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EDITORIAL

Why are children still therapeutic orphans?

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Index words: off-label prescribing, drug therapy, drug regulation.

(Aust Prescr 2003;26:122–3)

One of the paradoxes of drug regulation is that children have ended up being denied the protections afforded by the very laws which were introduced to ensure the efficacy and safety of drugs following disasters such as the thalidomide tragedy. Children have become therapeutic orphans[1] because they are either denied the use of many new medications or exposed to medications that have bypassed rigorous evaluation. Many marketed drugs that are commonly used, or could potentially be used in children, have not been studied in the relevant age groups[2] and so are not approved by regulatory authorities for use in children.

Information about the safety and efficacy of medications in the youngest, and most vulnerable, paediatric age groups is especially scarce.[2] Any prescription of drugs outside the specifications of the product licence (such as for a different age, dose, route or indication) is 'off-label' use.[3] Some medicines that are given to children are not registered by the Therapeutic Goods Administration for any indication in adults or children ('unlicensed' use).

This paradox poses significant clinical, ethical and legal dilemmas for prescribers.[4] It is difficult to practise evidence-based medicine when there is little (or no) evidence. Yet, clinicians tend to choose to prescribe a new drug despite a lack of paediatric data rather than deprive children of a potentially beneficial therapy. The practice is widespread; between 40 and 90% of paediatric prescribing is for off-label use or for unlicensed drugs.[3,5] Although unlicensed or off-label prescribing is not illegal, and in some cases may be entirely appropriate, it does bypass the safeguards of the drug regulatory process and places a greater onus of responsibility on the individual prescriber. The validity of 'informed consent' to therapy based on little or no information also raises ethical concerns.[4]

While unlicensed or off-label prescribing may be acceptable as an exception, it is clearly unacceptable when it becomes the rule. Children are disadvantaged in many ways by this situation.

First, extrapolating the results of adult studies means that children may be exposed to ineffective therapies (or to ineffective doses of potentially effective therapies) and to unknown risks of adverse effects. There are many biological differences between adults and children of different ages which mean that the evidence of effectiveness and safety in adult studies is not generally applicable to children (for example chloramphenicol and the grey baby syndrome).

While it may be tempting to give the benefit of the doubt to new drugs that have not been studied in children, this may place more children at risk than if the drug was used as part of a controlled trial.[6] Adverse effects are more common when drugs are used off-label[7] and some children have died as a result.[8] Ironically, this information is also hard to come by since spontaneous reporting of adverse drug reactions as part of standard post-marketing surveillance may be less likely with off-label prescribing.[2,4]

Second, the lack of information about new drugs means that children may be unable to benefit from therapeutic advances that are available to adults.

Third, even if a drug has good evidence of paediatric efficacy and safety, it may be unavailable in formulations (for example liquids) that are suitable for children.

In this issue...

The proverb 'You are what you eat' is relevant for medical practice. Lynne Daniels tells us that patients are likely to make a better recovery from surgery if they are well nourished, while John Wark and Caryl Nowson remind us of the importance of an adequate calcium intake.

The origins of the proverb are uncertain. Perhaps it came from China, where herbs have been used as medicines for centuries. George Li, Colin Duke and Basil Roufogalis discuss the quality of traditional Chinese medicines, and John McEwen and Fiona Cumming explain how these products are regulated by the Therapeutic Goods Administration.

Eight new drugs have been marketed in Australia since the previous issue of *Australian Prescriber*. How many of these new drugs will make the top ten? As usual, this year's top ten features several drugs which are used to treat conditions associated with an unhealthy lifestyle, including a poor diet.

Fourth, evidence from well-conducted studies in children may not always be reflected in the product information, if it becomes available after marketing of a new drug. This results in the contradictory and confusing situation (for the prescriber and consumer) where prescribing is evidence-based yet not consistent with the product information, which may state 'Not approved for use in children'. As Consumer Medicine Information leaflets are based on the product information, children and parents are further disadvantaged by not having access to appropriate drug information.

Fifth, the current system also means that children are denied equitable access to subsidised medication. The Pharmaceutical Benefits Scheme does not include off-label prescribing.

Finally, uncritical acceptance of widespread off-label drug use by prescribers additionally disadvantages children by removing the incentive for the pharmaceutical industry to properly evaluate drugs for paediatric use.

The pharmaceutical industry has been reluctant to conduct drug studies in children, mainly because of the low profitability and perceived greater risks of paediatric drug research. Many of the other obstacles to drug research in children have been largely overcome by recent advances in research methods and development of collaborative approaches between investigators.[9,10] Drug studies that are scientifically valid, feasible and ethical are now possible and 'there is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents'.[6] The Food and Drug Administration in the USA now requires manufacturers of new and marketed drugs to conduct paediatric studies and in some circumstances will provide financial incentives for this research.[9] Similar changes are currently being proposed by the European Union.[11]

The policy changes in the USA have vastly increased the number of drug studies in children and expanded the evidence base for paediatric therapeutics. However, it is evident that these initiatives have favoured the study of more profitable drugs. Drugs lacking patent protection (for example most older antibiotics) and those with a small market still remain unstudied.[12] Public funding is therefore being made available in the USA specifically for the study of off-patent drugs used in children. This initiative should go a long way towards remedying the woeful state of the evidence base for paediatric therapeutics. Australian children will no doubt benefit greatly from these global initiatives, but much more work needs to be done before they enjoy truly equitable access to useful medicines.

Developing successful solutions for this age-old problem requires new ways of thinking and action by all concerned. Clinicians should work with researchers to ensure that the study of medicines likely to deliver the greatest health benefit to children receives the highest priority. Drug companies should be encouraged to conduct more high quality research on drugs that may be used in children and to ensure that available research is incorporated into the product information. They should be encouraged to ensure children's continued access to new and old drugs in suitable formulations, even if this may not be very profitable. Withdrawal of useful medications should be strongly discouraged, unless there are safety concerns or clearly superior alternatives are available.[13] Clinicians, researchers, policy makers and consumers should work together with the pharmaceutical industry to develop innovative ways of achieving these goals as a matter of urgency.

We have allowed children to remain therapeutic orphans for far too long. Clear and feasible solutions now exist to remedy this problem. It is time that we stopped discriminating against our children and high time that we finally gave them their rights to the benefits of full therapeutic 'citizenship'. They deserve nothing less and nothing less will do!

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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.

Generics – equal or not?

Editor, – I read with interest the article by Professor Birkett on generics (Aust Prescr 2003;26:85–7). However, the recent introduction of a generic form of the immunosuppressive drug cyclosporin confuses one of the key messages.

The abstract of the article states, 'There are no generic formulations of drugs with a narrow therapeutic index as it would be difficult for them to meet the required standard of bioequivalence'. The body of the article then explains why there are no generic forms for drugs such as digoxin and phenytoin where the dose is critical. It is therefore difficult to understand the reasoning behind the current situation with cyclosporin. This is arguably the most critical dose drug on the market. The fine balancing act between immunosuppressive efficacy and nephrotoxicity (and other dose-dependent adverse effects) is perhaps the most challenging part of practice for transplant clinicians, and requires careful and frequent monitoring of drug concentrations. The use of cyclosporin is further complicated by numerous significant drug interactions.

The generic form of cyclosporin seems to invalidate a key message in Professor Birkett's article and has left this reader confused. Generic forms of established medications have an important place in the Australian market, however, clinicians and consumers need to be very aware of the need for careful monitoring when a generic form of a 'difficult' drug such as cyclosporin becomes available. It is critical to minimise interchange between formulations without clear awareness by all parties involved in the patient's care.

Randall Faull
Consultant Nephrologist
Renal Unit
Royal Adelaide Hospital
Adelaide

Editor, – In the article 'Generics – equal or not' (Aust Prescr 2003;26:85–7), Professor Birkett mentions that '...there are no generic products in Australia, for example, for digoxin...' Unfortunately there is! There is a generic of digoxin called Sigmaxin/Sigmaxin PG made by Fawns and McAllan which is available on the Pharmaceutical Benefits Scheme. I have not had a look at the tablets to see how similar they are to Lanoxin/Lanoxin PG and as I have recently come back from overseas, I am not sure how long they have been available.

Maureen M. Hendry
Pharmacist
Quality Medication Care Clinical Pharmacy Services
Wynnum, Qld

Editor, – The recent article by Professor Birkett (Aust Prescr 2003;26:85–7) was an interesting contribution to the debate on generic drugs. However, we wish to point out a serious flaw in the argument for patients with chronic paroxysmal diseases like epilepsy. Generics are licensed for use if they show acceptable bioequivalence in short-term pharmacokinetic studies. We have no argument with this standard for drugs used to treat short-lived conditions, often using supra-therapeutic doses, such as antibiotics for bacterial infection. Similarly, for chronic conditions like hypertension or diabetes where there is a physiological marker that is a continuous variable, minor dosage adjustments can easily be made using a generic without adverse clinical consequences even if bioequivalence is imperfect.

In contrast, epilepsy is characterised by a state where the patient is apparently physiologically normal with seizures punctuating their lives in an episodic and unpredictable manner. Issues related to antiepileptic drugs are often identified as the cause for unpredictable seizures, including poor absorption associated with intercurrent infection, other drugs, diarrhoea or non-compliance. The type of evaluation done for generics to establish bioequivalence simply does not match what is required for conditions with a narrow therapeutic window such as epilepsy. There are many uncontrolled and anecdotal reports of patients having breakthrough seizures on changing from one form of an antiepileptic drug to another.[1,2] Unfortunately, because of the nature of the problem, it is difficult to plan rigorous clinical trials to test the frequency and severity of such adverse events.[3]

We have no problem with the use of generic antiepileptic drugs, if a patient uses the same formulation continuously. However, the principle that patients requiring chronic therapy can be safely **switched** from one formulation of the drug to another, based on short-term bioequivalence studies, is a view that we cannot endorse. The consequences of a single seizure in an otherwise controlled patient can be devastating in terms of loss of driving licence, loss of job, physical injury or even loss of life. The temptation for the patient to take the cheaper alternative, often without the doctor's knowledge, needs to be corrected. The importance of this issue should be reinforced by the prescribing doctor and other healthcare professionals, particularly pharmacists.

Samuel F. Berkovic
Director
Epilepsy Research Institute
University of Melbourne
President, Epilepsy Society of Australia
and
Frank J.E. Vajda
Director
Australian Centre for Clinical Neuropharmacology
Raoul Wallenberg Centre
Chair, Standing Committee on Antiepileptic Drugs
Epilepsy Society of Australia

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Professor D. Birkett, the author of the article, comments:

In reply to the letters from Dr Faull and Ms Hendry, the point I was making was that the regulatory limits might need to be tightened for narrow therapeutic index drugs, but this would make it more difficult (and expensive) to demonstrate bioequivalence between products.

In relation to digoxin, the Schedule of Pharmaceutical Benefits for 1 August 2003 showed Lanoxin is manufactured by Sigma Pharmaceuticals. The 'generic' brand, Sigmaxin, is manufactured by Fawns and McAllan which is identified in the Schedule as 'a member of Sigma group of companies' and has the same address as Sigma Pharmaceuticals.

Three brands of cyclosporin were listed in the August 2003 edition of the Schedule – Cicloral, Cysporin and Neoral. Cysporin was a Faulding Pharmaceuticals product and has been listed since 2002. Cicloral is a product of Hexal Australia and appeared in the August 2003 Schedule. Cysporin and Cicloral are in fact the same product marketed under different names. This product has presumably been accepted as bioequivalent and therefore clinically equivalent to Neoral by the Therapeutics Goods Administration.

Drs Berkovic and Vajda make some sensible points – particularly that patients with conditions such as epilepsy might be better maintained on the same brand of an anticonvulsant drug. The Pharmaceutical Benefits Scheme makes allowance for this through the 'no substitution' rule. However, they do confuse the issue by using the term 'cheaper alternative'. They imply elsewhere in the letter that it is not the particular brand used, but the switching between brands that may cause problems due to patient confusion or minor differences in bioavailability. These issues apply equally to generic and innovator brands. For patients with a chronic condition cost is an important factor. The establishment and maintenance of treatment with a brand that provides the lowest cost for the patients will be in their interest.

Insomnia treatment – an update

Editor, – I would like to inform the readers of *Australian Prescriber* about the ongoing technical appraisal of the newer hypnotics by the UK National Institute for Clinical Excellence. The final statement should appear in the very near future.[1] It will offer information which might complement the recent excellent article by Professor Tiller (Aust Prescr 2003;26:78–81), particularly in clarifying pharmacoeconomic issues.

Dragan Milovanovic

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Book review

Therapeutic Guidelines: Cardiovascular. Version 4.

Melbourne: Therapeutic Guidelines Limited; 2003. 265 pages.

Price $33, students $25.30, plus postage.

Aniello Iannuzzi, General Practitioner, Coonabarabran, NSW

This book goes far beyond what its title suggests. Not only does it provide therapeutic guidelines, but it also addresses current diagnostic and epidemiological considerations relevant to the management of cardiovascular disease in Australia. In essence, it is a mini-textbook; it is much more than a guide.

The first chapter is a concise summary of cardiovascular drugs available in Australia. The next two chapters deal with smoking and the prevention of cardiovascular disease. The rest of the book is more like how one would expect the guidelines to be set out, with chapters devoted to each category of cardiovascular disease (for example, dyslipidaemia, hypertension, heart failure, arrhythmia). There are interesting sections on preoperative considerations for cardiac patients and deep vein thrombosis prophylaxis for airline travellers.

A most noteworthy feature of this book is that non-pharmacological therapies are given just as much emphasis as drug prescribing. It is a salient reminder for clinicians that our roles extend far beyond just selecting medicines for our patients. Current national recommendations on exercise and diet are included in the text.

The information contained in the guidelines is succinct, current and highly relevant to all clinicians. Medical students, junior doctors, pharmacists and general medical practitioners could comfortably use this book as their complete resource for the management of cardiovascular disease. Specialist physicians and cardiologists may find this a useful tool to compare their own individual management regimens against those most commonly used by their colleagues. Hospitals would find this a most useful addition to libraries and ward reference collections.

