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EDITORIAL

Electronic prescribing in general practice: one small step

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Index words: drug utilisation, drug interactions.

(Aust Prescr 2000;23:50–1)

The use of computers in general practice has grown dramatically over the past 12 months. A study of general practice computerisation undertaken for the (then) Commonwealth Department of Health and Family Services in 1997[1] reported that 31% of Australian general practices used computers primarily for administrative purposes such as appointments and billing. At that time, only 15% of general practitioners used computers for activities such as prescription writing or other clinical purposes at the time of consultation. Only 7% of general practitioners reported the use of electronic clinical records.

The introduction of the 'Information Technology' component of the Practice Incentives Program (PIP) has been the major contributor to the recent acceleration in the use of computers in Australian general practice. This program offers financial incentives to general practices which use computers for electronic prescribing and those with the capacity for electronic communications. There has also been a dramatic improvement in the quality of general practice prescribing software.

Recent figures provided by the Department of Health and Aged Care indicate very high participation in the PIP. By February 2000, 5088 practices were participating in the program.* Of these practices, 65% qualified for the 'electronic prescribing' component of the payment, which requires the majority of doctors in the practice to use an electronic prescribing package to write the majority of their scripts. Seventy-six per cent of participating practices qualified for the 'data connectivity' component, requiring an e-mail address and a modem. While not directly comparable to the earlier study, these figures certainly suggest a dramatic increase in the number of computers in use in Australian general practice.

A great deal of effort has been undertaken to support general practitioners making this transition to electronic prescribing. Funding provided by the Department of Health and Aged Care to Divisions of General Practice has enabled the appointment of information technology support officers in most divisions. These officers aim to provide practical assistance to general practitioners. This may be in the form of training programs, assistance with set-up and trouble-shooting, or mediation with computer vendors and software providers. Many such officers report enormous demands on their services along with a great deal of success in 'getting general practitioners started'. While some divisions have made a significant commitment to information technology support for several years, many of these programs are less than 12 months old and more formal evaluation data are needed to tell us about their effectiveness.[2]

With such a rapid increase in the number of doctors using computers to generate prescriptions, and the level of resources being spent supporting this change, it is fair to ask what impact we might expect in general practice and in patient health.

Much of the international research analysing the effect of computers in general practice has been less than positive.[3] Computerisation is generally costly, whether measured in

In this issue...

The increased use of computers is changing prescribing in general practice. The legibility of a printed prescription gives the computer a clear advantage over the pen. Frank Quinlan explains why electronic prescribing may be the precursor of even greater changes in practice, but Andrew Nolan questions the wisdom of exposing doctors to advertisements during the consultation.

Advertising may contribute to the public popularity of paracetamol. Peter Hewson reminds us that parents can sometimes give too much of this drug, particularly if their child is feverish.

Head lice are also a problem for children. Most cases will, however, respond to the approach suggested by Orli Wargon.

Drugs which affect acid secretion feature regularly in *Australian Prescriber*'s Top 10 Drugs. Neville Yeomans reviews these drugs with an emphasis on the different actions of H_2-receptor antagonists and proton pump inhibitors.

* These practices serviced approximately 75% of Australia's SWPEs (standard whole patient equivalents) providing an approximation of the percentage of Australian practices that are part of the program i.e. 75%. The actual number of practices in Australia is currently unknown.

terms of capital outlay, training, maintenance, length of consultation or organisational change. There is also concern that the computer may interfere with the doctor-patient relationship or overload doctors with large amounts of information, such as rare and clinically unimportant drug interactions. Consisting of a range of independent practices, general practice does not have access to the support services available from the information technology departments of large organisations.

The main benefits anticipated from electronic prescribing include decision support with drug interaction and allergy warnings, greater legibility of prescriptions and an improved medication history. Other potential benefits include improved public health and greater efficiency in the health system. As computer systems allow the immediate transfer of data, the doctor will always have the very latest information available. The data available to health planners will also be up to date.

Many general practitioners remain unconvinced of the benefits of computerisation, with any benefits taking some time to achieve.[3] In the longer term, however, electronic prescribing is likely to yield great benefits to the general practitioner, the patient and the health system as a whole. Only through greater levels of computerisation and improved information management are we likely to realise benefits such as:

- improved patient care through recall and reminder systems
- the timely provision of consumer medicines information
- greater evaluation and assessment at the practice or divisional level through age/sex/disease registers and other data analysis
- improved practice through greater implementation of evidence-based treatments and guidelines
- improved public health planning through enhanced data analysis
- better targeting of resources through notification and early warning systems.

Electronic prescribing offers many general practitioners an opportunity to commence the process of computerisation; one step towards improved information management. This will be the first step towards a complete electronic patient record. A great deal of effort is currently being spent developing the standards and infrastructure that will allow the computer-using general practitioner to realise all the potential benefits.[4] Those who have now commenced this process will be well placed to reap the benefits.

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Electronic prescribing: a personal view

John Marley, Professor, Department of General Practice, University of Adelaide, Royal Adelaide Hospital, Adelaide

Many doctors have been suspicious of computers and easily deterred from using them in their practices. I viewed with some trepidation what I thought would be a long and painful learning experience in moving to electronic prescribing.

Like most converts, I am now a zealot. The learning period was surprisingly short and now the painful part of the experience is limited to having occasionally to write a paper prescription. How did I ever manage before! The time and frustration saved is sizeable. The program inserts names, addresses and PBS quantities and a repeat prescription is but two keystrokes. For Authority scripts, all the patient information is automatically displayed and inserted, the Authority phone number is given, the words needed to be read appear on the screen and the cursor is in the box ready for the phone approval number.

