabolic and are banned.

HGH abuse can produce acromegalic adverse effects and impaired glucose tolerance, while HCG is used to mimic the effect of testosterone. Polypeptide anabolic agents also include insulin, and because this drug is available without prescription it has become fashionable amongst body builders and strength-training athletes. Insulin injections are reportedly taken with high carbohydrate meals and exercise to produce gains in muscle bulk and strength.

A urine test for testosterone is positive if the ratio of testosterone to epitestosterone is greater than six. Testing for the polypeptide anabolics is still being developed.

Diuretics

Diuretics are banned. They are used by athletes to 'make weight'. Sports in which athletes are classed by weight include weightlifting, judo and boxing. Doping control checks routinely test for diuretics as the drugs can also be used to dilute the urine and mask prohibited drugs in the urine.

Glycoprotein and polypeptide hormones

A recent addition to the banned list of hormones is EPO. This injectable recombinant hormone promotes red cell production by the bone marrow and thus enhances aerobic (endurance) activity in athletes – hence its infamous popularity amongst competitive road cyclists. It carries a risk of thrombosis and has been implicated in a number of deaths amongst cyclists. A test for EPO is currently being developed in Australia and it is the fervent wish of officials and honest competitors that the test be introduced at the Sydney Olympic Games.

Prohibited methods

There are a number of prohibited methods which are used for performance enhancement. These include blood doping (using homologous or autologous blood), the use of masking agents such as probenecid (which blocks the renal excretion of testosterone), providing substitute urine samples for testing and chemical manipulation of urine to be tested. Dope tests therefore screen for masking agents and analyse a range of chemical and physical properties of urine to detect manipulation of the sample.

Restricted use

The IOC also specifies a list of drugs subject to certain restrictions. Alcohol, for example, may be banned in certain sports, as are marijuana and beta blockers, because of specific pharmacological effects which may assist performance. For example beta blockers control tremor and heart rate, so they may be useful in target sports, such as shooting.

Local anaesthetics (excluding cocaine) are permitted for local and intra-articular use only, and written notification is requested by some sports at the time of competition. Similarly corticosteroids are permitted **only** for topical application, by inhalation for the treatment of asthma, or by local or intra-articular injection (including depot formulations).

Another important restriction is the use of beta-agonists. Only salbutamol, salmeterol and terbutaline are permitted and they can only be used for the treatment of asthma if they are given by inhaler. The sporting authorities require written notification of the athlete's asthma.

Permitted use of 'banned drugs'

In Australia, the Australian Sports Drugs Medical Advisory Committee (ASDMAC) has been empowered by Parliament to provide advice to national sporting bodies on the therapeutic use of IOC 'banned' drugs. If an athlete suffers ulcerative colitis, for example, and requires corticosteroid therapy, the treating medical practitioner may write to ASDMAC* and seek advice on this therapy. All medical details must be provided, with the athlete's permission. ASDMAC, in consultation with the relevant national sporting organisation, can grant permission for medication to be used in stated doses for particular conditions for a period of time. During this time sanctions will not be imposed if the athlete tests positive. The decision on whether or not to 'approve' therapeutic use is based on the necessity for such treatment to maintain health, the absence of alternatives in therapy and the decision that no unfair gains in sports performance may be obtained by using

* Australian Sports Drugs Medical Advisory Committee
PO Box 345
CURTIN ACT 2605

such medication in prescribed doses. It should be recognised that ASDMAC 'approval' currently applies within Australia only and 'approval' to use outside Australia must be obtained either directly from the IOC (where Olympic Games are concerned) or from the appropriate national sporting body in the country of competition.

If there is any doubt, it is better for the athlete **not** to take the medication in question. If medication is necessary, the athlete should withdraw from competition.

Dope testing

Drug testing in Australia is conducted by the ASDA. The testing is strictly controlled to ensure that the athlete is guaranteed security, privacy and fairness. Guidelines cover notification of the athlete selected for testing, chaperoning and supervision while a urine sample is obtained, sealing of specimens, secure delivery of the sample to the IOC-accredited laboratory, sample analysis and notification of results.

There is a detailed process for appeals and hearings, should sanctions by a sporting organisation be considered. The penalties are severe for drug abuse, trafficking, doping and using prohibited methods. In many sports a second offence for anabolic steroid abuse results in a life ban from the relevant sport.

Supplements

There are countless enterprises in Australia touting supplements, vitamins, amino acids and herbal extracts to promote health and improved performance. Some supplements such as creatine and amino acids are not 'banned' but the purity of such products must be guaranteed before the athlete is safe from testing positive. The truly risky area is that of herbal extracts and compounds. Some include ephedra which is banned, and the botanic (or Chinese) name may not help the unwary. Similarly guarana contains caffeine, which is 'banned' above a level of 12 microgram/mL in urine.

Caution must also be exercised when buying any product over the internet, for the same concerns apply with respect to content and purity. What you buy may not necessarily be what you get, and you may get more than you bargained for.