Calcium supplementation: the bare bones

John D. Wark, Professor of Medicine, Department of Medicine, The University of Melbourne, and Bone and Mineral Service, The Royal Melbourne Hospital; and Caryl Nowson, Associate Professor, School of Health Sciences, Deakin University, Melbourne

SYNOPSIS

An adequate calcium intake is an essential part of the prevention and treatment of osteoporosis. Two to three serves of calcium-rich foods each day provides sufficient calcium for most non-pregnant adults. If this target is not achievable, calcium supplementation is generally effective, cheap and safe for most people. Calcium carbonate (without vitamin and mineral additives) is the preferred supplement in most cases. Problems with calcium absorption arise due to factors including high-fibre vegetarian diets, achlorhydria, long-term glucocorticoid therapy and vitamin D deficiency. Vitamin D deficiency is extremely common in some ethnic groups and the elderly who are housebound or in residential care. These at-risk groups generally require vitamin D supplementation to achieve adequate intestinal absorption of calcium.

Index words: osteoporosis, diet, vitamin D.

(Aust Prescr 2003;26:126–7)

Introduction

There is strong evidence that an adequate calcium intake is important for healthy bones, and as part of the preventive strategy in individuals at high risk for osteoporosis (for example, patients receiving long-term glucocorticoid therapy). It is also an adjunctive treatment in patients with osteoporosis.[1] An adequate calcium intake (and vitamin D status) was a prerequisite for the clinical trials assessing the anti-fracture efficacy of all of the currently available medications for treating osteoporosis, with the exception of calcitriol. Patients being treated for osteoporosis should therefore always have an adequate intake of calcium, and a normal vitamin D status.

Dietary calcium

For most people, calcium requirements are in the range 800–1500 mg daily. These requirements are best met by consuming at least two or three servings of high calcium foods daily (for example, milk products, calcium-fortified soy products). A serving of dairy food contains 200–300 mg of elemental calcium.[2] (When checking the true calcium content of foods and supplements, it is the **elemental** calcium that matters.) Daily physiological needs may be at least 1000 mg during growth, in pregnancy and possibly in the late postmenopausal stage of life. Recommended dietary intakes of calcium (under review) indicate an additional 300 mg daily in pregnancy and an additional 400 mg daily for lactation.

Currently, approximately 60% of dietary calcium comes from dairy foods[2] (although this proportion may fall with the introduction of more calcium-fortified foods). People who avoid dairy products usually have an inadequate dietary calcium intake. Where necessary, calcium intake should be boosted by increasing the intake of high calcium foods such as dairy products and calcium-fortified soy products if possible. These products also contain a range of other essential nutrients including protein, phosphorus, magnesium and some vitamins which are of particular importance during growth, pregnancy and ageing.

Calcium supplements: how much, which type, how taken?

Calcium supplements are a very useful way of helping individuals who are unable to consume sufficient calcium from dietary sources. An extra 500–700 mg elemental calcium per day will suffice for most people. The cheapest, easiest way to achieve this objective is with a single calcium carbonate tablet containing 600 mg elemental calcium.

Calcium carbonate contains 40% elemental calcium by weight compared with 21% in calcium citrate. Although calcium citrate is more soluble and its bioavailability may be approximately 25% greater than that of calcium carbonate[3] it is also more expensive. Calcium citrate was found to be less cost-effective than a calcium carbonate preparation in a recent study.[4] Clinical situations where calcium citrate may be preferred over calcium carbonate include achlorhydria (calcium carbonate requires an acid environment to dissolve, calcium citrate does not), and in patients who need calcium supplements but have a history of kidney stones (citrate in the urine inhibits calcium oxalate precipitation).[5] Calcium phosphate preparations have not been studied extensively, but appear to be absorbed adequately.[6]

In general, it is recommended to prescribe or advise the use of widely available, major brand-name calcium preparations whose absorbability has been well documented. This is because the absorbability of some marketed products is only 40–60% of that of plain calcium carbonate.

Administration

It is generally not important when calcium supplements are taken in relation to meals. Patients with achlorhydria appear to be an exception. Calcium carbonate is very poorly absorbed in these patients when fasting, but is absorbed satisfactorily when ingested with a meal.[5] There is some evidence that taking calcium supplements in the evening may be advantageous, by suppressing the nocturnal rise in bone resorption. It is critical that calcium and oral bisphosphonates are taken at least several hours apart as calcium binds with these medications and prevents their absorption.

Factors that impair the absorption of calcium supplements

Some dietary constituents can impair calcium bioavailability by forming insoluble calcium complexes.[7] These substances include phytates (found in cereals, bran, soybeans, seeds) and oxalates (found in spinach, rhubarb, walnuts). Some vegetarian diets may therefore adversely affect calcium balance, particularly if the calcium content is low due to the avoidance of dairy products.

Inadequate vitamin D nutrition is associated with impaired intestinal calcium absorption and must be corrected for ingested calcium to be effective. As the vitamin D content of our diet is generally low, people with low levels of sunlight exposure (the chronically-ill, housebound, people in residential care, some ethnic groups) are at high risk for vitamin D deficiency. Dark-skinned people, especially veiled women, are an important risk group. Their vitamin D status in pregnancy is a particular concern. Daily needs are probably of the order of 800 IU in these high-risk groups. This can be given as oral vitamin D2 1000 IU daily.

Long-term glucocorticoid treatment also causes calcium malabsorption. In general, when calcium supplements are recommended, vitamin D nutritional adequacy should be assured and other bone-protective interventions may be indicated. Renal impairment is associated with calcium malabsorption and this aspect of the care of patients with renal disease requires specialist advice. Achlorhydria reduces the absorption of calcium carbonate. In theory, proton pump inhibitors might impair calcium absorption, but evidence is lacking. It may be preferable for patients taking proton pump inhibitors to take calcium supplements with meals and perhaps to take calcium in the form of calcium citrate.

Adverse effects

Calcium supplements are usually well tolerated. Occasional adverse effects include constipation, bloating and flatulence. Changing preparations (for example, from calcium carbonate to calcium citrate) may alleviate these adverse effects. Calcium supplementation is contraindicated in the presence of hypercalcaemia or marked hypercalciuria, and during calcitriol therapy for osteoporosis, because of the risk of inducing hypercalcaemia or hypercalciuria. Measurement of the serum calcium, albumin and creatinine should therefore be part of the pre-treatment evaluation of patients presenting with apparent osteoporosis. Caution is also required in renal impairment, sarcoidosis and when there is a history of nephrolithiasis.

Other than the above circumstances, ingested calcium has very low toxicity and over-consumption of calcium is very uncommon. Historically, milk-alkali syndrome (hypercalcaemia, alkalosis and renal failure) was described in the context of peptic ulcer treatment with large amounts of milk and sodium bicarbonate. The ingestion of large amounts of calcium carbonate, sometimes in combination with dairy products, also can cause this syndrome. Typically, affected patients have ingested 5000 to 15 000 mg calcium daily.

What about the additives?

Evidence is lacking that the small amounts of various mineral and vitamin additives present in some marketed calcium supplements improve the effectiveness of the supplements. In theory, the addition of vitamin D might be beneficial, but the amount of vitamin D added (100–200 IU) is insufficient to prevent vitamin D deficiency in someone at risk. An adequate vitamin D supplement of 1000 IU is therefore recommended for these individuals.

Conclusion

There is a strong case in favour of calcium supplementation when an adequate dietary calcium intake cannot be achieved. In most non-pregnant adults, a daily supplement of 600 mg elemental calcium as calcium carbonate is sufficient, though occasionally more may be required. Coexisting vitamin D deficiency is common, particularly in the elderly in residential care, and also needs to be corrected.

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Conflict of interest: none declared

Self-test questions

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

1. Weight for weight, supplements containing calcium carbonate contain more elemental calcium than calcium citrate supplements.
2. Calcium supplements and oral bisphosphonates should not be taken simultaneously.

The quality and safety of traditional Chinese medicines

George Q. Li, Co-ordinator, Colin C. Duke, Senior Lecturer, and Basil D. Roufogalis, Professor of Pharmaceutical Chemistry, Herbal Medicines Research and Education Centre, University of Sydney, Sydney

SYNOPSIS

Modern chemical and pharmacological research has greatly contributed to our understanding of Chinese medicine. The quality of Chinese medicines may be controlled by understanding their pharmacognosy and applying pharmaceutical methods. Chinese medicines may have intrinsic toxicity. They can also be contaminated and adulterated. Interactions with prescription drugs are also possible. Regulation, backed by education and research, is needed to improve the quality and quality use of traditional Chinese medicines.

Index words: complementary medicines, herbal preparations, pharmacognosy.

(Aust Prescr 2003;26:128–30)

Introduction

Traditional Chinese medicine is a medical system based on theory, pathology, diagnosis, treatment and herbal pharmacology principles that differ from those of orthodox medicine or Western naturopathy. The practice of traditional Chinese medicine has developed from knowledge accumulated through clinical observation and treatment over several millennia. Traditional Chinese medicine has an established history in Australia and has expanded rapidly in recent years. Chinese medicines now account for 3.2% of the total use of complementary medicines.[1] The Chinese Medicine Registration Act was approved by the Victorian Parliament in 2000, to regulate the qualifications of traditional Chinese medicine practitioners and dispensers to encourage the safe use of traditional Chinese medicines in Victoria.

In parallel with the growth of Chinese medicine, serious issues have been raised about its quality and safety in Western countries. Chinese medicines have been contaminated with toxic heavy metals and adulterated with prescription drugs.[2] There is therefore a need for quality assurance of Chinese medicines in Australia.

Active principles and therapeutic effects of Chinese medicines

Modern research has revealed that many Chinese herbs act through one or more pharmacological mechanisms. Many active components have been isolated from herbs used in Chinese medicine and some are used in modern pharmaceutical drugs. They include ephedrine for hypotension (from ephedra (*Ephedra sinica* Stapf)), artemisinin for malaria (from Chinese wormwood (*Artemisia annua* L.)), and berberine, an antibacterial component (from Chinese goldthread (*Coptis chinensis* Franch)). Active components have been defined in many other Chinese herbs, for example anthraquinone glycosides in rhubarb (*Rheum officinale* Baill), and gingerols in ginger (*Zingiber officinale* Rosc).

The chemistry of herbal medicines is the foundation of their pharmacology. It is also important for the manufacture and quality assurance of herbal preparations. For example, aconite (*Aconitum carmichaeli* Debx.) is an 'internal warming, hot and pungent herb' and is used to restore Yang deficiency in heart failure. Its cardiotonic active substance has been isolated and identified as higenamine, a beta adrenergic agonist with an isoquinoline structure related to catecholamines. The active components responsible for analgesic and toxic effects are aconitine, mesaconitine and other diterpene esters, which are largely hydrolysed during processing and boiling. The toxicity of aconite is well understood in traditional Chinese medicine and the herb is only listable at very low concentrations in Australia. Red sage (*Salvia miltiorrhiza* Bunge) is a herb that is said to 'promote blood circulation and remove blood stasis'. It purportedly dilates the coronary arteries and increases the peripheral circulation so it has been used to treat angina pectoris. However, for most Chinese medicines the active components responsible for their pharmacological activities and clinical applications are not well defined.

The level of clinical evidence to support Chinese medicine does not generally meet the internationally accepted standards of clinical trials of new drugs. Many preclinical and clinical studies carried out in China have been published in the Chinese literature, but the results are not readily available to Western communities.

Quality control from agriculture to fingerprinting

As for pharmaceutical products herbal medicines require professional and government control to ensure their quality, safety and efficacy. The Chinese pharmacopoeia (2000)[3] contains monographs and standards of *materia medica* and patent preparations. Australia relies mainly on imported herbal materials and has not developed a herbal pharmacopoeia.

The quality of a herbal medicine refers to the intrinsic properties of the herb, that is, the amount and range of medicinally useful or active constituents present. The correct identification of a plant with reference to its accepted scientific name(s) is a

primary step in the quality assurance process, as a single common name may often refer to different plant species, with potentially dangerous consequences. Other factors influencing the quality of herbal medicines are:

- agriculture
- harvesting
- processing
- good manufacturing practice.

Chinese herbal medicines are usually used as a decoction of a mixture of herbal materials defined in a formula, which therefore contains hundreds of components. The clinical application of Chinese medicines is related to the multiple chemical components and not a single component. A pharmaceutical approach to testing for the content of a single component may therefore not reflect the quality, safety and efficacy of a herbal preparation. Methods of chromatographic fingerprinting, such as high-performance thin layer chromatography and high-performance liquid chromatography, are being developed to define the profiles and variations between herbal medicines.

Safety and regulation of traditional Chinese medicines

The issues associated with the safety and quality of Chinese herbal medicines include toxic herbs, contamination with heavy metals, microbial organisms, and other contaminants, and deliberate combination or adulteration with pharmaceutical drugs. Chinese herbal products in Australia are regulated by the Therapeutic Goods Administration (TGA) and need to meet quality and safety standards (see page 130).

The importation and dispensing of raw herbs are not effectively regulated or closely monitored by the TGA. At present, raw herbs can be imported and dispensed legally over the counter without registration with the TGA. These herbs may not meet the standards for herbal products.

Toxic herbs

Some herbs or minerals are known to be toxic and, when appropriate, need to be used with care under the supervision of highly qualified practitioners. Aconite poisonings have occurred repeatedly overseas and in Australia. Aconite (*Aconitum carmichaeli* Debx., *Aconitum kusnezoffii* Reichb.) contains aconitine, a cardiotoxin and neurotoxin causing arrhythmia and ventricular fibrillation. Thornapple (*Datura metel* L.) and black henbane (*Hyoscyamus niger* L.) contain hyoscyamine, an antimuscarinic alkaloid. Other toxic herbs requiring special regulation include nux vomica (*Strychnos nux-vomica* L.) which contains strychnine, Chinese arum (*Arisaema erubescens* (Wall.) Schott), and tri-leaved pinellia (*Pinellia ternata* (Thunb.) Breit).