Perhaps above all, the impression of being in control is the most important. I now have a comprehensive list of all medications that the patient has had and when they have been prescribed, all without having to wade through reams of handwritten notes. As well as dosage information, I have instant answers to all those difficult patient questions, such as, 'Should I take it with or without food, doctor?'. The system knows more reliably than my memory what drugs the patient is taking, so it flags interactions and allergies that I might well miss. The invaluable electronic Therapeutic Guidelines are but a mouse click away.

So, if you haven't already done so, don't just sit there, jump in!

Pharmaceutical advertising in clinical software

A. Nolan, General Practitioner, and Research Fellow for Therapeutic Guidelines Ltd, Toronto, NSW

SYNOPSIS

General practitioners are being encouraged to make more use of computers in their work. Computers can help the doctors write accurate prescriptions. Many of the available prescribing packages, however, are sponsored by the pharmaceutical industry. Presenting electronic advertisements during a consultation is a new avenue for the pharmaceutical industry to promote its products. The patient may also be exposed to this advertising if they can see the computer screen. Unless the amount and content of advertisements are controlled the advantages of using a computer may be lost.

Index words: drug industry, drug information, consumers.

(Aust Prescr 2000;23:52–3)

Introduction

Doctors are familiar with pharmaceutical advertising in professional journals and newspapers, as well as with direct marketing by pharmaceutical representatives. Such advertising serves not only to inform prescribers about new products and new or changed indications for existing products, but also to promote the sales of the products. There is a wide range of opinion on the effects of pharmaceutical advertising, with long-standing opposition in some quarters pitted against ready acceptance in others. This situation is mirrored by some of the conflicts inherent in Australian pharmaceutical industry policies. The Commonwealth Department of Health and Aged Care (DHAC) seeks to control the cost of the Pharmaceutical Benefits Scheme by co-payments, premium brand pricing and authority prescriptions, whereas the Department of Industry, Science and Resources works to promote the profitability of the pharmaceutical industry. Other conflicts have arisen by accident – the government was a founding shareholder in Heath Communications Network (HCN) which has recently acquired one of the prescribing software companies which uses advertising.

The market

General practitioners are increasingly using computer software for accounting, prescribing and medical records. The development of computer technology has encouraged efforts to develop clinical systems to do more than prescribing. However, because of the limited number of users of clinical software, there have been problems with the viability of medical software companies. Until recently there have been no incentives for the use of clinical software, other than the potential for improved patient care. Doctors even had to purchase special prescribing paper for their computers whereas the printed prescription pads were provided free of charge by the Health Insurance Commission (HIC). Medical software companies faced with increased costs could put up the prices of their products, abandon research and development for product improvement, or find supplementary sources of income. Advertising was one such source. Two of the three largest prescribing software suppliers have allowed pharmaceutical companies to advertise on screen. This has enabled the software companies to develop and supply their products at an affordable price.

Current trends

The use of prescribing software by general practitioners is increasing with the provision of specific payments for users under the Practice Incentives Program (PIP) of the DHAC. The increased number of users will perhaps allow software suppliers to be less dependent on advertising. According to personal communication with one source within the DHAC, it has been proposed that the PIP payments might eventually be made subject to the use of approved software not containing advertising. However, there may be a continued role for advertising which meets new, yet to be decided, standards.

Advertisements were shown to be effective some 17 years ago in promoting better quality antibiotic prescribing.[1] Perhaps this strategy could be used in computer prescribing. As consumers will (and should, according to an expert general practice computing group) view the screen during the consultation, any regulations should take the educational potential of computers into account.

Advertising in prescribing packages

Currently two of the three main prescribing packages contain advertising. One package has full-screen advertisements which are displayed after the choice of drugs has been made and the print button is pressed. The other package has smaller adverts approximately 10 x 4 cm (about 12% of the screen). These are present in the drug selection area of the program at the top right-hand corner of the screen and are changed several times per minute. Neither of these programs has any linkage of the advert to the drug class or the patient's condition.

Potential disadvantages of advertising

Using a computer in the prescribing process can improve the quality of care through improvements in prescription legibility, interaction checking and patient medication management.[2] Advertising may negate many of these benefits because of the new ways in which it can appear in a prescribing package. The obvious important issue is the degree to which advertising in prescribing programs influences the prescribing decisions of the doctor. For quite some time, normal print-based advertising has been known to influence prescribing. What is new about computer-based advertising is that it is much closer to the act of prescribing. The adverts may be much more effective from the advertiser's point of view, by being activated when the decision to choose one drug over another is taken. This is analogous to point-of-sale advertising. Linking advertisements to the patient's condition or to the class of drug being chosen is technically feasible. Previous versions of some prescribing software have included these links. Accurately aimed advertising probably increases its effectiveness.

The advertisements appear on screen during the consultation so the patient will also view the advertising. This might result in embarrassment for the patient and doctor if, for example, sexual themes, as used in some print-based adverts, are used to promote treatments for sexually transmitted diseases. Patients are not equipped to critically view advertisements claiming breakthroughs in treatment, or those that are visually appealing and may unduly influence the interaction between doctor and patient. The presence of inappropriate material may damage the credibility of the doctor if they seem to be receptive to advertisements.

Industry self-regulation

The Australian Pharmaceutical Manufacturers Association (APMA) has developed a code of conduct for drug advertising. This code has recently been redrafted to include product advertising within computer software.[3] Both the government and the software industry have contributed to this redrafting. The pharmaceutical industry has been allowed to retain control of advertising because of its willingness to self-regulate. The redrafted code could have set stricter controls on the advertisements which can be screened by member pharmaceutical companies.