Conclusion

Health professionals should not become involved in doping or prohibited procedures which are intended to enhance sporting performance. They also need to be aware that in treating an athlete's medical condition they can unwittingly prescribe a banned or restricted substance. Inappropriate prescriptions can prejudice an athlete's career, so checking that a drug is permitted before prescribing it is recommended.

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Self-test questions

The following statements are either true or false (answers on page 87)

3. Some over-the-counter medicines are prohibited substances for athletes.
4. Athletes should not use hydrocortisone cream.

Newtelephone services

The National Prescribing Service (NPS) has launched a telephone service for health professionals wanting independent drug and therapeutics information. The Therapeutic Advice and Information Service (TAIS) will give immediate access to information and respond to patient-related enquiries such as:

- interactions with other drugs, foods or complementary therapies – and how to manage these
- adverse effects, especially unusual ones not included in the product information
- use of drugs for unlicensed indications – is there good evidence to support use?

General practitioners, community pharmacists and other community-based health practitioners are expected to be the main users of the service.

Contact the Therapeutic Advice and Information Service for health professionals on **1300 138 677**, or the NPS on (02) 9699 4499.

The NPS is planning a parallel service for the general public, to be launched later this year. This consumer service will provide information about medicines in lay language, and aims to promote communication between patients and health professionals.

The service will not replace the counselling role of a health professional who knows the patient, however it may help the patient to identify issues that should be discussed with their doctor or pharmacist.

An alternative stream? *Serenoa repens* for benign prostatic hypertrophy?

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SYNOPSIS

Extracts from the berries of the saw palmetto plant (*Serenoa repens*) can have a beneficial effect on the symptoms of benign prostatic hypertrophy. This effect is small and the mechanism of action is unknown. Comparisons show that extracts of *Serenoa repens* and finasteride have similar effects on urine flow. At present there is no clear role for the extracts in the treatment of lower urinary symptoms and the long-term adverse effects are unknown. Patients with symptoms should have prostate cancer excluded before trying *Serenoa repens*.

Index words: complementary medicine, herbal medicine, saw palmetto, urinary tract disorders.

(Aust Prescr 2000;23:79)

Introduction

Studies show that 24–90% of new or existing patients attending urology clinics in America with symptoms of benign prostatic hypertrophy (BPH) use or have tried some form of complementary medicine. The most popular extract comes from saw palmetto berries (*Serenoa repens*, also known as *Serenoa serrulata* or sabal).

Saw palmetto

Saw palmetto is a dwarf palm tree native to North America. It gets its name from the saw-like ends of the leaf blades which can cut into the clothing and skin of those coming into contact with them.

Lipophilic constituents extracted using hexane or ethanol are thought to be responsible for the plant's effects in BPH. Hence products extracted with water, such as teas, would not be expected to produce the same effects. However, the mechanism of action is unclear. The effects are generally attributed to a combination of the spasmolytic, anti-androgen and anti-inflammatory activities of the extract. Adverse effects occur rarely and include headache, nausea and diarrhoea.

Evidence of efficacy

A previous editorial in *Australian Prescriber* questioned the relevance of the intermediate outcomes used in studies of finasteride.[1] Since this challenge was made, a company-supported four year study of finasteride has shown a reduction in the development of acute urinary retention and in the need for surgery.[2]

A recent systematic review of *S. repens* extracts for BPH included 18 (of the 24) randomised controlled trials.[3] Thirteen of these (with 1118 participants) compared an extract of *S. repens* (alone or combined with other phytotherapies) versus placebo, and showed a statistically significant improvement in urinary symptoms and flow measures. Two studies made a direct comparison with finasteride, and their pooled results showed there was no difference in urinary symptom scores between the extracts and finasteride. The weighed mean difference was 0.37 IPPS points (scale 0–35) (95% CI –0.45 to 1.19). Similarly there was no difference in the secondary outcomes peak urine flow, nocturia/mean urine flow (Permixon study only) and residual volume (Pro study only). Drop-out rates and gastrointestinal adverse effects were similar for *S. repens* and finasteride (9% versus 11%, 1.3% versus 1.5% respectively). Erectile dysfunction rates were lower for *S. repens* than for finasteride (1.1% versus 4.9%, $p<0.001$).

Conclusion

So should patients who cannot have surgery for prostatic symptoms now take *S. repens* once prostate cancer has been excluded? At this stage the available evidence does not provide a clear answer. Since this patient group is currently highly motivated to use complementary medicines and studies suggest some individuals may benefit from using *S. repens*, it seems reasonable to see if symptoms improve during a one to three month trial. Prostate cancer should first be excluded and patients developing urinary retention, urinary tract infections, bladder calculi or deterioration of renal function should be discouraged from using phytotherapeutic agents.

Clarification of the mechanism of action and data on long-term effectiveness and safety are required as well as studies comparing the extracts with α-antagonists such as prazosin. The other unknown factor is whether saw palmetto extracts available locally are comparable in quality and would replicate the results seen in the European trials. There is considerable variation in saw palmetto content of Australian products, and some provide lower daily doses than published recommendations. Hence questions remain when considering if this alternative (or complementary) stream leads to the same sea.