Some species of plants with similar Chinese names differ in their indication and toxicity and cannot be used interchangeably. Guang fang ji (*Aristolochia fangchi*) and han fang ji (*Stephania tetrandra*) have similar names and clinical indications in traditional Chinese medicine, but *Aristolochia fangchi* contains the highly toxic aristolochic acids. *Aristolochia fangchi* has been found to cause renal failure and urothelial carcinoma. The nephropathy is characterised by extensive interstitial fibrosis leading to a severe atrophy of the proximal tubules.[4, 5]

Contamination or adulteration

Chinese herbal products have been found to contain heavy metals, such as mercury and arsenic, and non-prescription or even prescription drugs such as paracetamol, indomethacin, chlorpheniramine, aminopyrine, caffeine and hydrocortisone. The unapproved presence of these substances may have originated from mineral components, contamination or adulteration.[2] Currently quality monitoring relies on TGA post-marketing surveillance. Extra resources would be required to carry out routine surveys of the quality of Chinese herbal products in the Australian market to detect drug contamination or adulteration.

Drug-herb interactions

The combination of pharmaceutical drugs and Chinese herbal medicines is a common practice in China and must be considered when patients are using preparations obtained outside Australia. Similarly, patients in Australia may use Chinese medicines together with pharmaceutical drugs without informing their medical practitioners. The potential for drug-herb interactions remains to be investigated.

Regulation of herbal dispensers/pharmacists

Herbal medicines are usually dispensed by the practitioner who prescribes them, even though it is not accepted Australian practice for practitioners to have both prescribing and dispensing functions. It seems reasonable that dispensers should have sufficient training in the theory and properties of herbal medicines, equivalent to that found in pharmacy in Australia and traditional Chinese medicine pharmacy in China, in order for them to dispense herbal medicines safely according to best practice. This would require training in the pharmaceutical aspects of herbal medicines.

Recommendation

Best practice for Chinese medicines in Australia requires understanding both the traditional Chinese medicine system and modern orthodox medicine. There is a need to establish a quality testing system for raw herbs and their preparations and herbal products. This would detect any mislabelling or misidentification and the presence of undeclared components. Herbs with toxicities equivalent to prescription pharmaceutical drugs require a regulatory control system, such as a special schedule to enable registered practitioners to prescribe them under appropriate monitoring. Herbal dispensers should have an adequate qualification for dispensing, which includes knowledge of Chinese medicine and modern pharmaceuticals.

Medical practitioners and pharmacists should have sufficient knowledge of traditional Chinese medicine and herbal medicines to allow them to discuss issues and give advice to patients, and to identify and manage drug-herb interactions. Education programs such as short courses on modern Chinese medicine or exposure to the subject in the undergraduate curriculum may be of benefit to healthcare practitioners.

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Conflict of interest: none declared

Editorial note:

Traditional Chinese medicines account for only a small part of the use of complementary medicines in Australia. The problems of quality mentioned in this article are not confined to traditional Chinese medicines. This year's recall of complementary medicines made by Pan Pharmaceuticals shows that problems can arise even when products are manufactured in a modern factory.

Self-test questions

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

3. Traditional Chinese medicines may contain therapeutic and toxic components.
4. The method of preparation of a Chinese medicine may alter its pharmacological effects.

The quality and safety of traditional Chinese medicines

Comment by John McEwen and Fiona Cumming, Therapeutic Goods Administration

It may seem strange that the Therapeutic Goods Administration (TGA) regulates the safety and quality of Chinese **herbal products**, but does not scrutinise the **raw herbs** dispensed by Chinese medicine practitioners in Australia. The explanation lies in the extent of federal powers under the Australian Constitution. The *Therapeutic Goods Act 1989* relies on federal controls of importations, infectious diseases (quarantine), interstate trade and corporations (companies) to regulate the supply of medicines. This Act does not control the behaviour of individual practitioners – indeed those who are unincorporated and do not trade across state boundaries are outside the federal powers.

Chinese medicine herbal products on lawful sale in Australia must have an AUSTR or AUSTL number on the label. All Australian and overseas manufacturers of these products are required to authenticate their starting materials and testing of final products, and their performance is audited. This is a more efficient mechanism than a customs barrier scrutinising documentation for, and on occasions testing, every import of a raw herb or manufactured Chinese herbal medicine. It does mean, as the authors point out, that raw herbs can be imported and dispensed without any TGA control, but that situation is not absolute. A number of herbs with recognised toxicity are prohibited imports or are subject to State and Territory poisons controls, or both. These herbs should not be being dispensed by herbal practitioners.

Toxicity can occur through substitution of a toxic herb for a relatively non-toxic herb. There are 11 herbs which are vulnerable to substitution by the nephrotoxic, carcinogenic herb *Aristolochia*, because of confusion over their similar names and appearance. In the few instances where such substitution has occurred, in herbal products regulated as therapeutic goods, the TGA has required the affected products to be recalled. The TGA maintains a regular testing program for potential *Aristolochia* substitution, and has stringent pre-market regulatory controls in place to help ensure such substitution cannot occur. Although raw herbs are outside the TGA's powers, the TGA has worked with the Australian Customs Service and the States and Territories to put in place additional scrutiny of herbs which may be at risk of substitution with *Aristolochia*.

The possibility of deliberate adulteration is very real, as illustrated by the experience in Singapore and Malaysia in 1992, with a herbal product for weight loss. Slim 10 was manufactured in China and promoted heavily. Adverse reaction reports of serious illness and death led to the identification of not one, but two, adulterants – dried thyroid gland extract, presumably of animal origin, and a fenfluramine derivative. In recent years the TGA has not identified any instances of a conventional pharmaceutical being used to adulterate herbal products with AUSTR or AUSTL numbers. In contrast, there has been a small number of instances of clinically significant adulterants being found in herbal products unlawfully supplied in Australia or purchased overseas.

Even when not surreptitiously adulterated, there can be dangers.

On two occasions in the past four years, Chinese herbal products containing oxyphenisatin have been found in Australia. One of these products was labelled as containing diacetyldiphenolisatin – an alternative name. Oxyphenisatin has been included in an Australian list of substances 'of such danger to health as to warrant prohibition of sale, supply or use' because of its association with severe jaundice.[1]

The TGA Laboratories Branch is skilled in analysing products for adulterants and all practitioners are urged to report suspected instances using the ADRAC blue card or the TGA web site.

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RADAR – Rational Assessment of Drugs And Research

RADAR is a new service from the National Prescribing Service (NPS). It will provide general practitioners, pharmacists and other health professionals involved in primary care with information about new medicines and changes to the Pharmaceutical Benefits Scheme (PBS).

RADAR will also provide commentaries on important research that may influence patient management. It will interpret clinical evidence and suggest where a new medicine might fit within the therapeutic armamentarium.

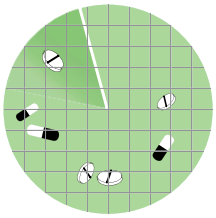
As RADAR will have access to information that has previously been unavailable, it will be able to provide the reasoning behind why a medicine has a particular PBS listing. If a medicine requires an authority prescription, RADAR will describe the reasons why this restriction is required.

The publication of RADAR will coincide with the quarterly publication of the Schedule of Pharmaceutical Benefits – the 'yellow book' – so it will be available at the same time as new drugs. The NPS is also investigating incorporating RADAR into prescribing and dispensing software so that, in the future, access will be even easier.

Register for the service at www.npsradar.org.au and the NPS will deliver each edition of RADAR directly to your computer.

Look out for RADAR in the upcoming months. NPS RADAR – keep track of what's out there.

Underneath the RADAR



The National Prescribing Service (NPS) produces RADAR (Rational Assessment of Drugs And Research) to inform people about changes to the Pharmaceutical Benefits Scheme. *Australian Prescriber* will be publishing some of the information underlying important changes, but a wider range of topics will appear in RADAR. The RADAR location is http://www.npsradar.org.au

On the RADAR: moxifloxacin

The quinolone antibiotic moxifloxacin has been listed on the Pharmaceutical Benefits Scheme (PBS), for the oral treatment of community-acquired pneumonia in adults and children over 12 years old who have immediate hypersensitivity to penicillin. An authority prescription will be required.

Underneath the RADAR

This new listing extends the number of patients who can be treated with moxifloxacin. The PBS already subsidises intravenous and oral moxifloxacin, but only for patients with severe community-acquired pneumonia who require admission to a high dependency unit or intensive care. The new listing means moxifloxacin can be prescribed in the community for patients who are hypersensitive to penicillin.

Comment

While moxifloxacin can now be used for less severe cases of pneumonia, it is not the drug of choice for most patients. The Therapeutic Guidelines: Antibiotic recommend that patients treated outside hospital should receive oral amoxycillin with either roxithromycin or doxycycline. In patients who are allergic to penicillin, but do not have immediate hypersensitivity, cefuroxime can be substituted for amoxycillin. Moxifloxacin is therefore reserved for patients with immediate hypersensitivity to penicillin.[1] These patients will have a history of anaphylaxis, urticaria, bronchospasm or angioedema developing within 60 minutes of taking penicillin.

While quinolone antibiotics are currently effective in community-acquired pneumonia, bacterial resistance can develop quickly. It is therefore essential that moxifloxacin is only prescribed in the community when other antibiotics are unsuitable. In addition to a clear history of immediate hypersensitivity to penicillin, radiological confirmation of the pneumonia will be required before the drug can be supplied by the PBS.

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DIAGNOSTIC TESTS

Oximetry

Iven H. Young, Clinical Associate Professor and Head, Department of Respiratory Medicine, Royal Prince Alfred Hospital, Sydney

SYNOPSIS

The oxygen stores of the body are small, so life-threatening hypoxaemia can develop very rapidly with few clinical signs. The availability of robust and reliable pulse oximeters has revolutionised the safe monitoring of patients with unstable cardiorespiratory conditions, and those having medical and surgical procedures. While oximetry is now best practice in these circumstances, care must be taken in interpreting the results. There are confounding factors that may produce an erroneous signal and physiological factors that will affect the interpretation of the result. In the absence of these factors, the instruments are accurate detectors of arterial oxygen saturation, in the range between 100% and 70% with varying but reasonable performance down to 55%. The basic principles of operation are important to understand so that physiological interpretation is adequate and erroneous results can be identified.

Index words: hypoxaemia, haemoglobin, oxygen.

(Aust Prescr 2003;26:132–5)

Introduction

Patients at risk of hypoxaemia may need continuous monitoring of their oxygenation. Blood gas analysis requires arterial puncture and only measures the oxygenation at the time of the sample. By measuring oxygen saturation (instead of partial pressure) pulse oximetry enables non-invasive monitoring. The continuous measurement of the pulse rate is a bonus.

The technology supporting clinical oximetry has been available for more than 80 years, but pulse oximeters have only been commercially available for about 20 years. Early oximeters required a cumbersome heated probe to 'arterialise' blood in the ear lobe. They were also difficult to calibrate and notoriously unstable. Nowadays relatively cheap and reliable oximeters have revolutionised the *in vivo* monitoring of patients' oxygenation during a wide range of critical clinical situations.[1]

Definitions

SaO_2	% of total haemoglobin combined with oxygen
SpO_2	Saturation as measured by pulse oximeter. This is a 'functional' saturation ignoring abnormal haemoglobin species such as carboxyhaemoglobin and methaemoglobin.
PaO_2	Partial pressure of oxygen in arterial blood (mmHg or kPa). The relation between SaO_2 and PaO_2 is shown in Fig. 2.
CaO_2	The content (in mL/100 mL blood or mol/L of blood) of oxygen in blood. The ordinate of Fig. 2 can be calibrated as content yielding the same shape curve.

Physiological principles

While oximeters may be used to assess the efficiency of pulmonary gas exchange, at least in relation to oxygen uptake, they are more suited to assessing the adequacy of tissue oxygen delivery. Measuring oxygen in the arterial blood is important because serious acute hypoxaemia is notoriously difficult to detect clinically and by the time clinical cyanosis develops, the patient is usually in a parlous state. The oxygen stores of the body are small so the viability of many tissues is critically dependent on continuous delivery of an adequate oxygen supply. Oxygen delivery is proportional to the blood flow and arterial oxygen content (CaO_2 [mL O_2 per 100 mL blood]). For the whole body:

oxygen delivery = cardiac output (Q) x CaO_2 x 10

These variables are difficult to measure directly and rapidly, however CaO_2 is linearly related, at least over relatively short periods of time, to the saturation of haemoglobin in arterial blood (SaO_2). As oximeters provide a rapid and reliable *in vivo* measure of SaO_2 this variable can be substituted for CaO_2. This has been a very valuable advance, as long as the principles and sources of error are understood.

Technical aspects

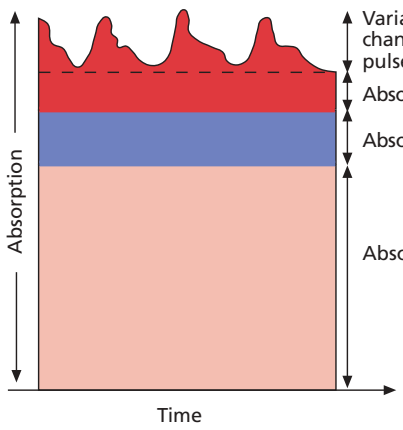
A pulse oximeter detects the change in transmission of two wavelengths of light across a capillary bed, usually in the finger. The sensor is placed on the nail with the light source against the finger pulp. The detectors can be small because they are only receiving two wavelengths, one to detect oxygenated haemoglobin (O_2Hb) and one to detect reduced haemoglobin (HHb). The absorption of light is related to the expansion of the capillary bed with the pulse (Fig.1). By comparing the light transmission through the pulsatile 'arterialised' capillary blood with the non-pulsatile venous blood the oximeter can calculate the haemoglobin saturation. Saturation is calculated as:

O_2Hb / [O_2Hb + HHb]

This is the so-called 'functional saturation', and is expressed as a percentage.[2]

Fig. 1

Absorption of light transmitted through the finger during pulse oximetry



It has been suggested that pulse oximeters should be called 'pulse spectrophotometers'. This would emphasise that they are inferring oxygen saturation from the well-known colour change between oxygenated and reduced haemoglobin and that, despite the elegant use of the pulse form to separate arterial blood from the other light absorbing structures in the finger, there are sources of error inherent in this technique which need to be appreciated.