A stricter code might have:

- limited the content of adverts to include only the brand and generic names and no other information
- excluded advertising from parts of the program where the patient record was opened, thus removing the direct intrusion of advertising into the clinical decision-making process
- banned the linking of advertisements to any special characteristic of the doctor, patient demographics or characteristics, or drug or drug class considered by the doctor.

In contrast to the pharmaceutical industry, few of the professional medical colleges have developed codes of conduct governing the use of electronic prescribing programs that contain advertising.

Conclusion

Pharmaceutical advertising has supported the availability of high quality software at lower prices. The need for this support has however hindered the ability of smaller players to compete on a level playing field, as they have been less able to attract advertising and hence have had less capital to devote to product development. While it is difficult to predict what effect any restriction on advertising might have, it may cut off smaller developers from this source of badly needed income. The DHAC is currently investing millions of dollars through the PIP to promote the use of computers. It should take care not to inadvertently reduce the industry to a monopoly through poorly conceived interventions. This might occur if the larger developers are allowed to overtake the others because of the money they receive from the pharmaceutical industry. There is currently an opportunity to ensure that any advertising at the point of prescribing is controlled and does not overwhelm unbiased drug information and clinical guidelines.

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Dr Nolan is currently undertaking a research project to test the effectiveness of an electronic decision support system comprising MIMS SCRIPT prescribing software and Therapeutic Guidelines: Antibiotic.

Self-test questions

The following statements are either true or false (answers on page 67)

1. Patients are not permitted to see on-screen advertisements for prescription-only drugs.
2. The Australian Pharmaceutical Manufacturers Association has to approve advertisements for prescription-only drugs before they are included in prescription writing software.

The Australian Standard Vaccination Schedule 2000–2002

The Australian Standard Vaccination Schedule shown here is that recommended by the National Health and Medical Research Council (NHMRC). In drawing up its recommendations the NHMRC has sought to reduce the number of injections given at each immunisation session through the use of new combination vaccines and to limit, as far as possible, the number of vaccine products that a practitioner would need to have available. For the immunisations at 2, 4, 6 and 12 months, two options for the use of combination vaccines which meet these criteria are recommended.

The Australian Standard Vaccination Schedule 2000–2002
For children born on or after 1 May 2000

New South Wales, Queensland, South Australia, Australian Capital Territory and Northern Territory follow Path 1. Victoria, Western Australia and Tasmania follow Path 2.

Immunisation Schedule

Age	*Vaccine*	
Birth	hepB[a]	
	Path 1[b]	**Path 2**[b]
2 months	DTPa-hepB and Hib (PRP-OMP) and OPV	DTPa[c] and Hib (PRP-OMP)-hepB and OPV
4 months	DTPa-hepB and Hib (PRP-OMP) and OPV	DTPa[c] and Hib (PRP-OMP)-hepB and OPV
6 months	DTPa-hepB and OPV	DTPa[c] and OPV
12 months	MMR and Hib (PRP-OMP)	MMR and Hib (PRP-OMP)-hepB
18 months	DTPa	
4 years	DTPa and MMR and OPV	
10–13 years	hepB[d]	
1 month later	hepB[d]	
5 months after 2nd dose	hepB[d]	
15–19 years	Td OPV	
Non-immune women who are post-partum or of child bearing age	MMR	
50 years	Td[e]	
50 years and over (Aboriginal and Torres Strait Islander people)	Pneumococcal vaccine (every 5 years) Influenza vaccine (every year)	
65 years and over	Pneumococcal vaccine (every 5 years) Influenza vaccine (every year)	

Notes

a. Hepatitis B vaccine should be given to all infants at birth and should not be delayed beyond 7 days after birth. Infants whose mothers are hepatitis B surface antigen positive (HBsAg+ve) should also be given hepatitis B immunoglobulin (HBIG) within 12 hours of birth.

b. When necessary the two paths may be interchanged with regard to their hepatitis B and Hib components. For example, when a child moves interstate, they may change from one path to the other.

c. Wherever possible the same brand of DTPa should be used at 2, 4 and 6 months.

d. Adolescent hepatitis B vaccination is not necessary for those children who have previously received three doses of hepatitis B vaccine.

e. Td should be given at 50 years of age unless a Td booster dose has been documented in the previous 10 years.

Vaccines used in the Schedule

Disease	*Vaccine*
Hepatitis B	hepB
Diphtheria, Tetanus, Pertussis	DTPa
Diphtheria, Tetanus, Pertussis, Hepatitis B	DTPa-hepB
Haemophilus Influenzae type B	Hib (PRP-OMP)
Haemophilus Influenzae type B, Hepatitis B	Hib (PRP-OMP)-hepB
Poliomyelitis	OPV
Measles, Mumps, Rubella	MMR
Diphtheria, Tetanus	Td
Pneumococcal disease	Pneumococcal vaccine
Influenza	Influenza vaccine

Transition from the old to the new schedule

All babies born on or after 1 May 2000 should commence the new Australian Standard Vaccination Schedule. Because of logistics, funding and vaccine interchangeability issues, all children born before this date should commence or continue with the previous schedule.

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.

Antidepressants

Editor, – I agree entirely with the sentiments of Dr O'Dempsey (Aust Prescr 2000;23:5) that newer drugs are rarely, if ever, measured against the performance of 'active' placebos. I think very few would pass muster if they were.