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Chemotherapy for elderly patients with advanced cancer: is it worthit?

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SYNOPSIS

Elderly patients with advanced cancer must be allowed to balance the potential risks and benefits of treatment when deciding whether or not to have chemotherapy. The response rates to aggressive chemotherapy are similar in younger and older patients. Disease-related survival is often similar, although the older age group has more deaths due to comorbid illnesses. Factors complicating chemotherapy in the elderly are the physiological changes of ageing, the presence of comorbidities and polypharmacy. Deterioration in renal or hepatic function may force the doses of chemotherapy to be adjusted. Organ toxicities may be more problematic in the elderly, but in most tumours, the efficacy of chemotherapy is not age dependent. Chemotherapy, where indicated for advanced cancer, can therefore be safely and effectively used in selected elderly patients.

Index words: ageing, adverse effects, antineoplastics.

(Aust Prescr 2000;23:80–2)

Introduction

Managing advanced cancer in the elderly is an increasing problem. The percentage of our population over 65 years old is climbing and the incidence and mortality of cancer increases with ageing. The problem is compounded by older patients being a heterogeneous population. They often have comorbid illnesses and are taking multiple drugs. Moreover the decision as to whether or not to use cytotoxic anticancer chemotherapy is made more difficult because the elderly are under-represented in clinical trials.

For each patient the decision whether or not to have cytotoxic chemotherapy for advanced cancer is a balance between the potential benefits and adverse effects. Both of these involve value judgements by individual patients. The perspective of older patients may differ from that of younger patients. Short-term quality of life and the ability to continue managing their activities of daily living may be more important than a modest survival advantage when deciding whether to accept chemotherapy. Conversely, some fit older patients may seek aggressive chemotherapy if they can expect a similar outcome to younger patients.

Ethics

Ethically, clinicians making decisions about chemotherapy for elderly patients are likely to be guided by a principle of non-maleficence: do no harm. This is usually interpreted as ensuring that the risk:benefit ratio is favourable. The patient will expect to be allowed to make an autonomous decision about chemotherapy, but will be reliant on accurate information about the potential risks and benefits.

There is a view that a doctor's inclination is to offer active treatment rather than offer 'no treatment' or symptomatic care. The opposite may apply in an environment of economic rationalism with limited resources, and is arguable in today's society with the increasing influence of palliative care.[1]

From society's viewpoint a major issue is resource allocation. To deny expensive drugs to the elderly purely because of age, is 'ageism' and is as difficult to justify as discrimination against any sub-group of society. There are complex issues here.[2] A resource allocation formula based on years of expected benefit certainly appears to disadvantage the elderly who place the same value on 'the rest of their lives' as younger patients, irrespective of that life's duration. Alternatively, it could be argued that preferentially allocating resources to younger patients and successfully treating them would allow more to reach older ages. However, if the risks of chemotherapy do increase substantially with age, then a medical decision based on the risk:benefit ratio may differ in older patients purely on that basis and not because of age.

Factors complicating chemotherapy in the elderly

To assist decision making about the treatment of advanced cancer in the elderly we need to examine the likelihood of response to chemotherapy and survival benefit. We also need to review the factors that may complicate chemotherapy in the elderly.[3] These factors include the physiological changes accompanying ageing and the impact of comorbid diseases.[4] Loss of organ function will affect cytotoxic drug metabolism. Changes in kidney or liver function or bone marrow reserve are particularly problematic when giving chemotherapy. It can be difficult to evaluate the physiological status of an elderly patient with the exception of renal function and the use of simple scales to assess their ability to perform the activities of daily living.

Renal function

The glomerular filtration rate decreases with age. Calculating the creatinine clearance using a formula, such as the Cockcroft-Gault formula (see box), that accounts for age and weight will reasonably accurately assess renal function. Just using the serum creatinine can overestimate renal function, given that less creatinine is produced as lean body mass decreases with age. Formulae have been developed to adjust the dose of renally excreted cytotoxic drugs, such as methotrexate and carboplatin, for changes in creatinine clearance. This ensures that the drugs can be given at an intensity which does not compromise efficacy, but avoids the excess adverse effects that occur if the drug accumulates because of delayed renal excretion.

Patients over 70 years old are similar to younger patients in developing nephrotoxicity when exposed to drugs such as cisplatin. They can be protected by hydration and diuresis, as long as they can tolerate the fluid load. Drugs such as doxorubicin or the taxanes that are predominantly metabolised by the liver can often be given in full doses to patients with renal impairment.

Liver function

Assessing the degree of liver impairment in the elderly that will impact on cytotoxic drug metabolism is difficult. Certainly, liver blood flow, serum albumin and cytochrome P450 function are all decreased with ageing. The cytochrome P450 mechanism may also be a problem if elderly patients are given cytotoxics in addition to other drugs metabolised by this system. Commonly used drugs, such as cimetidine, will inhibit the P450 system.