While the vast majority of devices in clinical use measure transmitted light, newer devices are being designed to measure the light reflected off pulsating tissue surfaces. These devices are being used in perinatal monitoring and in patients whose peripheral perfusion may be compromised, as in open heart surgery. Reflectance devices are currently hampered by poor signal-to-noise ratio and the need to detect very small pulsatile signals, but advances in technology are likely to overcome these difficulties.

Sources of error

The results of pulse oximetry can be affected by technical problems and physiological factors.

Calibration problems

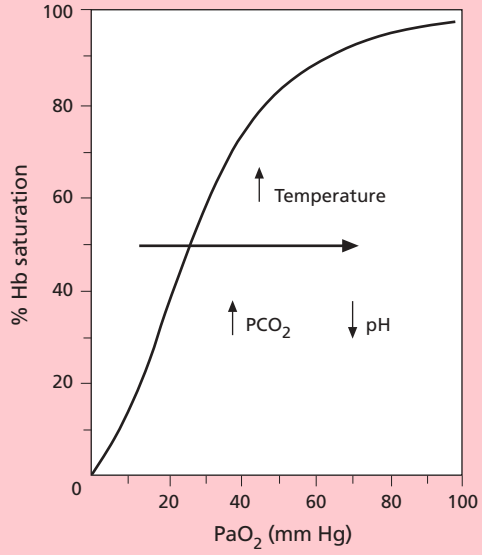
The machines do not need regular calibration by the operator and the probes and electronics are extraordinarily robust. The machine will not display a result and will warn if it cannot detect an adequate pulse signal. It is fitted with an alarm, which can be set at low (or high) saturation levels as desired. Original calibration by the manufacturer is based on the empirical relation between *in vivo* pulse oximetry (SpO_2) and the SaO_2 measured on simultaneously sampled arterial blood in a CO-oximeter.

CO-oximeters, so called because they measure carboxy- or CO haemoglobin, are now fitted to all modern blood gas analysers. They use multiple wavelengths of light to detect the four different forms of haemoglobin. The calibration process generally relies on data generated from healthy volunteers made hypoxaemic to generate SaO_2 values between 70% and 100%. When the SaO_2 is reduced to between 70% and 40% the pulse oximeters become significantly inaccurate, particularly below 55%, and fail to track rapidly developing profound hypoxaemia.[3] However, it can be argued that the accurate detection of falls between 85% and 70% is of most use in clinical monitoring.

Fig. 2

Oxyhaemoglobin dissociation curve

The relation between oxyhaemoglobin saturation and partial pressure of oxygen in blood can be changed by factors such as temperature and acid-base balance. An increased partial pressure of carbon dioxide (PCO_2), increased temperature or reduced pH move the oxyhaemoglobin dissociation curve to the right. The ordinate can be calibrated as oxygen content (CaO_2), yielding the same shape curve.



Physiological factors (Table 1)

The presence of abnormal haemoglobins disturbs the relation between SaO_2 and CaO_2. 'Functional saturation' ignores the possible presence of methaemoglobin, carboxyhaemoglobin and other abnormalities of haemoglobin. These abnormal forms will not carry oxygen normally and will add to the denominator of the O_2Hb / [O_2Hb + HHb] ratio. Usually abnormal haemoglobins only comprise a few percent of the total, even in heavy smokers who have increased concentrations of carboxyhaemoglobin. However, common drugs such as paracetamol and sulfa drugs can induce the formation of methaemoglobin. Anaemia will also reduce the oxygen content without changing the calculated functional saturation.

There will be difficulties relating the SpO_2 to PaO_2 if the position of the oxyhaemoglobin dissociation curve has been shifted by influences such as acid-base balance and carbon dioxide tension. If the SpO_2 is above 92% the partial pressure of oxygen (PaO_2) can change rapidly with very little change in saturation (Fig. 2). This latter physiological feature limits the

Table 1

Physiological factors which affect interpretation of a saturation measurement (when assessing oxygen content or partial pressure)

- Saturation above 92%
- Dyshaemoglobinaemia, commonly presence of methaemoglobin and/or carboxyhaemoglobin
- Anaemia
- Shift of the oxyhaemoglobin dissociation curve (e.g. acidosis, alkalosis, hyper- or hypocapnia)

usefulness of pulse oximetry in, for example, the assessment of pulmonary gas exchange efficiency and the detection of hyperoxia in preterm babies. Measurement of the partial pressure of arterial oxygen (PaO_2) from *in vitro* samples or transcutaneous electrodes may be preferable for monitoring hyperoxia in the 'flat' part of the dissociation curve.

Pulse oximetry has also been an enormous boon in intensive care units. However, measurements can be difficult to obtain in low perfusion states or where inotropes such as dopamine are being used to sustain blood pressure.

Confounding factors (Table 2)

Abnormal haemoglobins and anaemia are 'physiological' confounders but these abnormalities can also affect the accuracy of the measurements. In animal experiments, SpO_2 decreases as methaemoglobin increases up to 35%, and SpO_2 increases as carboxyhaemoglobin increases up to 70%. Modest concentrations of these haemoglobins will not substantially change SpO_2 which is a functional saturation. Anaemia has to be severe (50 g/L) before it interferes significantly with the measurement.

Abnormal dyes and pigments such as methylene blue (used to treat methaemoglobinaemia) and severe hyperbilirubinaemia may interfere. In most clinical circumstances, these disturbances will not be present to a significant degree, but they need to be kept in mind. Strong superficial pigments such as nail polish must be removed and signal failure may occur in black patients although careful positioning on the less pigmented nail bed usually overcomes this problem. Venous pulsation may confuse the signal, reducing the displayed saturation, particularly where a tourniquet is applied above the probe or in the presence of right heart failure or tricuspid incompetence. Excessive motion of the probe and strong incident light can also cause an erroneous or inadequate signal. Motion artifact is also a problem in many longer-term settings where movements can be interpreted as a pulse.

Table 2

Confounding factors causing an inaccurate or unobtainable SpO_2 measurement *in excess* of any physiological effect

- Methaemoglobin and carboxyhaemoglobin
- Anaemia
- Dyes and pigments
- Low perfusion
- Venous pulsations
- Motion artifact
- Excessive incident light

The pulse oximeter does not measure partial pressure of oxygen in arterial blood (usually expressed as mmHg) and the relationship between SpO_2 and PaO_2 is complex.

Clinical applications

Reliable pulse oximeters are now indispensable in all emergency departments, intensive care units (adult and neonatal) and operating theatres. Their use is considered to be good practice for procedures requiring sedation or instrumentation of the respiratory tract ranging from cardiac catheterisation to endoscopy and bronchoscopy. Their use in these procedures has uncovered quite alarming transient hypoxaemia requiring the use of supplemental oxygen. It is desirable to maintain the SpO_2 above 90%.[4]

The routine use of pulse oximeters in operating theatres and recovery rooms has coincided with a dramatic decrease in perioperative morbidity and mortality although, interestingly, a cause and effect relation has not been confirmed.[5] Clearly, disastrous errors such as incorrect connections in anaesthetic machines can be quickly recognised.

Patients presenting to emergency departments with cardiorespiratory disorders are routinely monitored with pulse oximetry. However, it is important to identify when the additional information available from *in vitro* analysis of an arterial blood gas sample is critical for management. Patients with worsening asthma, deteriorating pneumonia or left heart failure and those with chronic obstructive pulmonary disease developing clouded consciousness on supplemental oxygen all need arterial carbon dioxide partial pressure ($PaCO_2$), pH and base excess measurements (Fig. 2).

Pulse oximeters in sleep investigation laboratories have substantially contributed to the explosion of knowledge about sleep and breathing over the last few decades. They are also extensively used during exercise testing in pulmonary function and cardiac stress test units. Here, small falls in PaO_2 in the higher range will be difficult to detect, but hazardous falls will be readily identified.

Finally, pulse oximeters have a place in the non-procedural doctor's office where the detection of acute or chronic hypoxaemia may be important – as in the assessment of patients requiring home oxygen therapy. An SpO_2 above 90% in a patient with chronic obstructive pulmonary disease is reassuring whereas a lower measurement would suggest the need for confirmatory measurement of arterial blood gases. Experience with these devices, and their widespread adoption, have emphasised their status as a truly important advance in non-invasive patient monitoring and investigation.

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Conflict of interest: none declared

Self-test questions

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

5. Carboxyhaemoglobin causes pulse oximeters to show an increase in oxygen saturation.
6. Nail polish should be removed from a patient's finger before a pulse oximeter is attached.

Book review

Therapeutic Guidelines: Antibiotic. Version 12.

Melbourne: Therapeutic Guidelines Limited; 2003.

407 pages. Price $33, students $25.30, plus postage.

David Brookman, Discipline of General Practice, University of Newcastle, NSW

How can one review a book which has become such a common sight in general practitioners' surgeries, hospitals, and everywhere prescriptions are written, and which was the first in a wave of therapeutic guidelines in Australia?

This book has been used for the selection of antibiotics in several circumstances:

- where the practitioner has a limited knowledge of the infection they are treating
- where the comorbidity of the patient makes antibiotic selection more complex
- where there is unknown life-threatening sepsis
- where there have been previous adverse reactions to antibiotics which are the first or second choice
- in different physiological states – pregnancy, renal impairment, childhood.

The main section of the book is a set of headings of infections and infestations of all body systems with recommended first- and second-line therapy. For practitioners seeking third-line medications for a likely or known organism where there is a history of adverse reaction to the first- or second-line drugs, it is necessary to consult Table 49 which gives the likely antibiotic resistance for most organisms.

The appendices of this book are most useful. In Appendix 1 the adverse drug reactions are subclassified by their frequency which is actually given numerical status in the introduction.

Appendix 3 is a set of desensitisation protocols for antimicrobial therapy. This is extremely useful for remote and rural practice where alternative medications may not be available for several days, and in circumstances where life-threatening infections require an antibiotic to which the patient is sensitised. Appendix 10 provides a reproduction of the CARPA antibiotic guidelines which are well used by nurses and general practitioners in remote areas.

The guidelines on intravenous antimicrobial use in Appendix 6 could be an Australia-wide standard for hospitals, and home intravenous antibiotic therapy. Appendix 7 contains a guide on monitoring of blood levels with due emphasis on aminoglycosides. Appendix 8 provides a useful guide on paediatric dosing, while Appendix 9 deals with dosing during lactation and pregnancy and Appendix 11 advises on dosing in renal impairment with and without dialysis.

I have a dislike of guidelines that do not quote supporting evidence to help practitioners judge the reliability of the recommendations. To add references would swell the volume beyond pocket size, but without them the guidelines could appear to be based only on expert opinion. The detail of these guidelines also demands a more useful retrieval system than flicking through a book. Although an electronic version is available for use on a personal computer, more portability would be useful.*

Overall, this is an excellent little book. It should be owned by all prescribers in book or electronic form for quick reference.

* *Editor's note:* The supporting references are available in the electronic version of the guidelines (eTG Complete) and a palmtop format is being considered.

Good nutrition for good surgery: clinical and quality of life outcomes

Lynne Daniels, Associate Professor, Department of Nutrition and Dietetics, School of Medicine, Flinders University, Adelaide

SYNOPSIS

Undernutrition is common in patients admitted for surgery and is often unrecognised, untreated and worsens in hospital. The complex synergistic relationship between nutritional status and the physiological responses to surgery puts patients at high nutritional risk. There are clear prospective associations between inadequate nutritional status and the risk of poorer outcomes for surgical patients, including infection, complications and length of stay. However, practically and ethically evidence that nutritional interventions can significantly reduce these poor outcomes is difficult to obtain. Nevertheless health professionals have a duty of care to ensure our patients are properly fed, by whatever means, to meet their physiological requirements.

Index words: food, undernutrition.

(Aust Prescr 2003;26:136–40)

Introduction

Well-nourished patients respond to, and recover from illness and surgery better than undernourished patients. While overnutrition is widely thought to be the primary nutritional problem in Australia, undernutrition and/or malnutrition are prevalent in population sub-groups. Studies consistently show that 30–40% of patients show evidence of poor nutrition on admission to hospital and that both normal and sub-optimal nutritional status deteriorate in hospital.[1] The physiological and psychosocial stresses of surgery increase the risk of poor nutritional status, which is clearly linked to poorer outcomes.[2,3] Poor nutrition therefore has clinical, financial and quality of life consequences.[3]

Definitions of malnutrition and undernutrition

Adequate nutritional status is more than the absence of nutrient deficiency disease. It is a broad concept which infers that an individual can achieve a food intake sufficient to meet their requirements for specific nutrients to support optimal health and well-being.

There is no universally accepted definition of malnutrition. The term is widely associated with severe food deprivation and the classic consequences of kwashiorkor, marasmus or micronutrient deficiency. Malnutrition may refer to overnutrition, but more commonly is used interchangeably with undernutrition.

Undernutrition refers to a continuum of inadequate nutritional status. It extends from inadequate intake and increased risk of poorer health outcomes, through to measurable functional or clinical changes that influence outcomes and are potentially reversed by nutritional interventions, and finally to clear physical and biochemical evidence of protein, energy or micronutrient deficiency.

Nutritional screening and assessment – how to recognise undernutrition

There is no 'gold standard' for identifying either nutritional risk or nutritional status. Nutrition screening aims to identify factors associated with poor nutrition and hence individuals at nutritional risk. It needs to be valid, simple, easy to interpret and sensitive so that it can be widely and consistently implemented by non-specialists. A range of screening tools have been developed and variably validated.[4] They include self-reported indicators of either risk or direct evidence of poor or reduced intake (Table 1).

If screening identifies individuals at risk, they should be referred for detailed assessment of their nutrition. Nutritional assessment is a comprehensive process used to define the patient's nutritional status rather than risk. It helps to quantify the risk of complications and can be used to plan and monitor nutritional support[4] (Table 1).

Limitations of screening and assessment include reliance on self-reported data, inaccurate measurement of stature in injured or elderly patients and confounding of serum protein concentrations by infection and trauma. Nevertheless, the risk factors in Table 1 should be routinely considered in assessment and follow-up of pre- and postoperative patients. The general consensus is that unintentional weight loss, regardless of initial weight, is the simplest and most reliable way to identify nutritional risk[2,4] (see Box 1).