In the case of any antidepressant, I would personally be very surprised if any performed better than pheniramine *p*-aminosalicylate. I would be amazed if any hormone replacement therapy performed better than spironolactone 100 mg second daily. I would be astounded if any antipsoriasis treatment compared favourably against miconazole and zinc nappy ointment. I would also personally be stupefied if any ear drop could compare with half strength Burow's solution.

Peter Rout
General Practitioner
Darlington, NSW

Digoxin interactions

Editor, – During December 1999, I witnessed a case that motivated me to read the article 'Digoxin in the 21st century' (Aust Prescr 1999;22:136–7) with accentuated attention. The case was a 56-year-old woman who had suffered from schizophrenia six years ago and had since remained mentally balanced. She has been hypertensive for the past two years and was placed on medications. She had minor congestive heart failure last October (attributed to non-compliance with antihypertensive medications) and was admitted to a rural hospital. After rapid digitalisation she was placed on digoxin (0.125 mg/day) and hydralazine, but when the doctor started noting some neurological imbalance, chlorpromazine was added. On discharge, chlorpromazine and hydralazine were discontinued while digoxin was maintained. Sinepress (dihydroergotoxine 0.6 mg, reserpine 0.1 mg, hydrochlorothiazide 10 mg) was added. However, around the middle of December, she reverted back to a schizophrenic state, for which she is still being treated.

Does Dr Semsarian think that this bout of schizophrenia may have been precipitated by the adverse effects of digoxin ('digitalis delirium', confusion and hallucination) or to digoxin's common drug interactions, say, with the components of the combination antihypertensive drug?

Hypokalaemia induced by potassium-depleting diuretics is known to be the cause of adverse drug interactions between digoxin and such diuretics. The first self-test question

(p. 137) may mislead readers to assume that all diuretics can provoke digoxin toxicity. After all, potassium-sparing diuretics such as amiloride may even be beneficial in digoxin therapy.

S. V. Nwafor
Department of Pharmacology and Toxicology
Faculty of Pharmaceutical Sciences
University of Nigeria, Nigeria

Dr C. Semsarian, the author of 'Digoxin in the 21st century', comments:

The issue of determining whether or not a patient's clinical status is due to a drug effect is an important one. Unfortunately, this is often difficult to resolve in the setting of a patient with multiple diseases, taking several medications. The case presented by Dr Nwafor is interesting and could possibly be due to digoxin toxicity. 'Digoxin delirium' is seen rarely now because of more diligent efforts in prescribing correct doses of digoxin for individual patients based on factors such as age, gender and renal function. Furthermore, regular measurements of serum digoxin levels have become routine. The patient mentioned in Dr Nwafor's letter is taking a product containing two drugs, reserpine and hydrochlorothiazide, both of which can increase digoxin toxicity by lowering serum concentrations of potassium. We have no information on the patient's renal function, therefore the patient should have had an assessment of renal function, and their serum potassium and digoxin concentration measured. If all of these are normal, then it is less likely that digoxin is the cause of this patient's symptoms. If the combination product is to be continued, regular serum potassium measurements are recommended.

The second issue regarding the interaction of digoxin with diuretics is a common issue in clinical practice. Dr Nwafor seems unaware that **both** potassium-depleting (e.g. thiazides and frusemide) **and** potassium-sparing diuretics (e.g. spironolactone, which increases digoxin levels by prolonging its half-life) can result in altered digoxin levels. This is clearly shown in Table 3 of my article and the first self-test question aims to reflect this fact. Not **all** potassium-sparing diuretics, however, interact with digoxin.

Conquering chemotherapy

Editor, – Notwithstanding your desire to provoke correspondence, your potboiling editorial on chemotherapy (Aust Prescr 2000;23:5) has missed the point. The palliative management of advanced cancers is extremely difficult and what you are criticising is not chemotherapy, but lousy judgement. Most treatments for cancer, including I am afraid the immunotherapy which you favour, have a low therapeutic ratio. Judgement can be enhanced by training and education programs, such as those provided by the Medical Oncology Group of the College of Physicians and the Faculty of Radiation Oncology. We should also not forget that 'merely delaying the inevitable', albeit with unpleasant adverse effects, may be exactly what the patient wishes. The care of patients with advanced cancers must be individualised.

Roger Allison
Radiation Oncologist
Royal Brisbane Hospital
Herston, Qld.

Editor, – We would like to reply to your editorial 'Conquering chemotherapy' (Aust Prescr 2000;23:5). Although you acknowledge that chemotherapy can cure certain cancers, we believe that your references to chemotherapy in the palliative situation require comment. It is true that chemotherapy, like most drug treatment, has the potential for adverse effects. Most readers would be aware that the decision to proceed with chemotherapy in the incurable patient should follow careful, realistic consideration of the odds of palliating cancer symptoms and the impact of chemotherapy on the quantity and most importantly the **quality** of life. Modern phase II and III studies of chemotherapy in palliative settings now include quality of life measurements as major end points. This is in contrast to the image portrayed in the editorial in which 'patients are poisoned to the edge of their existence'. The use of growth factors such as G-CSF has developed and is approved under Section 100 of the Pharmaceutical Benefits Scheme for treatment given with **curative** intent in malignancies such as lymphoma and adjuvant breast therapy where there is strong evidence to support the need to maintain dose intensity. Caring for cancer patients on a daily basis, we look forward to the development of new cancer therapies such as immunotherapy. Until there is sound evidence to support its routine use, however, chemotherapy will remain the major thrust of treatment of many cancers into the 21st century. We believe that the judicious use of chemotherapy should be considered in the context of the large body of evidence, including quality of life data, which reveals its worth.

Keith Horwood
Medical Oncologist

David Wyld
Director of Medical Oncology
Royal Brisbane Hospital
Herston, Qld.