Several anticancer drugs need to have their doses adjusted if the patient's bilirubin is high. Anthracyclines and taxanes are the best examples, but there is a paucity of data on the precise adjustments required for various liver function abnormalities. Low albumin will lead to increased liver extraction of some drugs but the increase in body fat with age may decrease the peak dose of a drug, yet increase the half-life of fat-soluble drugs. The initial absorption of oral cytotoxics, such as etoposide, may be altered in patients with the atrophic gastritis of age.

Bone marrow

The elderly can have unpredictable myelosuppression, particularly if malnourished. The lack of bone marrow reserve may manifest itself as more prolonged myelosuppression with successive cytotoxic drug doses. The colony stimulating factors such as G-CSF which reverse myelosuppression may be required more often in elderly patients. They can allow adequate doses of chemotherapy to be given without as great a risk of life-threatening febrile neutropenia.

Non-haematological toxicity

Cytotoxic drugs such as the vinca alkaloids, taxanes and cisplatin can be neurotoxic or ototoxic. These toxicities can be considerably more debilitating in the elderly who may already have compromised mobility, sensation or hearing. Of the other non-haematological adverse effects only the cardiac toxicity of doxorubicin and lung toxicity of bleomycin are known to be accelerated in the elderly.

Cockcroft-Gault formula

Estimated creatinine clearance (mL/sec) – males

$$= \frac{(140 - \text{age}) \times \text{weight (kg)}}{48\,816 \times \text{plasma creatinine (mmol/L)}}$$

Estimated creatinine clearance (mL/sec) – females

$$= \frac{0.85 \times (140 - \text{age}) \times \text{weight (kg)}}{48\,816 \times \text{plasma creatinine (mmol/L)}}$$

Adverse effects

In fit elderly patients with normal organ function the adverse effects will be comparable to those seen in younger patients and are managed in a similar way.[5] Within hours many cytotoxic drugs will cause nausea and vomiting. This acute emesis is best managed by premedicating patients with $5HT_3$ receptor antagonists and dexamethasone. Less severe emesis can be treated with metoclopramide or prochlorperazine although prolonged emesis lasting for several days is best managed with dexamethasone in combination with these antiemetic drugs.[6] Patients may become neutropenic approximately 10 days after treatment. An infection at this time is potentially life threatening and should be urgently treated with intravenous broad spectrum antibiotics.[7] Subsequent courses of chemotherapy may require dose reductions or support with haematopoietic growth factors. Thrombocytopenia with bleeding can be managed with platelet transfusions. Mucositis occurs in the same time frame and requires symptomatic treatment with local anaesthetic mouth washes plus treatment of any secondary infections due to candida or herpes.

A further group of toxicities which require monitoring involve cumulative damage to organs over several months. This can be a particular problem in the elderly whose organ function may have deteriorated before chemotherapy. Liver and renal function should be measured with each course, and for specific drugs cardiac and pulmonary function should be monitored. Deterioration in organ function may require cessation of chemotherapy.

With worsening organ function the adverse effects of chemotherapy increase and the balance between efficacy and toxicity is no longer in the patients' favour. Adverse effects can impact on quality of life and the patients' ability to cope with daily activities. This also increases the burden on their carers.

The efficacy of chemotherapy in the elderly

There is no evidence that there is any general decrease in efficacy of chemotherapy in the elderly, although some studies

suggest that this is the case in Hodgkin's disease and acute leukaemia. In non-Hodgkin's lymphoma, for example, the complete response rates with aggressive chemotherapy are equal in patients over and under 60 years old. The survival of the older patients is less, however, because of deaths unrelated to the lymphoma or its treatment.[8] Overall response rates to chemotherapy in small cell lung cancer are also similar in younger and older patients, and age has not been found to be an adverse prognostic factor.[9] Survival rates are similar in older patients despite the dose intensity often being less and despite them having a greater number of comorbid conditions.

Some cancers may behave differently in the elderly and warrant different treatment approaches from those in younger patients. In breast cancer for example, the risk of local recurrence after lumpectomy declines with age. This may decrease the need for postoperative radiotherapy in older women. In the Oxford meta-analysis adjuvant chemotherapy was associated with decreasing survival benefit with increasing age particularly in the over 70 age group.[10] Individual older women at high risk of recurrence, however, may obtain some benefit from adjuvant systemic therapy.

Conclusion

In most cancers the elderly will respond as well as their younger counterparts provided the chemotherapy can be given safely. This may depend on physiological changes in organ function, particularly renal and hepatic function. Deteriorating organ function will make adverse effects and therefore an adverse impact on quality of life more likely.

Elderly patients should be given the option of chemotherapy for responsive advanced cancers. As with younger patients they make their decision balancing any predicted positive outcome against the treatment's adverse effects that, even if temporary, will impact upon their quality of life.