Box 1

Key indicators of undernutrition

Unintentional weight loss

- 5% body weight in one month
- > 10% body weight in six months

Underweight

- < 80% ideal body weight
- body mass index < 18
- mid-arm muscle circumference < 15th percentile

Table 1

Nutrition screening and assessment – commonly used indicators [4,12,13]

Nutritional screening identifies patients 'at risk'

Subjective/self-reported

- difficulty with access to food:
  money, shopping, cooking facilities, preparation, feeding, mobility, activities of daily living
- social isolation, depression, anxiety
- < two meals per day
- excess alcohol use
- poor/decreased appetite
- nausea, chronic pain
- gastrointestinal symptoms > two weeks
- vomiting, diarrhoea
- indicators of protein intake
  (< three serves/day of dairy, meat, fish, eggs)
- < two serves of fruit and vegetables/day
- unintentional weight loss
- fluid intake

Objective

- comorbidities, disease state, duration/severity of symptoms
- poor dentition, oral health
- polypharmacy (> three drugs/day)
- dysphagia, respiratory disease
- prescribed dietary restrictions
- unintentional weight loss
  10% in six months **or** > 5% in one month
- current weight, body mass index
- triceps skinfold (TSF), mid-arm circumference (MAC)
- mid-arm muscle circumference
  (MAMC cm) = MAC (cm) – TSF (mm) x 0.314
- ascites, fluid retention
- pressure sores, skin ulcers
- serum albumin < 35 g/L

Nutritional assessment assesses the nutritional status of patients identified as 'at risk'

- physical examination
- history – medical, social, nutritional
- current dietary intake
- anthropometric measures – weight, height (stature), TSF, MAC, MAMC
- estimates body composition
- functional status – grip strength
- laboratory data – serum albumin, transferrin, delayed hypersensitivity skin testing, lymphocyte count

Special attention should be paid to those patients whose disease status and symptoms incur particular risk of either compromised intake and/or increased requirements. Self-reported weight and height are unreliable so regular monitoring and documentation of weight becomes critical. Use of triceps skinfold (TSF) and mid-arm muscle circumference (MAMC) should be considered in patients with ascites or fluid retention (Table 1).

Reliable and valid measurements of triceps skinfold and mid-arm circumference are relatively difficult and training is needed. Reference percentile data are available[5,6] but care should be taken to ensure the reference group is relevant to the individual patient.

Prevalence of undernutrition in hospital patients

Self-reported unintentional weight loss, being underweight on admission, and a decline in nutritional status during admission, have all been associated with poor outcomes.[3] A 1994 study reported that 40% of 500 patients sequentially admitted across five sub-specialities (including general and orthopaedic surgery) were at least mildly undernourished (body mass index < 20, TSF or MAMC < 15th percentile).[1] Notably, only 34% of the patients were overweight. Nutritional information was documented for only 48% of the undernourished patients. Of the 112 patients in hospital for approximately seven days, 64% had lost 5–10% of their body weight when they were discharged. At discharge, 75% of the patients who were undernourished on admission had lost weight and only 13% had gained weight. There are a range of structural and practical issues that contribute to the exacerbation or development of undernutrition in hospitals (see Box 2).

There have been few prospective studies of the prevalence and outcomes of documented weight loss before admission. A study of 221 surgical patients showed objective weight loss during the month before admission in 26% (mean loss 6%) with 10% losing more than 5% of their weight (mean loss 10%), which was associated with increased length of hospital stay.[4]

The role of the general practitioner

The prevalence of undernutrition on admission means that this problem and the attendant implications for health and well-being must exist in the community. If general practitioners are alert to the possibility they may be able to prevent or ameliorate undernutrition before admission or at least warn the hospital that the patient may be undernourished.[7]

Pre- and post-surgery it is necessary that general practitioners closely monitor weight and the self-reported screening indicators outlined in Table 1. Where appropriate it is important to encourage and highlight the need for a high-energy intake. It may be helpful to recommend use of oral nutritional supplements, although these are expensive and compliance is

Box 2

Issues contributing to the exacerbation or development of undernutrition in hospitals

- limited awareness, knowledge and training of staff at all levels
- the perception that the provision of food and nutrition is of low priority and more aligned with patient services rather than medical care
- resource-strapped food services that cannot respond to patient preferences for type of food and timing of meals and snacks
- lack of capacity (food and staff) at ward level to provide nutritious snacks and drinks when patients feel hungry
- limited support at ward level for patients who need help with opening packages and containers, feeding and/or encouragement and the important social aspects of eating
- removal of trays before patients are finished
- repeated fasting and missed meals associated with procedures
- confusion over which staff are responsible for patient feeding at ward level

often poor. Referral to a dietitian for ongoing monitoring and management should be considered for patients at particular risk (e.g. dysphagia, gastrointestinal problems) and those who are substantially underweight or consistently losing weight.

The impact of surgery on nutritional status

The complex response to the physiological stress of surgery and injury, mediated via hormonal changes and the sympathetic nervous system, is one of hypermetabolism and catabolism.[2] There is marked salt and water retention and increases in basal metabolic rate and hepatic glucose production. Wound healing accounts for 80% of the increased glucose production and also requires protein synthesis.[2] Fat (adipose tissue) and protein stores (lean muscle mass) are mobilised to meet the needs of glucose and protein synthesis which results in negative nitrogen balance and weight loss. Overall, the catabolic response increases energy and protein requirements, the magnitude and duration depending on the extent of the surgery.[2] A critical point is that semi-starvation (that is, intake consistently below potentially increased requirements) is also catabolic and further exacerbates negative nitrogen balance and weight loss. Indeed, recent evidence suggests the catabolic response to surgery may not be obligatory and can be prevented by adequate intake.[2,3]

Adequate energy and protein intakes are essential to limit net protein and fat losses. However, many patients are unable to eat enough to meet increased needs and/or prevent losses after surgery. Common and often underrated issues such as pain, nausea, medication, dry mouth, gastric discomfort and distension, fasting, unpleasant procedures, anxiety, unfamiliar food and hospital routines all potentially reduce appetite and intake. Inadequately or unfed patients will rapidly deplete their reserves of protein and fat. This has significant clinical consequences, particularly for those with preoperative undernutrition.

The impact of nutritional status on outcomes of surgery

Positive outcomes for surgery depend heavily on adequate immune defence and wound healing. Both rely on enhanced synthesis of new proteins, which is significantly limited by negative nitrogen and energy balance. A key point is that positive nitrogen balance (net protein synthesis) cannot be achieved with negative energy balance. Semi-starvation will result within days rather than weeks, when intake fails to meet requirements, particularly for protein and energy.

The consequences of significant semi-starvation in healthy persons are summarised in Table 2. These problems are also common after surgery, so it is likely that the undernutrition associated with the surgery is contributing to poor outcomes for surgical patients (Table 2).

Table 2

Outcomes associated with semi-starvation and undernutrition in healthy people and surgical patients

Semi-starvation – healthy people and surgical patients [8]	*Undernutrition – surgical* [2,3,4,10,11]
• weight loss	• ↑ postoperative infection
• anxiety, irritability	• impaired wound healing
• depression	• ↓ quality of life
• apathy, malaise	• ↓ gut function
• ↓ organ function – gut, respiratory, cardiac	• ↓ respiratory and cardiovascular function
• ↓ thermoregulatory function	• ↑ complications (pneumonia)
• impaired immunity	• ↑ length of convalescence
• ↓ resistance to infection	• ↑ length of stay
• poor wound healing	• ↑ readmission
• ↓ intellectual function	• ↓ return to own home
• ↓ concentration	• ↑ mortality
• ↓ work capacity	• ↑ costs
• ↓ growth	

Estimation of energy and protein requirements

Nutritional interventions can only be effective if energy requirements are both accurately estimated and then achieved. The standard approach is to estimate energy requirements from basal energy expenditure, using regression equations and activity and stress factors (see e-table 3*). Energy requirements range from 85–150 kJ/kg. Protein requirements are usually set at 7–8% of energy needs, although severely ill or injured patients may require 15–20% of their energy as protein. This is approximately 1.5–2.0 g of protein/kg of body weight.[2] Further research is required to characterise specific amino acid and micronutrient requirements in surgical patients.[3]

Ongoing monitoring is needed to evaluate the accuracy of the patient's estimated requirements. This also ensures that the patient is receiving the prescribed level of nutrition support to meet these requirements.

Nutrition interventions – options and outcomes

The indications, options and limitations of nutritional support are summarised in e-table 4*. The golden rule is 'if the gut works, use it'. There is little evidence that parenteral is more effective than enteral nutrition, but it is certainly costlier and associated with higher risks of serious complications, particularly infection.[3,8] There is evidence that early (within 24 hours) enteral feeding has significant benefits over late enteral and parenteral feeding.[2,3] Prolonged absence of nutrients from the gut alters gut flora and may compromise amino acid metabolism. It also changes and reduces mucosal structure and function.[2]

The golden rule is 'If the gut works, use it'

There is a wide range of proprietary oral and enteral polymeric (intact macronutrients) feeding products that are isotonic and nutritionally balanced. If energy intake is adequate, these products will meet the requirements for macro- and micronutrients. They are lactose free and usually provide 1.0 Cal/mL (4.2 kJ/mL). There are also more nutrient dense, higher osmolality formulae (1.5 and 2.0 Cal/mL).

Overall, there are few differences between the formulae that result in demonstrable clinical advantage although there is some variation in the quantity and type of fibre and fatty acids. The hyperosmolar, hydrolysed, elemental feeds are intended for patients with impaired digestion and there are condition specific feeds, for example for liver or renal failure, critical care, or pulmonary disease. These formulae are expensive and there is insufficient independent evidence of clinical advantage.[9]

Routes of feeding should be considered as complementary not competitive. The central issue is that nutrient requirements are met and withdrawal of enteral or parenteral support should be gradual in response to clear evidence that the individual is able to consistently meet the deficit in energy intake by the oral route. Commonly, tubes and lines are removed after a day or two of very limited oral intake in the belief (or hope) that the patient has started eating. In reality, it may take days or weeks for oral intake to fully meet requirements and meanwhile the advantages of the early nutritional support are eroded.

Two recent studies[10,11] present evidence for the effectiveness of oral supplements in surgical patients. Patients with only marginal undernutrition and not needing enteral or parenteral nutrition were randomised post-gastrointestinal surgery to oral supplements (n = 43) or usual ward diet (n = 43). These supplements contained 6.3 kJ/mL and 0.05 or 0.06 g protein/mL. The treatment group lost less weight (2.2 versus 4.2 kg ($p < 0.001$)), had fewer complications (n = 4 versus 12, $p < 0.05$) and felt less fatigued.[10] A 10-week study[11] showed that malnourished postoperative patients who received oral supplements (n = 52) lost less weight and showed improved quality of life and lower antibiotic use than controls (n = 49) randomised to receive a normal diet.

Limitations of the evidence and ethical considerations

There is good evidence that undernutrition, particularly in surgical patients, is prospectively associated with increased risk of poor outcomes.[2,3,8,10,11] However, there is not a clear cause and effect relationship and it is very difficult to isolate the confounding effect of the disease process. There is a paucity of 'gold standard' evidence that nutrition support will reverse poor outcomes. Well-designed prospective randomised controlled trials are rare and exceedingly difficult to implement (see e-table 5*). A key issue is that in many studies too little nutrition support is given for too short a time and potential effects may be diluted. Absence of quality evidence is not the same as evidence of absence of effect.

Conclusion

The clinical and financial outcomes of undernutrition are frequently unrecognised, underrated and unacknowledged in surgical and other groups of hospital patients. Much undernutrition remains undiagnosed and untreated, despite the existence of tools to identify the problem and availability of nutritional support. Factors contributing to undernutrition in hospital patients include lack of awareness, inadequate nutrition knowledge and training of staff, limited availability of multidisciplinary specialist clinical nutrition teams and services, and lack of policies, procedures, guidelines and standards of care.[9] Large, well-designed studies are required to find out if nutritional interventions are independently effective, but given the ethical and practical problems, these studies may not be carried out. However, we have a duty of care to ensure our patients are properly fed, by whatever means, to meet their physiological requirements. Hospitals should review their systems to assess patients' nutritional needs and ensure these are met.

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* The e-tables are available in the internet version of this article at www.australianprescriber.com

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Conflict of interest: none declared

Self-test questions

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

7. Postoperative patients' basal energy requirements reduce while they are immobile in bed.
8. Poor dentition is a risk factor for undernutrition.

Top 10 drugs

These tables show the top 10 subsidised drugs in 2002–03. The tables do not include private prescriptions.

Table 1

Top 10 drugs by defined daily dose/thousand population/day *

Drug	*PBS/RPBS* †
1. atorvastatin	66.021
2. simvastatin	43.469
3. diltiazem hydrochloride	41.072
4. ramipril	26.292
5. omeprazole	22.6
6. rofecoxib	20.614
7. salbutamol	20.433
8. frusemide	19.44
9. irbesartan	18.067
10. irbesartan with hydrochlorothiazide	17.628

Table 2

Top 10 drugs by prescription counts

Drug	*PBS/RPBS* †
1. atorvastatin	6,201,212
2. simvastatin	5,459,490
3. omeprazole	4,663,100
4. paracetamol	4,635,415
5. celecoxib	3,533,718
6. salbutamol	3,316,135
7. irbesartan	3,073,008
8. atenolol	2,968,624
9. rofecoxib	2,928,032
10. codeine with paracetamol	2,717,636

Table 3

Top 10 drugs by cost to government

Drug	*PBS/RPBS* † *DDD/1000/day*	*PBS/RPBS scripts*	*Cost to government ($A)*
1. atorvastatin	66.021	6,201,212	335,848,732
2. simvastatin	43.469	5,459,490	319,422,899
3. omeprazole	22.6	4,663,100	206,516,360
4. salmeterol and fluticasone	–	2,490,246	154,529,922
5. olanzapine	2.835	689,321	144,494,201
6. pravastatin	12.587	1,955,495	113,036,241
7. clopidogrel	4.883	1,218,762	96,996,332
8. celecoxib	15.756	3,533,718	94,697,313
9. rofecoxib	20.614	2,928,032	90,538,887
10. pantoprazole	8.809	2,008,266	85,609,475

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people, in every thousand Australians, are taking the standard dose of a drug every day.

† PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

Source: Drug Utilisation Sub-Committee (DUSC): Drug Utilisation Database © Commonwealth of Australia

EXPERIMENTAL AND CLINICAL PHARMACOLOGY

Antineoplastic antibodies – clinical applications

Robyn Ward, Associate Professor, Department of Medical Oncology, St Vincent's Hospital, Sydney

SYNOPSIS

Trastuzumab and rituximab are genetically engineered antibodies which are now available for the treatment of metastatic breast cancer and non-Hodgkin's lymphoma respectively. The adverse effects of these drugs are mild compared with conventional chemotherapy, but they require intravenous infusion in a supervised setting. Trastuzumab and rituximab are most effective when given with chemotherapy rather than as a substitute for standard therapies. Such combination therapy offers incremental but significant clinical improvements. The challenge remains to identify optimal antibody dosing schedules and the cancer subtypes which best respond to these treatments.

Key words: trastuzumab, rituximab, breast cancer, lymphoma.

(Aust Prescr 2003;26:141–3)

Introduction

The first monoclonal antibodies were generated, using hybridoma technology, almost three decades ago. The hope was that these 'magic bullets' would target cancer cells without damaging normal cells thus offering a clear advantage over conventional cancer treatments. Major trials using genetically engineered antibodies to treat non-Hodgkin's lymphoma and breast cancer have now been completed and it appears that the clinical utility of some antibodies has at last been realised. The results from these trials have changed old notions of the ideal therapeutic antibody. They show that monoclonal antibodies are most effective when used in combination with, rather than instead of, chemotherapy.

Mechanism of action of therapeutic anticancer antibodies

Antibodies are large molecules (150 KiloDaltons). They consist of a variable region, which binds specifically to a target antigen, and a constant region, which mediates a variety of effector functions such as cell-mediated killing and complement activation.

In their native form, unconjugated antibodies have a wide range of antitumour activities. Antibodies can directly influence tumour cell growth by blocking a growth factor receptor or they can cross link cell membrane antigens to deliver signals that control the cell cycle or even induce cell death. Alternatively, they can influence tumour growth indirectly by activating host immune effector functions such as antibody-dependent and complement-mediated cell cytotoxicity. Given the diversity of actions of unconjugated antibodies, it is often impossible to identify those specific actions which are operative in a given individual.

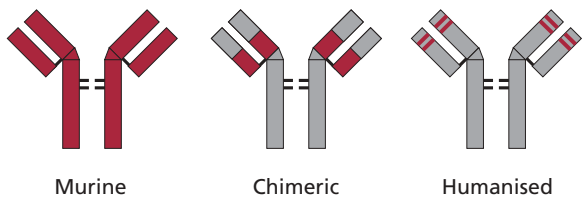
Antibodies raised in mice (murine) have significant disadvantages as therapeutic agents. They are immunogenic, a feature which limits their repeated administration, and they have poor cytotoxicity as their constant region does not interact with human effector cells.

Molecular techniques now make it possible to transform murine antibodies into human antibodies. A chimeric antibody is generated by substituting a human constant region (usually IgG1) for the murine constant region so that the new antibody is 60% human and 40% murine (Fig. 1). A further step on from a chimeric antibody is a humanised antibody (95% human and 5% murine). In this process the structural amino acids in the variable region as well as in the constant region are replaced by human sequences (Fig. 1). Only a small number of amino acids directly responsible for binding to the antigen are retained from the mouse antibody.

Coupling antibodies to cytotoxic agents such as drugs, toxins and radionuclides potentially links the unique specificity of antibodies with powerful tumouricidal activity. Despite the theoretical advantage of such an approach, there are as yet few practical examples of its implementation. One notable success is the use of a humanised anti-CD33 antibody (gemtuzumab) covalently linked to a derivative of a cytotoxic antibiotic, calicheamicin. This drug, called gemtuzumab ozogamicin, has shown activity in elderly patients with acute myeloid leukaemia who are unsuitable for conventional chemotherapy.

Fig. 1

The structure of a chimeric and humanised antibody compared with its mouse counterpart. The red indicates mouse, the grey represents human protein.



Trastuzumab – breast cancer

Trastuzumab is a humanised antibody which targets the HER2/*neu* receptor, a cell surface protein which is overexpressed in a proportion of breast cancers. Original reports suggested that HER2 was overexpressed in 20–30% of breast cancers and therefore a significant number of women would potentially benefit from trastuzumab. Unfortunately this figure was an overestimate; overexpression is probably closer to 10%.

Suitability for trastuzumab therapy is predicated on the accurate identification of HER2 overexpression. This presents a significant challenge as it requires specialised and expensive techniques such as immunostaining and fluorescent *in situ* hybridisation (FISH) analysis. Neither of these tests is perfect.

Trastuzumab is currently available in Australia for the treatment of HER2 positive tumours under two circumstances:

- monotherapy in women who have received one or more chemotherapeutic regimens for metastatic disease
- in combination with taxanes (such as paclitaxel) in women who have not previously received chemotherapy for metastatic disease.

Monotherapy

Approximately 15% of women with HER2 positive tumours have an objective response to weekly intravenous monotherapy.[1] This response rate is comparable to that seen with chemotherapy drugs such as paclitaxel (25%), docetaxel (35%), vinorelbine (22%), 5-fluorouracil (25%) and capecitabine (20%). While the incidence of serious toxicity is probably lower with trastuzumab, it is difficult to draw meaningful conclusions about the relative merits of each drug as they have not been directly compared in a single study. With regard to costs it is clear that drugs such as trastuzumab, paclitaxel and docetaxel are many times more expensive than capecitabine and 5-fluorouracil.

Combination therapy

As predicted by *in vitro* studies, there is considerable synergy between trastuzumab and chemotherapy. As first-line treatment for metastatic disease, the addition of trastuzumab to paclitaxel increases the response rate (complete and partial) from 17% to 41%, the median time to disease progression from 3.0 months to 6.9 months and the median survival from 20.3 to 25.1 months.[2] The precise impact of trastuzumab on overall survival may have been underestimated. A number of factors confound this analysis, for example, patients who were randomised to chemotherapy were permitted to receive trastuzumab subsequently once their cancer progressed.

Importantly, the clinical advantages of trastuzumab were obtained without additional negative effects on quality of life. Most treatment adverse effects were attributable to the chemotherapy. However, trastuzumab cannot be safely used with all chemotherapy. There was an unexpectedly high incidence of cardiac dysfunction (27% of patients) when the drug was combined with anthracyclines.

On balance, it is reasonable to conclude that the combination of trastuzumab and chemotherapy results in a modest improvement in response rates and probably overall survival in a very select group of women. As yet unresolved issues include the necessity for weekly antibody infusions, the best means of identifying women whose tumour growth is dependent upon HER2 overexpression, and the true value of trastuzumab in the adjuvant setting.

Rituximab – lymphoma

Rituximab was the first antibody to be approved by the US Food and Drug Administration for the treatment of malignancy. It is a chimeric antibody which binds strongly to the CD20 antigen found on normal mature B cells as well as on tumour cells in nearly all B cell non-Hodgkin's lymphomas.

Monotherapy

Low-grade lymphoma is a chronic illness usually requiring intermittent, but long-term, treatment to control disease symptoms. The listing of rituximab on the Pharmaceutical Benefits Scheme has expanded the range of therapeutic options for patients with low-grade lymphoma whose disease is not responsive to alkylating agents. The evidence supporting the use of rituximab was provided by an open label single arm phase III study. In the 151 evaluable patients who had previously received chemotherapy nine had complete responses and 67 had partial responses.[3]

Treatment with rituximab involves four infusions given at weekly intervals. A number of patients have received further courses of therapy with good effect.

Most patients experience fever, chills and rigors within two hours of commencing the first infusion. The incidence of infusion-related symptoms decreases to 40% with subsequent infusions. Approximately 10% of patients develop serious symptoms including immediate hypotension, bronchospasm and rarely a late onset cytokine release syndrome characterised by severe dyspnoea and hypoxia up to two days after the infusion. Rituximab binds to normal B cells which are the precursors of the immunoglobulin producing plasma cells. Serum immunoglobulin levels can fall after treatment, however this is not usually clinically significant.

In terms of relative therapeutic effect rituximab appears to offer comparable efficacy, but with less toxicity than intensive combination chemotherapy or drugs such as fludarabine. The optimal schedule of administration remains a key unresolved issue. Rituximab is detectable for three to six months following a single course of therapy so it is possible that infrequent single doses may provide maximum therapeutic effectiveness.

Combination therapy

About 30% of patients with non-Hodgkin's lymphoma have diffuse large B cell lymphoma, and more than half of these patients are over 60 years old. For about 25 years the standard treatment for this form of lymphoma has been a regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) given every three weeks for six months. Over the years more complicated combinations have been tried, but none have improved on the 30–40% cure rate observed with CHOP. The results of combination therapy with rituximab and CHOP have therefore sparked considerable interest.

The addition of rituximab to CHOP significantly improved the complete remission rate (75% versus 63%) and overall survival at two years (70.2% versus 57.3%) in patients aged between 60 and 80 years.[4] Importantly, these gains were made without apparent increase in overall toxicity.

The apparent success with combination therapy cannot yet be applied to all patients with lymphoma. Lymphoma is a heterogenous disease and the responses to treatment are clearly dependent upon a number of factors including the exact type of lymphoma and the age of the patient. For instance, there are currently no data supporting any role for the combination of rituximab and chemotherapy in people under 60 years old.

The cost of treatment needs consideration. One cycle of treatment with rituximab-CHOP costs approximately $4000 compared with $500 for CHOP alone. Another consideration is the new data which show that increasing the frequency of CHOP to fortnightly produces comparable improvements, in overall survival and complete remission rates, to those seen with rituximab-CHOP. Given these findings, and the cost of rituximab, it will be important to establish the optimal number of infusions, as well as the specific sub-group of patients for whom this drug is truly beneficial.

Conclusion

Therapeutic antibodies have not revolutionised the management of patients with cancer. However, the incremental gains associated with the use of these drugs have cemented their place in the clinical management of a select group of individuals. Over the next few years the precise role of these and other antibodies as adjuvant or first-line treatment for specific diseases will become apparent.

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Conflict of interest: none declared

Self-test questions

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

9. Trastuzumab is only indicated for women with breast cancers which overexpress the receptor HER2.
10. A serious adverse reaction to rituximab may not develop until two days after the infusion.

Book review

Australian Medicines Handbook Drug Choice Companion: Aged Care.

Adelaide: Australian Medicines Handbook; 2003.

218 pages. Price $50, students $45, plus postage.

Shanthi Kanagarajah, Geriatrician, Melbourne

The Companion is intended for use in conjunction with the Australian Medicines Handbook (AMH), the well-known and highly valuable drug formulary. It aims to assist those working in aged care, especially in residential facilities. The nearly pocket sized volume with a ring binding is easy to handle and the cover is probably resistant to contamination by bodily fluids.

The text itself is organised into common clinical problems in the aged care setting, with dementia and other neurological conditions heading the list. Following the instructions inside the front cover, I used the index to trace my way through typical clinical questions. Each topic is subdivided into consistent subheadings that include diagnostic issues and non-drug issues. The subsections on 'evidence' are a neat way of giving credence to the book's assertions.

There are useful summaries on conditions that one meets much more often in nursing homes than in textbooks of medicine – restless legs syndrome, managing stroke risk in people with advanced morbidity, and (not) crushing or splitting tablets. Several practice points and warnings are highlighted as call-outs, an effective device to focus one's attention to key messages.

The brevity of the work does present difficulties, for example there is no evidence section under insomnia. In Parkinsonism the problem of a poor clinical response to dopaminergic therapy is clearly stated, but the difficulty of existing postural hypotension (such as in multisystem atrophy) being aggravated by the drugs, is only hinted at. I found the inclusion of the section on irritable bowel syndrome puzzling, given that it may be 'less common in older than in younger people' and 'convincing evidence for the efficacy of drug treatments… is lacking'. Disabling stroke is a difficult management problem in nursing homes and hostels and a section on the therapeutics of spasticity would have been useful.

The Companion reasonably succeeds in its aim of assisting the busy aged care worker at the bedside. Doctors, nurses and pharmacists, particularly those doing medication reviews, should find this extremely useful. It is a 'first of its kind' in Australia.

BCG vaccine in Australia

Graham Simpson, Director of Thoracic Medicine and Regional TB Control Unit, Cairns Base Hospital, and Adjunct Associate Professor, James Cook University, Queensland

SYNOPSIS

Australia has low rates of tuberculosis, but there are still high rates in immigrants and indigenous people. BCG vaccination is indicated in high-risk groups, particularly children who may be exposed to tuberculosis, and possibly in healthcare workers. The vaccine reduces the risks of invasive tuberculosis and death from tuberculosis by about 70%. The degree of protection against pulmonary tuberculosis is uncertain. Adverse effects are uncommon and can usually be managed conservatively.

Index words: tuberculosis, Mantoux test.

(Aust Prescr 2003;26:144–6)

Introduction

Tuberculosis is a global emergency. One third of the world's population is infected and there are eight million new clinical cases and three million deaths each year. Australia currently enjoys one of the lowest notification rates for tuberculosis in the world at fewer than four cases per 100 000 population per annum. This annual rate declined from 48 per 100 000 in the late 1940s as a result of a highly successful national tuberculosis control program involving active case finding, standardised treatment, mass X-ray surveys and widespread BCG vaccination.[1] Most of these strategies were abandoned in the mid-1980s with the decline in tuberculosis, but there are worrying signs that the decline has halted and that rates of infection in Australia may be rising. Three quarters of all cases of tuberculosis in Australia now arise in people born overseas, usually in high-risk countries, but the Aboriginal population also has much higher risks of tuberculosis than other people born in Australia.