Dr J.S. Dowden, Editor, and the author of 'Conquering chemotherapy', comments:

Predicting the future is not easy. I hope that in that future we will be able to offer effective, well-tolerated treatments to patients with advanced cancer. The critical comments of the Queensland oncologists clearly reflect treatment in the dying days of the 20th century. Will chemotherapy still be as important at the end of this century? I am sure that all oncologists look forward to a time when patients will not suffer from severe toxicity or from 'lousy judgement'.

EXPERIMENTAL AND CLINICAL PHARMACOLOGY

Drugs that inhibit acid secretion

Neville D. Yeomans, Professor of Medicine, University of Melbourne, Western Hospital, Melbourne

SYNOPSIS

Histamine H_2-receptor antagonists and proton pump inhibitors are the main classes of drug used to inhibit gastric acid secretion. The former act by reversibly blocking the action of histamine, which is released from other mucosal cells in anticipation of a meal or when food enters the stomach. The proton pump inhibitors have a long-lasting effect on acid secretion. They inactivate the final step in acid secretion – the transport of hydrogen ions from the parietal cells to the lumen of the gastric glands.

Index words: H_2-receptor antagonists, gastro-oesophageal reflux, proton pump inhibitors, peptic ulcer.

(Aust Prescr 2000;23:57–9)

Introduction

Safe and effective inhibition of gastric acid secretion has been a long-desired goal of clinicians who treat acid-related diseases such as gastro-oesophageal reflux disease and peptic ulcer. Nowadays, two classes of drug – the histamine H_2-receptor antagonists and the proton pump inhibitors (PPI) – achieve this goal with a high level of success.

The pharmacodynamics of the PPIs are easier to grasp because they block the final step in acid secretion. To understand the effects of H_2-receptor antagonists requires some knowledge of the signalling pathways that lead to acid secretion.

Histamine H_2-receptors

When acid secretion is stimulated with histamine, the systemic adverse effects of histamine can be prevented by a conventional antihistamine drug without affecting acid secretion. This suggests the existence of two classes of histamine receptors, one mediating acid secretion (H_2-receptors) and the other mediating all other effects of histamine (H_1-receptors).

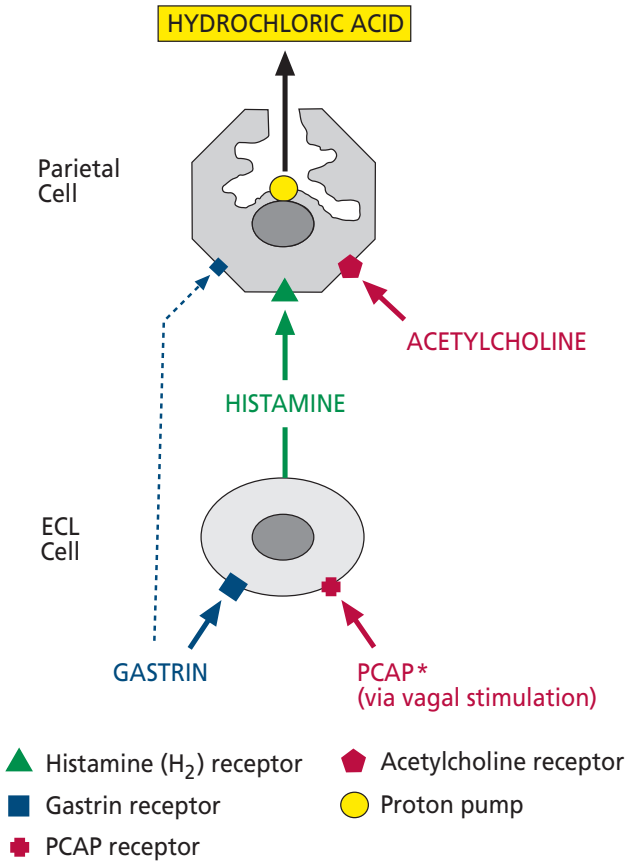
Enterochromaffin cells

Histamine H_2-receptors are located on the basolateral membranes of the acid-secreting parietal cells in the stomach. They are activated by histamine derived from neighbouring mucosal cells. We now believe the main source of this histamine to be the principal endocrine cell of the gastric body or corpus – the enterochromaffin-like (ECL) cell. The ECL cells are mainly located in the lower part of the gastric glands, well-positioned to deliver their histamine into the capillaries which flow past them and the parietal cells (Fig. 1).

The ECL cells have receptors on their cell membranes for the peptide hormone gastrin, and a neurotransmitter released in response to vagal stimulation. The parietal cell basal membrane carries receptors for histamine (H_2), gastrin and acetylcholine. We used to believe that the gastrin and acetylcholine receptors on the parietal cell were particularly important in acid secretion. However, current evidence suggests that the gastrin receptors on the parietal cell are more concerned with cell growth than signalling for acid secretion. The high affinity gastrin receptors that activate acid secretion are actually the receptors on the ECL cells.

Fig. 1

Two cell types in the mucosa of the corpus of stomach are principally responsible for secretion of acid. Histamine secreted from nearby enterochromaffin-like (ECL) cells stimulates the parietal cells to secrete acid. A variety of substances can stimulate the ECL cell to secrete histamine.



* PCAP = pituitary adenylate cyclase activating peptide (released from enteric nervous system interneurones in gastric mucosa)

Acid secretion

The main messages that tell the stomach to secrete acid after a meal are the release of gastrin and acetylcholine. These messages are channelled via the ECL cells which then release histamine. Histamine then stimulates the parietal cells to secrete acid.