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Self-test questions

The following statements are either true or false (answers on page 87)

5. In general, the efficacy of chemotherapy is reduced in the elderly.
6. The physiological changes of ageing may require increased doses of chemotherapy to be given.

Chemotherapy for elderly patients: a personal experience

Editor's note:

'Snow' Partridge was 81 years old when he developed a small cell carcinoma of unknown primary. He was treated with six cycles of cisplatin and etoposide.

AP: *How did you find out you had cancer?*

SP: I noticed a small lump at the front of my neck. I did not think much about it, but about a month later I mentioned it to my general practitioner when I consulted her about another problem. My doctor sent me for a biopsy.

I was told that the biopsy was 'positive' and I was referred to a surgeon. The surgeon recommended that I have the lump removed so I had an operation. After the operation I was referred to an oncologist. I had to have scans of my whole body.

AP: *How did you feel when you were told you had cancer?*

SP: I do not know what kind of cancer I had. I knew that cancer was serious so I was slightly alarmed by the diagnosis.

AP: *Were you told what choices you had for treating your cancer?*

SP: I was not given a choice of treatment. The oncologist advised me to have chemotherapy to 'clear up any nasties'. I decided to take the oncologist's advice.

AP: *Before you had your treatment, what did you think it would be like?*

SP: I knew other people who had been given chemotherapy. They had felt crook all the time and had problems with vomiting. I knew it would not be pleasant, however I coped well with chemotherapy.

I did not know what I was treated with, but my treatment was for three days every three weeks. This was repeated six times. I had blood tests before each treatment and I had to stay in hospital for two nights each time.

AP: *What adverse effects did you have?*

SP: The doctors and nurses were very good – they told me what side effects to expect and what I could do about them. I only vomited twice, but all my hair fell out after the second treatment. I think I coped well. Apart from a couple of days when I overdid things, I did not feel too unwell.

AP: *Were you relieved when the treatment was completed?*

SP: I hoped the treatment was curing the cancer but I was pleased when the chemotherapy was over. I felt more lively and my hair grew back.

It is now nearly two years since I finished treatment. I am still playing golf and a few sets of tennis.

AP: *Would you make the same choice if you had to make the decision about being treated again?*

SP: I would have chemotherapy again if the doctors advised it.

AP: *Do you have any advice to help elderly people with cancer decide about having or continuing treatment?*

SP: It would be a bit rough to say that old people with cancer should not be treated. I think if you are reasonably fit you should go for the treatment. If you are advised to have chemotherapy, think positively and go for it.

Dental implications

Prepared by Associate Professor R.G. Woods of the Australian Dental Association

Chemotherapy for elderly patients with advanced cancer: is it worthit? (page 80)

The oral adverse effects of chemotherapy may complicate dental treatment in patients with cancer.[1] Systemic adverse effects, for instance immunosuppression, are likely to complicate endodontic treatment or surgery. Taking a pre-treatment medical history is essential to obtain information about the drugs being used to treat the cancer. You should also ask if the patient has had radiotherapy, particularly in the region of the head and neck.

Dental treatment needs to be planned with care. The risks of post-operative infection and delayed wound healing should be minimised. This could include antibiotic surgical prophylaxis. An increased risk of infection from periodontal disease and its treatment should be anticipated. Stomatitis may occur with or without oral ulceration and may be relieved by topical steroid therapy (triamcinolone).

Where possible, a comprehensive oral and dental examination should be made and any infection treated before chemotherapy begins. Following chemotherapy provision should be made for dentate patients, to have a regular preventive dentistry program to minimise the need for invasive dental treatment.

Dental management of any patient, young or old, can be complicated by chemotherapy. Where there is any doubt concerning the effects of medication used or precautions needed, dentists should discuss the case with the patient's oncologist.

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International success

In June Dr John Dowden, the Editor of *Australian Prescriber*, received an outstanding service award from the Drug Information Association (DIA). The presentation ceremony took place at this year's annual meeting of the DIA in California. Dr Dowden accepted the award in front of an audience of approximately 7000 people in the San Diego Convention Centre.

While the award is primarily for Dr Dowden's work with the South-west Asia-Pacific Steering Committee of the DIA, it reflects well on *Australian Prescriber*. The journal is an important source of independent drug information in Australasia. The Executive Editorial Board congratulates the Editor on his award.

For more information about the DIA follow the Links from the *Australian Prescriber* web site at *www.australianprescriber.com*

Newdrugs

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 Board 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 Board is prepared to do this. Before new drugs are prescribed, the Board 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.

Aldesleukin

Proleukin (CSL)

vials containing 18 million IU as powder

Approved indication: renal cell carcinoma

Australian Medicines Handbook Section 14.2

Renal cell carcinoma is increasing in incidence. Many patients present with metastases and have a poor prognosis. Chemotherapy does not improve survival. In some patients the cancer may spontaneously regress suggesting an immune response. This has prompted research into the role immunomodulators, such as interferon, could play in treatment.

Aldesleukin is a recombinant form of the cytokine interleukin 2. This cytokine stimulates the production of killer cells and enhances the cytotoxicity of lymphocytes. It is also involved in the production of interferon and tumour necrosis factor.