BCG vaccine

BCG (Bacillus Calmette-Guérin) is a living attenuated strain of *Mycobacterium bovis* which stimulates cell-mediated immunity by producing a localised and self-limiting infection. The vaccine is given intradermally, normally in the arm, but in parts of northern Europe often in the thigh or buttock (an important consideration if looking for a scar to prove previous vaccination). Vaccination should be given around the site of the insertion of the deltoid muscle, slightly posteriorly (Fig.1). This minimises keloid scar formation and also ensures that the lymphatic drainage of the site is to the axilla, rather than to the neck glands. The cosmetic effects of persistent lymphadenopathy or scars from suppurating lymph nodes are thus minimised. Normally one to three weeks after vaccination a small red papule appears. This usually vesicates and a scab forms. The site should be kept clean and dry and exposed to air as much as possible. It can be washed with clean warm water, but should be dabbed dry and kept open. Antiseptics, creams and other local applications should not be used. Normally the vaccination site heals leaving a small, depressed scar over a three to four month period. The duration of immunity is thought to be 10–15 years, but usually patients are not revaccinated.

Indications for BCG

BCG should be used in the following circumstances:

- newborn Aboriginal and Torres Strait Islander babies in areas where tuberculosis is prevalent
- neonates and children who are likely to travel to or live in countries where tuberculosis is common
- newborn babies, if either parent has leprosy
- children and adults who have been in contact with tuberculosis and remain Mantoux negative three months after last contact.

BCG may also be considered in the following circumstances:

- healthcare workers in frequent contact with patients with tuberculosis, especially multi-drug resistant tuberculosis
- adults who will spend prolonged periods in countries where tuberculosis is common
- newborn babies living in households where they may be exposed to migrants or visitors from overseas countries with high tuberculosis rates

Fig. 1

Intradermal injection of BCG vaccine

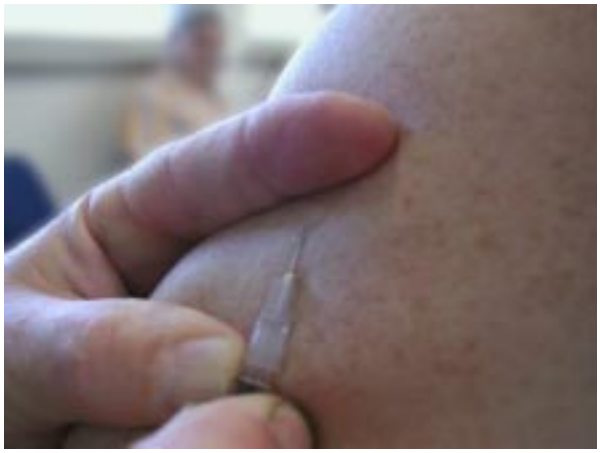

Photo courtesy of the author

- children under 16 years who are in contact with a patient with tuberculosis where the infection is resistant to treatment or where the child cannot take prophylactic antituberculosis treatment.

Healthcare workers

Healthcare workers represent a special group and there are two quite different views on how they should be managed with respect to potential tuberculous infection. The American view is that BCG should not be given and that healthcare workers should be monitored with regular Mantoux tests to detect tuberculous infection which can then be treated appropriately. This is expensive and labour intensive.

In parts of Australia where exposure to environmental mycobacteria is high and where many healthcare workers have had prior BCG, Mantoux tests may prove difficult to interpret. The alternative view, that new staff should be screened by Mantoux testing and then offered BCG vaccination if the result is negative, has become less popular and has been abandoned in some states which have adopted the American policy. Nevertheless, this approach is a viable option for staff likely to be exposed to tuberculosis regularly and certainly for those exposed to multi-drug resistant tuberculosis, although this is still uncommon in Australia.

The role of Mantoux testing

Over a century after the Mantoux test was introduced, it remains the standard test for detecting prior tuberculous infection. Guidelines recommend that it precede BCG vaccination in all but those under six months of age. Mantoux testing involves the intradermal injection of mycobacterial proteins (purified protein derivative – PPD) into the volar aspect of the forearm. Contraindications include a previous strongly positive test, past history of tuberculosis and recent vaccination with live vaccines.

The test is read by measuring the transverse diameter of induration (**not** erythema) at the injection site after 72 hours. Unfortunately, the interpretation of the result is highly complex and dependent on many factors including the patient's age, prior BCG vaccination, other medical conditions and geographical location – this last probably representing exposure to environmental mycobacteria. In general, reactions of less than 5 mm can be considered negative (though Mantoux conversion may not occur for 6 to 12 weeks after primary infection as it represents a cell-mediated response). Larger reactions however do not necessarily indicate tuberculous infection and expert advice from the local chest clinic should be sought.

Contraindications to BCG vaccination

BCG should not be given to:

- patients with current or previous tuberculosis
- patients with a current febrile illness
- patients with skin conditions such as eczema or dermatitis
- patients who have had a previous live vaccination within the past four weeks
- patients with a history of a positive reaction to a Mantoux test
- people who are HIV positive, or are in a high risk group for HIV and have not been tested
- patients receiving immunosuppressive medication such as corticosteroids or cancer chemotherapy or with other conditions likely to suppress immunity.

Adverse effects of BCG

Immediate adverse effects include vasovagal attacks or, extremely rarely, anaphylaxis. These should be managed conventionally.

The amount of inflammation at the injection site varies considerably. There may be a localised erythematous rash which settles within three days and there may be a low-grade fever for the first 24 hours. Inadvertent subcutaneous inoculation can result in localised abscess formation. Large local reactions are usually accompanied by more prominent lymphadenopathy, but usually settle without treatment.

Lymphadenopathy, which if the vaccination site is correct should be in the axilla, is common and usually settles without treatment. If the lymph nodes are not tethered to the skin and are not fluctuant, observation is the best policy. Minor enlargement of the lymph nodes may be permanent. If there is skin tethering and erythema and it looks as if an abscess may be forming, drug treatment is indicated. Isoniazid 5–10 mg/kg daily for three months is usually adequate. Surgery is rarely necessary. Isoniazid treatment would also be appropriate if secondary spread to other sites occurred. This is only really seen if patients with eczema or other skin conditions are inadvertently vaccinated. Should disseminated infection occur because of vaccination of an immunosuppressed person multi-drug therapy with rifampicin, isoniazid and ethambutol will be needed. Pyrazinamide is of no use as BCG is resistant to this drug.

Does BCG work?

The precise efficacy of BCG vaccine has been contentious for many years and there seems to have been a recent tendency to underestimate its effectiveness. A widely quoted meta-analysis estimates an overall reduction in the risk of developing tuberculosis of 50%.[2] The true protective effect, however, may be higher. The meta-analysis was considerably skewed by one very large trial in South India which showed no protection whatsoever. Other studies in more temperate climates have found protection rates of up to 80%. The explanation for the widely different results remains obscure but exposure to environmental mycobacteria and subsequent modification of the immune response has been suggested.

The protection rates refer to protection against pulmonary tuberculosis. There is strong evidence that BCG offers very good protection against the disseminated forms of tuberculous infection. Miliary and meningeal tuberculosis and also deaths related to tuberculosis are reduced by about 70%. Although it is far from perfect, BCG clearly provides significant and worthwhile protection against tuberculosis. If Australia does not manage to avoid the worldwide epidemic of multi-drug resistant tuberculosis then the protective effects of BCG may be of increasing value.

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Conflict of interest: none declared

Self-test questions

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

11. Eczema is a contraindication to BCG vaccine.
12. With the exception of babies under six months of age, Mantoux testing is recommended before patients are given BCG vaccine.

Tuberculosis testing and immunisation in the Australian Defence Force

Prepared by Air Vice-Marshal Bruce Short, Surgeon General, Australian Defence Force

In the course of peacetime service in Australia, the exposure of Australian Defence Force personnel to tuberculosis, and hence risk of infection, is similar to that of the general population. However, when operationally deployed, particularly in Australia's region of interest, personnel may be exposed to infected people. This risk is heightened during humanitarian or peace-keeping operations.

In the past, the mainstay of prevention was immunisation with BCG vaccine. In recent times the widespread use of BCG vaccination has been shown to prevent few cases in regions with low incidence rates. The vaccine may also cause false positives in Mantoux tests and this may increase the difficulty in diagnosing tuberculosis infection.

The Australian Defence Force has followed the guidelines of the US Centers for Disease Control and Prevention and, therefore, does not recommend routine BCG vaccination.[1]

Within the Australian Defence Force, screening for tuberculosis is undertaken by skin testing all personnel on entry, using 10 units of tuberculin purified protein derivative. Tuberculin skin testing may also be performed in two steps if the initial induration is less than 15 mm diameter. It is not performed by using multiple puncture tests (Heaf test).[2]

The tuberculin skin test is also used to screen personnel after redeployment or removal from a country with a high incidence of tuberculosis, provided that the period of redeployment has been at least three months. This testing is performed three months after the personnel return to Australia. A high incidence country is one in which the annual tuberculosis incidence is at least 49 per 100 000. For people visiting and residing in such an area for at least 3–12 months, incidence rates for tuberculosis infection have been reported as 1.8%.[3]

Personnel who have been exposed to high risk situations are also tested. This latter group includes those people who have spent a total of eight or more hours with an infected person in a confined environment, as well as healthcare workers who have had regular close contact with an index case.

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New drugs

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

Eptifibatide

Integrilin (Schering Plough)

10 mL vial containing 2 mg/mL

100 mL vial containing 0.75 mg/mL

Approved indications: unstable angina, myocardial infarction, intracoronary stenting

Australian Medicines Handbook section 7.2.1

Eptifibatide is the latest of several glycoprotein IIb/IIIa receptor antagonists such as tirofiban and abciximab, to be marketed in Australia. These drugs work in acute coronary syndromes by inhibiting platelet aggregation.[1]

Patients with unstable angina or non-Q wave myocardial infarction are given an intravenous bolus of eptifibatide. This is followed by an infusion which continues, for up to 72 hours, until the patient has a coronary bypass or leaves hospital. In

most patients this regimen will inhibit more than 80% of platelet aggregation. The half-life of eptifibatide is 2.5 hours with half of the dose being cleared by the kidney.

The efficacy of eptifibatide was assessed in a study of 10 948 patients with acute cardiac ischaemia. They were given eptifibatide or a placebo, in addition to aspirin and heparin. Eptifibatide significantly reduced the number of patients who died or suffered a myocardial infarction within 30 days.[2]

Eptifibatide can also be used in patients who require intracoronary stenting. A trial randomised 2064 patients to receive two doses of eptifibatide and an infusion, or a placebo before the non-urgent percutaneous implantation of a stent. The primary end-point of the trial was a composite of death, myocardial infarction, urgent revascularisation and 'bailout glycoprotein IIb/IIIa inhibitor therapy'. This trial was stopped early because of a significant difference in the primary end-point between eptifibatide and placebo (10.5% versus 6.6%).[3]

Predictably, bleeding is an important adverse effect of eptifibatide. In the pivotal study 11.6% of patients needed a transfusion.[2] This bleeding most often occurred in patients who require coronary artery bypass grafting and was also a problem for the patients given a placebo. Approximately 9% of the patients given a placebo needed a transfusion.[2] Common sites for bleeding are the femoral artery access point, the genitourinary system and the gut.

Monitoring the patient includes checking their blood counts within six hours of starting treatment and then at least once a day. The activated clotting time should be measured in patients having percutaneous coronary interventions.

Although the effect of eptifibatide in acute ischaemia is statistically significant the absolute reduction is only 1.5%. (Eptifibatide reduces deaths and myocardial infarctions from 15.7% to 14.2%.[2]) In the stenting study the overall benefit was accounted for by a reduction in myocardial infarctions. The difference in mortality between eptifibatide and placebo was not significant. The benefits of eptifibatide need to be balanced against the cost of managing the extra haemorrhages it causes.

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Escitalopram oxalate

Lexapro (Lundbeck)

10 mg and 20 mg tablets

Approved indication: major depression

Australian Medicines Handbook section 18.1

Citalopram is a selective serotonin reuptake inhibitor (SSRI). It is a racemic compound, but most of its activity is thought to reside in the S-isomer (escitalopram).

Starting doses of escitalopram are half those of citalopram. The isomers of citalopram have different pharmacokinetics, with escitalopram being metabolised by pathways which include cytochrome P450 2C19, 3A4 and 2D6. The metabolites are mainly excreted in the urine.

Escitalopram has been compared with placebo and citalopram, but not all of these studies have been published in full. One trial, involving 491 patients, found that escitalopram was more effective than placebo, but not significantly more effective than citalopram after eight weeks of treatment.[1] Another study lasting six months also found that 10 mg escitalopram was at least as efficacious as 20 mg of citalopram.

The adverse effects of escitalopram resemble those of citalopram and other SSRIs. In the comparative trial 4.2% of the patients taking 10 mg escitalopram discontinued treatment because of adverse effects.[1] These effects included nausea, diarrhoea, insomnia, dry mouth and ejaculation disorders.

There is insufficient published evidence to say that escitalopram should replace citalopram. The Health Research Group in the USA said that 'the primary purpose for developing escitalopram appears to be nothing more than a strategy to protect sales as citalopram nears the end of its patent protection'.[2]

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Ezetimibe

Ezetrol (Merck Sharp & Dohme)

10 mg tablets

Approved indications: hypercholesterolaemia and sitosterolaemia

Australian Medicines Handbook section 6.6

Familial hypercholesterolaemia is caused by a mutation in the gene which codes for the receptors for low density lipoprotein (LDL) cholesterol. The homozygous form of the disorder results in very high concentrations of cholesterol in the blood. This greatly increases the patient's risk of cardiovascular disease.

Sitosterolaemia (phytosterolaemia) is another genetic disorder which can cause hypercholesterolaemia. There is increased absorption of cholesterol and plant sterols from the gut.

Ezetimibe may benefit homozygous patients with familial hypercholesterolaemia or sitosterolaemia because it selectively inhibits absorption of cholesterol and phytosterols from the small intestine. The drug is taken once a day and its absorption is not affected by food. It is metabolised in the small intestine and mostly excreted in the faeces. The half-life of ezetimibe and its main metabolite is approximately 22 hours.

Monotherapy with ezetimibe reduces concentrations of LDL cholesterol by approximately 17%. As patients with hypercholesterolaemia are often treated with an HMG CoA reductase inhibitor, ezetimibe has been studied in combination with these 'statins'.