Once the histamine H_2-receptors on the parietal cell are activated, acid secretion is started via intracellular cyclic AMP. This in turn activates the acid transporter (H^+/K^+-ATPase) on the luminal side of the parietal cell. These proton pumps are stored in intracellular tubules and vesicles, and are rapidly inserted into the cell membrane – the invaginated secretory canaliculus (Fig. 1) – so they can transport hydrogen ions out of the cell and into the gastric glands.

H_2-receptor antagonists

In Australia, the available drugs are cimetidine, ranitidine, famotidine and nizatidine. Their pharmacological properties are much more similar than they are different. All are competitive inhibitors of the histamine H_2-receptor on parietal cells. Their duration of action mirrors their plasma elimination half-lives, and is measured in a few hours. Large doses can produce marked inhibition of basal or stimulated acid secretion, although the effect disappears quickly. This is true whether the acid secretion is stimulated physiologically by eating (mediated by gastrin and cholinergic pathways), or the sight, smell or taste of food (vagal pathways, gastrin); or experimentally by infusion of histamine, gastrin or acetylcholine.

As the drugs have a relatively short duration of action, they are normally given twice daily for reflux disease or healing gastric ulcers. For healing duodenal ulcers, giving the full daily dose in the evening is as effective as dividing the dose into two. Nowadays, however, the main priority for healing ulcers is treating *Helicobacter pylori* if the organism is present.

Standard doses of H_2-receptor antagonists usually elevate intragastric pH by about one unit, averaged over 24 hours. This is only a modest elevation compared with that achievable with proton pump inhibitors, but nevertheless is often sufficient for successful treatment.

Tolerance

One interesting feature of blockade of the parietal cell H_2-receptor is that tolerance develops after a few days of dosing. As a result, the degree of inhibition reduces, often by half. This is usually not a clinical problem, although it may be one reason why H_2-receptor antagonists are less successful than PPIs for the treatment of severe reflux disease. This tolerance does become a major problem for patients with massive hypersecretion of acid – as in the Zollinger-Ellison syndrome. Tolerance becomes a limiting factor and the control of acid secretion usually fails after some weeks of treatment. In this rare disease, control of acid secretion with a PPI should be the normal approach.

Tolerability

This class of compound is generally very well tolerated. Histamine H_2-receptors are present in other tissues, e.g. the heart and the brain. However, in clinical practice it is unusual for patients to be aware of any adverse effects from these drugs. Prescribers need to be aware that H_2-receptor antagonists (especially cimetidine) may interfere with the metabolism of some other drugs.

Proton pump inhibitors

This newer class of drugs includes omeprazole, lansoprazole and pantoprazole. All these drugs substantially inhibit acid secretion. Their chemical structures differ only minimally, and for practical purposes their pharmacology is identical.

Pharmacology

Omeprazole was developed by a Swedish research group during a search for a drug that might inhibit the release of gastrin from the gastric mucosa. However, it soon became apparent that omeprazole was inhibiting the newly discovered acid pump on the surface membrane of the acid-secreting cell (Fig. 1).

The PPIs are effectively pro-drugs. They are converted into an active form by a high acid concentration, e.g. omeprazole becomes a sulfenamide. In the gastric lumen this activation by acid is a problem. The sulfenamide is a short-lived compound and cannot reach the acid pump on the parietal cell membranes by diffusing the long distance from the stomach lumen down into the pits and glands of the mucosa. For this reason, the PPI needs an enteric-coated form so that most of it can survive the passage through the stomach. It is then released in the small intestine where it is absorbed and travels to the parietal cells in the stomach via the circulation. The diffusion distances are then very short (micrometres) and the PPI is converted to its active form as soon as it reaches the acid space just outside the acid pump itself. It is then perfectly positioned to bind covalently to the H^+/K^+-ATPase on the parietal cell membrane. This binding is long lasting but is overcome by the synthesis of new pump molecules. Since the average half-life of the pump molecules is about 24 hours, this is the average half-time for the suppression of acid secretion.

Although the plasma half-lives of PPIs are quite short, their mechanism of action enables most patients to be satisfactorily treated with once-daily dosing. Generally it does not matter whether the dose is given in the morning or the evening. However, acid secretion recovers faster in some patients than others and it may be worth experimenting with switching the dose to the evening. This may benefit patients with reflux whose nocturnal symptoms are not relieved when the PPI is given in the morning. About 10–20% of patients with severe reflux disease will get better relief of symptoms with a twice-daily dose.

PPIs elevate intragastric pH much more readily than H_2-receptor antagonists. In untreated individuals, median

24 hour pH in the gastric lumen is about 1.5. This increases to about 2.5 with an H_2-receptor antagonist while PPIs in standard dosage can usually increase the median pH to about 4-5. This is of particular value when treating resistant gastro-oesophageal reflux disease. This elevation of pH also seems to be an advantage when acid suppression is used as part of the triple therapy strategies for treating *H. pylori* infection.[1]

One interesting property of the current generation PPIs is that their effects can be a little more unpredictable when the dosage is lowered. For example, one study with omeprazole showed that a 10 mg dose once daily had little effect on 24 hour median pH in three of eight volunteers while several of the remainder had marked acid suppression. This phenomenon may be explained by variability in the rate of regeneration of acid pump molecules.

Tolerability

The PPIs are extremely well tolerated. In the trials that established their efficacy, the adverse events reported by patients taking the drugs were usually not statistically different from those of placebo. This presumably relates to the very specific drug delivery and the very tissue-specific localisation of this particular hydrogen/potassium pump.