A randomised trial compared aldesleukin, interferon alpha-2a or a combination of both treatments in 425 patients with progressive metastatic renal cell carcinoma. The response to treatment was assessed using CT scans to measure the regression of the tumour. After 10 weeks 6.5% (9/138) of patients given aldesleukin had responded. The response rate at 25 weeks was 2.9%. Patients who received the two treatments in combination had significantly higher response rates (18.6% at 10 weeks, 13.6% at 25 weeks).[1]

Aldesleukin given intravenously has many adverse effects, so it has only been approved for subcutaneous injection. This requires daily injections for five days a week for four weeks. After four weeks the patient has one week's rest and then the cycle is repeated.

The subcutaneous injection has a bioavailability of 35–47%. It is metabolised and excreted by the kidneys with a half-life of 5–9 hours.

In studies involving a total of 103 patients, subcutaneous injections produced a complete response in four patients. The overall response rate was 14%.

Most patients will develop adverse reactions to aldesleukin, chills and fever being particularly common. Approximately 12% of patients develop hypotension. This may be part of a 'capillary leak syndrome' which also includes oliguria, pulmonary oedema and weight gain. More than half the patients will become anaemic or have altered liver function. Patients may develop antibodies to aldesleukin and some of the antibodies will have neutralising activity. Autoimmune and inflammatory diseases may flare up during treatment.

Aldesleukin does not increase survival. In the comparative study median survival was only 12 months.[1] However, the studies of subcutaneous aldesleukin showed that the response was prolonged in the few patients who had a complete response. The median response duration was 64 months. Further studies are needed to identify which factors predict a favourable response.

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Eprosartan mesylate

Teveten (SmithKline Beecham)

300 mg and 400 mg tablets

Approved indication: hypertension

Australian Medicines Handbook Section 6.4.5

Eprosartan is another one of the recently approved angiotensin$_1$ receptor antagonists (see 'Angiotensin receptor antagonists for the treatment of hypertension' Aust Prescr 1998;21:95–7). As this class expands, there is clearly a need for comparative studies. In the meantime, the precise role of the class in the treatment of hypertension remains unclear. While the drugs do have a low short term incidence of adverse effects, there is little knowledge about their long-term effect on outcomes, either adverse or beneficial.

The absorption of eprosartan is reduced by food, but this is considered to be clinically inconsequential. Absolute bioavailability is 13%. Eprosartan is partly metabolised and excreted in the bile and urine. Its pharmacokinetics are affected by severe liver or kidney disease. Lower starting doses are recommended in the elderly and patients with sodium/volume depletion. The half-life is 5–9 hours, but the manufacturer recommends only once daily dosing. If a patient is not responding, consideration can be given to changing to twice daily dosing before increasing the total daily dose.

Clinical trials show that eprosartan reduces diastolic blood pressure by 2–5 mmHg more than placebo. Studies comparing eprosartan and enalapril show that they are equally effective at lowering diastolic blood pressure. In one study, eprosartan had an effect on systolic blood pressure which was statistically greater than the effect of enalapril.

Like other members of this class, eprosartan has a low risk of adverse reactions. In placebo-controlled trials, 4% of patients taking eprosartan dropped out because of adverse events compared with 6.5% of the placebo group. The incidence of cough is lower than with ACE inhibitors.

Hydromorphone

Dilaudid (Knoll)

2 mg, 4 mg and 8 mg tablets

oral solution containing 1 mg/mL

ampoules containing 2 mg/mL, 10 mg/mL and 50 mg/5 mL

vials containing 500 mg/50 mL

Approved indication: moderate to severe pain

Australian Medicines Handbook Section 3.2

Hydromorphone is an opioid analgesic.[1] It has been available overseas for a long time, but has not been marketed in Australia for many years.

Patients with chronic cancer pain, requiring an opioid analgesic, may tolerate one opioid better than another. Hydromorphone may be an alternative analgesic for patients troubled by the adverse effects of morphine.

Oral hydromorphone is rapidly absorbed, but first-pass metabolism reduces the bioavailability to 25%. The drug is rapidly and widely distributed throughout the body. Most of the absorbed dose is metabolised, so hydromorphone is contraindicated in hepatic impairment. As the major metabolite is excreted in the urine, the drug is also contraindicated in renal impairment. As the half-life of hydromorphone is 2–3 hours, the dose can be rapidly titrated.

The recommended starting dose for oral treatment is 2–4 mg every four hours. A daily oral dose of hydromorphone 6.5–7.5 mg is equivalent to 40–60 mg of morphine or 10–20 mg of methadone. An intramuscular or subcutaneous dose of hydromorphone 1.3–2.0 mg is equivalent to 10 mg of morphine or methadone. A high potency formulation is available for use in narcotic-tolerant patients; this should not be confused with the standard parenteral formulation as an overdose may result.