In a study of 50 patients with homozygous familial hypercholesterolaemia 12 weeks of treatment with ezetimibe and either atorvastatin or simvastatin had greater efficacy than statin therapy alone. Combined treatment reduced LDL cholesterol by 20.7% while high-dose (80 mg/day) statin therapy reduced it by 6.7%.[1] Adding ezetimibe to the treatment regimen of 37 patients with homozygous sitosterolaemia reduced their sitosterol concentrations by 21% and their campesterol concentrations by 24%.

Caution is needed when prescribing ezetimibe to patients who are being treated with a bile acid binding resin such as cholestyramine. The drugs interact resulting in reduced concentrations of ezetimibe. Combined therapy with fibrates is not recommended. When ezetimibe is combined with a statin the patient's liver enzymes should be checked. The combination is contraindicated in patients with altered liver function.

Although 5% of patients treated with ezetimibe may complain of myalgia, there are currently no reports of rhabdomyolysis. Other symptoms reported in clinical trials include abdominal pain, diarrhoea, chest pain, headache and dizziness.

Ezetimibe does improve patients' lipid profiles, but it will be several years before any effect on morbidity and mortality emerges. Familial hypercholesterolaemia is a relatively uncommon form of primary hypercholesterolaemia. Although ezetimibe has also been approved for other forms of primary hypercholesterolaemia its use for this indication will probably be limited to patients who cannot tolerate statins.

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Lutropin alfa

Luveris (Serono)

vials containing 75 IU as powder for reconstitution

Approved indication: gonadotrophin deficiency

Australian Medicines Handbook section 10.6.1

Some women with infertility have a severe deficiency of follicle stimulating hormone (FSH) and luteinising hormone (LH). To induce ovulation they can be treated with these hormones, but the preparations may be derived from urine. Urinary human chorionic gonadotrophin (HCG) is often used to mimic LH as it has a similar structure and action.

Genetic engineering has now enabled the production of recombinant LH. A double-blind trial randomised 259 infertile women to receive either recombinant LH or urinary HCG for the induction of ovulation. There were no significant differences between the treatments in the number of oocytes retrieved or the number of subsequent pregnancies.[1]

Lutropin alfa is a recombinant form of LH. It is genetically engineered using Chinese hamster ovary cells. There are only slight differences in the structure of lutropin and the hormone derived from urine.

The recommended regimen for lutropin is designed to assist the development of one follicle, but HCG is still used to induce ovulation. Patients have daily subcutaneous injections of lutropin and FSH. The patient's response is assessed by oestrogen secretion and measuring the follicle size with ultrasound. When an optimal response is obtained HCG is given 24–48 hours after the previous injection of lutropin. Approximately 70% of the women taking a daily lutropin dose of 75 IU respond to this regimen.

The response has to be carefully monitored because of the risk of ovarian hyperstimulation syndrome. Other adverse effects include injection site reactions, abdominal or pelvic pain, breast pain and nausea.

Infertility due to gonadotrophin deficiency is rare, so lutropin has been studied in relatively few patients. It will initially be reserved for women with a severe deficiency (LH less than 1.2 IU/L) because those with a less severe deficiency may respond to FSH alone.

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Omalizumab

Xolair (Novartis)

vials containing 150 mg as powder for reconstitution for injection

Approved indication: asthma

Australian Medicines Handbook section 14.1.4

Inflammation of the airways plays an important part in the pathogenesis of asthma. Allergens stimulate the production of IgE which then binds to mast cells resulting in the release of inflammatory mediators. Omalizumab is a recombinant monoclonal antibody which forms complexes with free IgE to prevent it binding to mast cells.

The concentration of free IgE is reduced within a few hours of a subcutaneous injection, even though it takes six to ten days for the drug to reach its peak plasma concentration. As well as slow absorption omalizumab has a slow clearance. Its half-life is approximately three weeks. Some patients may only need one injection a month depending on their weight and IgE concentration.

Two doses of intravenous omalizumab were compared with placebo injections in 317 patients who required corticosteroids for the control of allergic asthma. After a period of dose titration, patients were injected every two weeks for 20 weeks. In the later part of the study attempts were made to reduce the patients' doses of corticosteroids. Treatment reduced the patients' free IgE concentrations by 95% and resulted in a reduction of asthma symptoms. Half the patients given omalizumab were able to reduce their dose of inhaled steroids and 33–43% of those taking oral steroids were able to stop them. During the study period there were fewer exacerbations in the patients receiving omalizumab.[1]

Another study also found that subcutaneous omalizumab reduced exacerbations and enabled some patients to reduce or stop their inhaled corticosteroids.[2]

Omalizumab is generally well tolerated, but as it is a protein there is a risk of anaphylaxis and other allergic reactions. The most common adverse effects are reactions at the injection site.

Although omalizumab improves the symptoms of asthma it does not have a profound effect on lung function. In the trial of intravenous omalizumab FEV_1 increased by approximately 2%, while subcutaneous omalizumab resulted in a 4% improvement.

Omalizumab is only approved for subcutaneous injection into patients with moderate allergic asthma who have a raised IgE concentration and are already taking steroids. It is therefore not indicated for the majority of patients with asthma who have a normal IgE concentration and no history of allergy. Childhood asthma often has an allergic component, however, although omalizumab has been studied in children[3], it is not approved for patients less than 12 years old.

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Peginterferon alfa-2a (with ribavirin)

Pegasys (Pegasys-RBV) (Roche)

pre-filled syringes containing 135 microgram/0.5 mL and 180 microgram/0.5 mL

(Pegasys-RBV is packaged as pre-filled syringes with 200 mg tablets of ribavirin)

Approved indication: chronic hepatitis C

Australian Medicines Handbook section 14.2.2

The interferons are cytokines which can enhance the immune response. They have been used to treat patients with hepatitis to try and halt the progression to cirrhosis. To prolong the effect of a dose of interferon the genetically engineered molecule has been conjugated to polyethylene glycol. Peginterferon alfa-2b and ribavirin is an effective combination for treating chronic hepatitis C.[1]

Peginterferon alfa-2a has also been studied as a treatment for hepatitis C. One trial compared weekly injections of peginterferon alfa-2a with thrice weekly interferon alfa-2a in 531 previously untreated patients. After 48 weeks of treatment and a further 24 weeks of follow-up, 38% of the peginterferon group and 17% of the interferon group had normal aminotransferase concentrations and no detectable viral RNA. Liver biopsies showed a response in 63% of the peginterferon group and 55% of the interferon group.[2]

Peginterferon alfa-2a has also been compared with interferon alfa-2b. All 444 patients randomised to take interferon alfa-2b and 453 of the patients randomised to take peginterferon alfa-2a also received ribavirin. The other 224 patients took peginterferon alfa-2a and a placebo for up to 48 weeks. When the patients were assessed at 72 weeks, 56% of the patients treated with peginterferon alfa-2a and ribavirin had no detectable viral RNA. This was significantly greater than the sustained virological response seen in patients taking a placebo (29%) or interferon alfa-2b and ribavirin (44%).[3] The sustained response rate in patients with genotype 1 virus was lower (46%), but still significantly greater than in the other groups.

Doses of peginterferon alfa-2a are injected subcutaneously into the abdomen or thigh. The serum concentration peaks after 6–8 days and accumulates during the first two months of treatment. As the half-life is 50–130 hours the serum concentrations are sustained between each weekly injection.

Injection site reactions are among the many common adverse reactions reported in clinical trials. Other common complaints are fever, fatigue, myalgia and headache. Treatment was discontinued by 22% of the patients taking peginterferon alfa-2a with ribavirin and 32% of these withdrawals were because of adverse events. Laboratory abnormalities accounted for another 12% of withdrawals.[3] These abnormalities included neutropenia and thrombocytopenia, so it is important that haematological and biochemical tests are monitored during treatment. Peginterferon alfa-2a may also alter thyroid function and exacerbate autoimmune disease. It can also cause depression and patients' quality of life reduces during the 48 weeks of treatment.

While peginterferon alfa-2a may be superior to interferon alfa-2b[3], peginterferon alfa-2b can also induce sustained virological responses in more than 50% of patients[1] so a direct comparison of their effectiveness would be useful. Both drugs should be used in combination with ribavirin unless ribavirin is contraindicated or not tolerated. Even if the treatment is tolerated, it should probably be stopped if it has not significantly reduced viral RNA within 12 weeks.

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Pimecrolimus

Elidel (Novartis)

15 mg tubes containing 1% cream

Approved indication: atopic dermatitis

Australian Medicines Handbook section 8.1

Sirolimus and tacrolimus are immunosuppressants that can be used to prevent the rejection of kidney transplants. These drugs act by inhibiting the activation of T-lymphocytes. Pimecrolimus acts in a similar way and prevents the release of

inflammatory mediators from mast cells. It has therefore been studied in conditions such as atopic eczema.

As atopic eczema is common in children, pimecrolimus cream has been compared with placebo in 186 infants. After a six-week double-blind trial the dermatitis had improved in 55% of the infants given pimecrolimus and in 24% of those given a placebo cream.[1] Pooled results of short-term studies in older children show the eczema cleared in 35% of those given pimecrolimus and 18% of those given placebo.

In other studies, pimecrolimus has been compared with corticosteroid creams. An early study suggested that the efficacy of pimecrolimus 1% cream was less than that of betamethasone 0.1% cream.[2] Another trial studied 713 patients for up to one year to see if pimecrolimus could stop their eczema flaring up. They applied pimecrolimus or its vehicle and added topical corticosteroids if the eczema flared up. The eczema was controlled in 28% of patients given the vehicle and in 51% of those applying pimecrolimus.[3] The drug has therefore been given approval for intermittent long-term treatment, as well as short-term use.

The cream is applied twice a day. Only a small amount is absorbed through the skin. Most of the absorbed drug is metabolised by the liver and excreted in the faeces.

Nearly half the infants dropped out of the placebo-controlled clinical trials. This was mainly because of a poor response to the placebo. In the long-term study 52% of the control group dropped out compared with 32% of the pimecrolimus group.[3] Suspected drug-related adverse effects occurred in 25% of the patients given pimecrolimus and 19% of the control group.[3] Burning at the site of application is a common complaint with pimecrolimus, but it is also associated with skin infections such as folliculitis. Although phototoxicity was not a major problem in clinical trials, pimecrolimus enhanced the carcinogenicity of ultraviolet light in animal studies. Patients should therefore minimise their exposure to sunlight.

Although pimecrolimus will reduce the need to expose children to the adverse effects of topical corticosteroids, it may expose them to other risks of immunosuppression. In long-term studies fever and viral infections such as influenza occurred more frequently in association with pimecrolimus. Lymphomas and thyroid adenomas have occurred in animal studies. Long-term therapy should therefore be restricted to intermittent use by patients who cannot be managed with topical corticosteroids, which cost less. If there is no response to six weeks of treatment pimecrolimus should be stopped.

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Thalidomide

Thalidomide Pharmion (Pharmion)

50 mg capsules

Approved indication: erythema nodosum leprosum, multiple myeloma

Australian Medicines Handbook section 14

Thalidomide was originally marketed as a sedative, but was withdrawn in 1961 because of its association with birth defects. The drug was still made available for research purposes, and by chance it was found to be effective in erythema nodosum leprosum. This prompted further research into thalidomide's effects on inflammation and the immune system. Despite this research, the mechanism of action remains unclear and our knowledge of thalidomide's pharmacokinetics is incomplete.

Patients with leprosy may develop painful papules on the limbs. In more severe cases this erythema nodosum leprosum can be more widespread and make the patient systemically ill. Studies in the 1960s found that 66–75% of patients would respond to a seven-day course of thalidomide. Although thalidomide is effective for the cutaneous manifestations of erythema nodosum leprosum, it has no known action on *Mycobacterium leprae*.

The birth defects associated with thalidomide may have been related to its inhibition of angiogenesis. As neovascularisation occurs in the bone marrow of patients with multiple myeloma, thalidomide has been tried after other treatments have failed. A study of 84 patients with refractory multiple myeloma found that 32% responded to a course of thalidomide (median duration of treatment 80 days).[1] Despite this response rate, the hypothesis of thalidomide acting by inhibiting angiogenesis was not supported. There was no significant difference in the microvascular density of the bone marrow between patients who responded and those who did not.

Patient responses in studies of multiple myeloma are primarily judged by changes in the concentrations of paraprotein. It is not certain how these responses correlate with survival. The median event-free survival for the 84 patients was three months. After a year 58% of the patients were still alive.[1] An Australian study, which had an overall response rate of 28%, found that the median overall survival was 14.6 months. Increasing age may be associated with a poorer outcome.[2]

The optimum dose for thalidomide in refractory multiple myeloma is not yet clear. Many patients in the clinical trials were not able to increase their dose according to the maximum planned in the study design.[1,2] Higher doses are associated with an increased frequency of adverse effects.

Some of the adverse effects of thalidomide, such as sedation, are predictable. Before the drug was withdrawn in the 1960s there had been reports associating it with peripheral neuropathy, which may be irreversible. In the Australian study 29% of patients developed a degree of motor neuropathy and 47% developed some sensory neuropathy.[2] Patients need regular checks to detect early signs of neuropathy. The white blood cell count also needs regular monitoring as thalidomide may

cause neutropenia. Fatigue and constipation are the most frequent adverse effects of thalidomide.

Women of childbearing age who are prescribed thalidomide must not have intercourse or should use two types of contraception. As it is unknown if thalidomide is present in the semen of male patients they must use barrier contraception, even if they have had a vasectomy. As even a single dose may cause birth defects prescription of thalidomide will be tightly controlled. Only specialists and pharmacists registered with the Pharmion Risk Management Program will be allowed to prescribe and dispense thalidomide. Patients will need to give written informed consent before treatment.

REFERENCES*

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2. Mileshkin L, Biagi JJ, Mitchell P, Underhill C, Grigg A, Bell R, et al. Multicenter phase 2 trial of thalidomide in relapsed/refractory multiple myeloma: adverse prognostic impact of advanced age. Blood 2003;102: 69-77.

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

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

Answers to self-test questions

1. True	3. True	5. True
2. True	4. True	6. True
7. False	9. True	11. True
8. True	10. True	12. True

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