Long-term safety

Initial concerns about potential risks from long-term acid suppression in humans seem to be unfounded. A slightly increased risk of some enteric infections (mainly *C. jejuni*) has been observed. Data accumulated over the first decade of use do not raise any significant concerns about neoplastic potential in humans. If there are any long-term risks, they are likely to be outweighed by the risks of **not** treating troublesome acid-related diseases adequately.[2]

Future developments

H_2-receptor antagonists appear to be a mature family of drugs, with further improvements probably unlikely. Blockade of the proton pump is still evolving, through the development of variants with even more predictable effects, as well as inhibitors that are shorter or longer acting than those currently marketed.

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Self-test questions

The following statements are either true or false (answers on page 67)

3. Proton-pump inhibitors have a long duration of acid secretory inhibition because of their long plasma half-lives.
4. Histamine provides the most important final input to stimulate the gastric parietal cell to secrete acid.

Drug interactions

Warnings for cisapride

Cisapride will be withdrawn from the American market in July. The drug is being withdrawn because of concern about serious adverse effects. By the start of 2000, the Food and Drug Administration had reports of 341 cases of arrhythmia and 80 deaths. Many of these adverse reactions were the result of cisapride interacting with other drugs.

The metabolism of cisapride mainly involves cytochrome P450 3A4. If this metabolism is inhibited by other drugs (see box), plasma concentrations of cisapride increase. This prolongs the QT interval on the ECG and can provoke arrhythmias. These arrhythmias include torsades de pointes and ventricular fibrillation.

Cisapride is contraindicated in patients who already have a prolonged QT interval. This abnormality can be congenital, but may be present in patients with:

- heart disease
- diabetes mellitus
- electrolyte abnormalities.

In the USA, cisapride was approved for the treatment of night-time heartburn due to gastro-oesophageal reflux disease. In Australia, the approved indication for reflux oesophagitis limits treatment with cisapride to six months or less.

Cisapride is contraindicated in combination with:

- macrolide antibiotics (e.g. erythromycin, clarithromycin)
- azole antifungals (e.g. fluconazole, itraconazole, ketaconazole, miconazole)
- HIV protease inhibitors (e.g. indinavir, ritonavir)
- nefazodone

Paracetamol: overused in childhood fever

Peter Hewson, Paediatrician, Geelong, Vic.

SYNOPSIS

Paracetamol has a mild beneficial effect on the symptoms of viral illness in childhood. However, the child may still remain unwell. Data suggest that fever may have an immunological benefit and that paracetamol may not decrease the number of recurrent febrile convulsions. There are good reasons, particularly related to toxicity, for limiting the use of paracetamol in children.

Index words: fever, toxicity, overdose, febrile seizures.

(Aust Prescr 2000;23:60–1)

Introduction

Some years ago Frank Shann warned us of the routine use of paracetamol in febrile young children.[1] (See also 'Paracetamol: use in children' Aust Prescr 1995;18:33–5). Evidence continues to mount against its indiscriminate use. The mild symptomatic benefit must be balanced against the increasing incidence of mistaken dosage and toxicity. As we live in a society which relies on drugs, both doctors and pharmacists should remind parents about the dangers of paracetamol.

Reasons for caution

Immunological

Humans and other animals given paracetamol are likely to shed virus for longer than controls.[2]

Toxicity

Several factors increase the risk of toxicity.

Cultural factors

It has previously been mistakenly accepted that all febrile children with infective illness require medication. We need to question this phenomenon as another example of society's reliance on drugs. The widespread use of antipyretic drugs (mainly paracetamol) means that mistakes in dosage will inevitably occur.

Psychological

Parental fever phobia has been documented.[3] Parents and doctors understandably need to feel they have something to offer sick, miserable children. However, cuddles, comfort and fluids are likely to be a safer and healthier alternative to drugs.

Drug toxicity

Whilst the frequency and dangers of intentional paracetamol overdosage are well known[4], until recently, only occasional accidental overdoses were reported. However, a recent report found that over a 13-year period 11 of 18 cases of fulminant hepatic failure were associated with accidental paracetamol ingestion. Two children died and one suffered serious neurological sequelae.[5] In another study of 47 children who were mistakenly given toxic doses of paracetamol 24 (55%) of the children died.[6] In the UK, package restrictions limiting the number of tablets per package have been introduced in an attempt to decrease the risk of self-poisoning. Similar steps may be necessary to minimise accidental overdosage in children.

The toxicity appears to occur when maximum total per kilogram daily doses are exceeded (90 mg/kg/day) and when repeated doses are given to children with pre-existing liver disease e.g. viral hepatitis.

Preparation variability

There are 23 non-tablet paracetamol preparations available on the Australian market. The available mixtures have various strengths including 24 mg/mL, 50 mg/mL and 100 mg/mL. An 8 kg infant only requires three mistaken 5 mL doses of the 100 mg/mL infant preparation (instead of the 24 mg/mL paediatric mixture) before a potentially hepatotoxic dose is reached (more than 150 mg/kg/24 hours).

Difficulty in proving benefit

The best study investigating the possible symptomatic benefits of paracetamol compared the drug to placebo.[7] The double-blind trial, using parental observations, analysed 225 febrile children's mood, comfort, appetite, fluid intake, activity and alertness. In the paracetamol treated group, activity and alertness significantly improved by one grade, mood and eating improved but not significantly, while drinking was worse. The parents' descriptions of comfort were equal in both groups. Interestingly, parents were unable to tell whether their child had been treated with paracetamol or placebo. The duration of fever was the same in both groups. Thus while some benefit was obtained, it does not justify its use if the risk of toxicity is real.