The adverse effects of hydromorphone resemble those of other opioids, e.g. dry mouth, dizziness, nausea and vomiting. Patients become dependent on hydromorphone, if it is taken regularly, within a few weeks. Tolerance can also be expected. Sudden withdrawal of treatment can cause a withdrawal syndrome.

REFERENCE

1. Chahl LA. Opioids – mechanisms of action. Aust Prescr 1996;19:63-5.

Lepirudin

Refludan (Aventis Pharma)

vials containing 50 mg freeze dried powder

Approved indication: heparin-associated thrombocytopenia

Australian Medicines Handbook Section 7.1.1

Heparin can induce two types of thrombocytopenia. Type I occurs early in treatment and the platelet count soon returns to normal. Type II occurs after 5–10 days of treatment and can result in thromboembolism. Clotting occurs because the formation of a heparin-platelet complex induces the production of antibodies. These antibodies not only cause thrombocytopenia, but also activate the platelets. If untreated, heparin-induced thrombocytopenia can be fatal.

While the heparin can easily be stopped the prothrombotic state may persist. Lepirudin is therefore indicated for patients with Type II thrombocytopenia and its thromboembolic complications.

The drug is a recombinant form of hirudin, a substance produced by leeches. Lepirudin acts by inhibiting thrombin. This effect can be monitored by measuring the activated partial thromboplastin time.

Lepirudin has to be reconstituted and then injected intravenously. This bolus dose is followed by an infusion for 2–10 days. The dose is reduced if the patient has impaired renal function, as lepirudin is metabolised and excreted by the kidneys. A lower dose should also be used if the patient requires thrombolytic therapy.

In clinical trials, patients given lepirudin have been compared with historical controls. Approximately 74% of the patients responded to the treatment with an increased platelet count and an effective degree of anticoagulation. The incidence of new thromboembolic complications, death or the need to amputate a limb was reduced in comparison to the control group. After seven days of treatment the cumulative risk of these complications was 17% in the lepirudin patients and 25% in the control group.

The main adverse effect of lepirudin is bleeding. Thrombolytic therapy increases the risks. While bleeding from wounds and puncture sites is obvious, 9% of patients will suffer a fall in haemoglobin for no obvious reason. Other common problems are allergic reactions, bronchospasm and oedema. Approximately 40% of patients will develop antibodies to lepirudin. This may have implications if a patient requires a second course of treatment. Although the risk:benefit ratio is not clear, there are no specific treatments for heparin-associated thrombocytopenia, so there may be a role for lepirudin.

Live cholera vaccine

Orochol (CSL)

Sachets containing 2–10 x 10^8 colony forming units of *Vibrio cholerae*

Approved indication: immunisation

Australian Medicines Handbook Section 20.1.2

Vaccines based on heat-killed suspensions of *Vibrio cholerae* are not very effective. The injectable vaccine is also associated with systemic adverse effects. A live vaccine given by mouth may have advantages.

The new product is a recombinant form of the bacteria with the deletion of the gene coding for part of the cholera toxin. This live strain is known as *Vibrio cholerae* CVD 103-HgR.

Adult volunteers took the vaccine and were then exposed to virulent *Vibrio cholerae* 8–180 days later. There was complete protection against cholera, if the bacteria were of the same serotype as the vaccine. This protection was present as early as eight days after vaccination.

People (including children more than two years old) who are at a high risk of infection when travelling through endemic areas can take the vaccine at least a week before travel. The single dose sachet has two sections. Their contents are mixed together in 100 mL of water then drunk. The traveller should not eat for an hour after taking the vaccine. Common adverse effects include abdominal pain, increased bowel sounds and headache.

Live oral cholera vaccine should be taken at least one week before starting chloroquine as the antimalarial drug can reduce the immune response. Oral typhoid vaccine and oral cholera vaccine should be given at least eight hours apart, as the cholera vaccine may affect the passage of the capsules, containing the typhoid vaccine, through the gut. If possible, vaccinees should avoid contact with immunocompromised people for eight days after taking the vaccine.

Although the vaccine protected the volunteers in the challenge studies, it was much less effective if the virulent bacteria were from a different serotype. There is also little published evidence yet of the vaccine's effectiveness in field trials. While 60–70% of people will seroconvert after vaccination, this may not reflect the intestinal antibody response or clinical effectiveness. Although a booster dose is recommended every six months the duration of immunity after a single dose is unknown. There is a Cochrane review of cholera vaccines but it currently contains no effectiveness data for this new product.[1]

REFERENCE

1. Graves P, Deeks J, Demicheli V, Pratt M, Jefferson T. Vaccines for preventing cholera (Cochrane Review). In: The Cochrane Library, Issue 3. Oxford: Update Software. 1999.

Repaglinide

NovoNorm (Novo Nordisk)

0.5 mg tablets

Approved indication: type 2 diabetes

Australian Medicines Handbook Section 10.1

Patients with non-insulin dependent diabetes have impaired insulin secretion and a resistance to the effects of insulin. If non-drug treatment fails, patients can be given a sulfonylurea, to stimulate insulin secretion, or metformin, to improve insulin sensitivity.[1] When these drugs fail to control the blood glucose concentrations, repaglinide can be considered.

Repaglinide is not a sulfonylurea, but it stimulates the release of insulin from the pancreas. A dose is taken before meals. It is quickly and completely absorbed, but has a bioavailability of 63%. The peak plasma concentration is reached within an hour of the dose, and a response begins within 30 minutes. Repaglinide is almost completely metabolised by the liver and is cleared from the circulation within six hours.

In clinical trials, repaglinide was more effective than a placebo at reducing blood glucose concentrations. Its efficacy, in trials lasting up to 14 months, seemed to be similar to that of glibenclamide. In a trial lasting several months, the combination of metformin and repaglinide decreased HbA_{1c} and fasting glucose more than either drug alone.

The most common adverse event in the clinical trials of repaglinide was hypoglycaemia. The incidence of hypoglycaemia was similar to that seen with other oral hypoglycaemic drugs. It is important that the dose is titrated for each patient. Patients begin with 0.5 mg and then increase the dose at 1–2 week intervals. The maximum daily dose is 16 mg. Other adverse events resemble those of the sulfonylureas.

Metformin is usually the first drug prescribed for obese patients with diabetes.[1] Repaglinide may be a useful addition, if treatment with metformin alone is inadequate. While repaglinide's quick action is beneficial, it is not clear if it has any advantage over short-acting sulfonylureas. If overseas prices are reflected in Australia, any advantages are likely to be outweighed by the cost of repaglinide.

REFERENCE

1. Proietto J. The management of type 2 diabetes. Aust Prescr 1997;20: 65-7.

Tibolone

Livial (Organon Australia)

5 mg tablets

Approved indication: postmenopausal symptoms and bone loss

Australian Medicines Handbook Section 17.2.3

Tibolone is a synthetic steroid with oestrogenic and progestogenic activity. It can therefore be used to treat menopausal symptoms such as hot flushes.

The activity of the drug involves several metabolites. These are rapidly formed after absorption so plasma concentrations of tibolone are very low. Only small amounts are excreted in the urine.

Several studies have assessed the effect of tibolone on bone density. One study followed healthy postmenopausal women for two years. Women who took 2.5 mg tibolone daily had increases in bone density, while bone density fell in the control group. By the end of the study, there were significant differences in bone density between the groups in the upper femur and lumbar spine.[1]

Another study compared tibolone with oral or transdermal hormone replacement therapy. After two years, bone density was preserved in women who were treated, compared with untreated controls. There were no significant differences in efficacy between tibolone and hormone replacement therapy.[2]

As tibolone has some progestogenic effects it may have an advantage over oestrogen alone, e.g. the risk of breast cancer may be reduced. However, endometrial proliferation can still occur and lead to vaginal bleeding. Any abnormal bleeding occurring after three months of treatment should be investigated. Compared with placebo, more patients taking tibolone experience leukorrhoea, vaginitis, breast pain and weight gain.

Tibolone reduces triglyceride concentrations, but can also reduce HDL cholesterol. As it may increase fibrinolytic activity there is a potential for interaction with anticoagulants. Drugs

which induce liver enzymes, such as carbamazepine and rifampicin, may decrease the effect of tibolone.

Although tibolone has been available overseas for several years its place in therapy is not clear. While it can prevent reductions in bone mineral density its effectiveness in preventing fractures is unknown.

REFERENCES

1. Beardsworth SA, Kearney CE, Purdie DW. Prevention of postmenopausal bone loss at lumbar spine and upper femur with tibolone: a two-year randomised controlled trial. Br J Obstet Gynaecol 1999;106:678-83.
2. Lippuner K, Haenggi W, Birkhaeuser MH, Casez JP, Jaeger P. Prevention of postmenopausal bone loss using tibolone or conventional peroral or transdermal hormone replacement therapy with 17 beta-estradiol and dydrogesterone. J Bone Miner Res 1997;12:806-12.

NEW FORMULATIONS

Pantoprazole

Somac (Pharmacia & Upjohn)

40 mg powder for injection

Ropivacaine hydrochloride/fentanyl citrate

Naropin with fentanyl (AstraZeneca)

2 mg/mL ropivacaine hydrochloride/fentanyl citrate 2 microgram/mL and 2 mg/mL ropivacaine hydrochloride/fentanyl citrate 4 microgram/mL

NEW STRENGTHS

Alendronate sodium

Fosamax (Merck Sharp & Dohme)

5 mg tablets

Pantoprazole

Somac (Pharmacia & Upjohn)

20 mg tablets

NEW COMBINATION

Salmeterol/fluticasone propionate

Seretide Accuhaler (Glaxo Wellcome)

50 microgram salmeterol/100 microgram fluticasone propionate, 50 microgram salmeterol/250 microgram fluticasone propionate and 50 microgram salmeterol/500 microgram fluticasone propionate

Answers to self-test questions

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

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