Difficulty in proving worth in preventing febrile convulsions

Febrile convulsions are associated with higher temperatures[8,9], but it is not known if lowering the temperature would have prevented these convulsions. Rate of rise of temperature is also thought important as 25% of convulsions seem to occur prior to, or at the commencement of, the fever. Previously, antipyretic prophylaxis has not been shown to be effective in reducing febrile seizures.[10,11]

Early data suggested antipyresis (including sponging) was of limited benefit in preventing recurrent febrile seizures. Further evidence now suggests that sponging does bring down the temperature faster than paracetamol or ibuprofen in the first 30 minutes, however, the effect of the drugs lasts for longer.[12]

Other medication options

Ibuprofen has been shown to be at least as effective as paracetamol[13,14] but is more likely to produce gastrointestinal and renal adverse effects. One suspects that if ibuprofen is used as widely as paracetamol then inevitably its toxicity and adverse effects will become a problem.

Further population studies are required to establish the safety and pitfalls of a regimen using a limited number of doses of paracetamol and/or ibuprofen.

While aspirin is also effective, its widespread use cannot be recommended because of its gastrointestinal and platelet effects, and an association with the rare Reye's syndrome.

Summary

- Paracetamol has a mild symptomatic benefit in childhood febrile illness
- Paracetamol toxicity data are increasingly worrying
- The various strengths of paracetamol mixtures are a major health hazard
- Paracetamol has not yet been shown to prevent febrile convulsions

Recommendations

1. There should be a concerted medical and pharmaceutical campaign to warn of the indiscriminate use of antipyretics in mild viral febrile illness in childhood.
2. An initial paracetamol dose of 15 mg/kg could be given, followed by three doses of 15 mg/kg over the next 24 hours if irritability continues.
3. No more than these four doses of paracetamol to be given for any one illness unless under medical or pharmacist supervision**.**
4. Each bottle of paracetamol mixture should have the mg/mL concentration in huge letters on the label, with the words '*Beware, potentially toxic*' on the 100 mg/mL bottle. Consideration should be given to withdrawal of all but the lowest strength.
5. Treat the child, not the thermometer.

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Self-test questions

The following statements are either true or false (answers on page 67)

5. Viral shedding times are reduced by paracetamol.
6. Antipyretic prophylaxis is effective at preventing febrile seizures.

Paracetamol: overused in childhood fever – a consumer perspective

Dell Horey, Maternity Alliance; and Helen Hopkins, Consumers' Health Forum

Dr Hewson's paper recommends a concerted medical and pharmaceutical campaign to warn against the indiscriminate use of medicines such as paracetamol to treat mild viral fevers in children. Perhaps a more appropriate focus for the campaign would be the safe and appropriate use of paracetamol in childhood illnesses, including information about other measures parents can use to help their child feel more comfortable while recovering.

Parents need the information in recommendations 2 to 4 of the paper. They need to know what dose of paracetamol to give,

how frequently this dose can be safely given and how long they should continue treatment before consulting a health professional again. It is also extremely important that parents and other carers, including grandparents and other family members who might help to supervise a sick child, know the importance of checking the strength of the paracetamol mixtures and the correct dose. People need to be aware that too much paracetamol may be toxic. Stressing how important it is to store the medicine safely where children cannot reach it would reinforce the message about the possibility of harmful overdose.

Changing family and social patterns may mean parents are turning to their general practitioner or pharmacist for practical advice and reassurance that previously came from family or friends. As well as reminding parents about the appropriate use of paracetamol and the dangers of overdose, doctors may need to provide practical advice about other care measures. It is important that doctors check that parents understand what is really meant by directions such as 'keep up the fluids', 'sponge if they are getting too hot' and 'plenty of rest'. Parents want the best for their children, but they may need guidance about what that comprises.

Recognising serious illness in babies

Useful information for parents on how to recognise serious illness in babies has been prepared by Professor Peter Hewson. It can be found in the internet version of Australian Prescriber Vol 23 No 3.

Treating head lice

Orli Wargon, Dermatologist, Sydney

SYNOPSIS

Head lice (Pediculosis capitis) is a common condition in children. It is usually detected in schools, when children are seen scratching their heads. The diagnosis can be confirmed by finding live adult lice or viable eggs. Lice are usually adequately treated with an over-the-counter topical permethrin preparation. Treatment failure results from inadequate therapy, re-infection, resistance to the insecticide or an underlying immunosuppression. Prescription drugs such as ivermectin may be needed in more difficult cases.

Index words: Pediculosis capitis, permethrin, maldison, ivermectin.

(Aust Prescr 2000;23:62–3)

Background

Blood sucking lice of the order Anoplura are successful obligate ectoparasites of humans.[1] *Pediculus humanus capitis*, the head louse, is a distinct clinical form. It clings to hair with its claws and feeds by sucking blood from the scalp. Its life cycle is about 17–20 days with eggs hatching 7–10 days after they are laid, and adults are fully developed about 10 days later.[2] Head lice spread by head to head contact.

Diagnosis

A child found to be scratching their head at school is often checked by the teacher, school nurse or public health personnel. If they are well trained or experienced they will look for live adult lice on the crown of the scalp, immature nymphs or viable eggs. Empty shells or nits adhere to the hair, 1 cm from the scalp surface, with a glue-like substance. They are unlike seborrhoeic scales, hair casts and hair spray, which are easily brushed off.

Treatment

Three types of insecticide are marketed worldwide. In my local pharmacies all insecticide products for head lice are either permethrins 10 mg/mL as shampoos, lotions or creme rinses or maldison products with 0.5% alcohol bases, 1% foam bases, shampoos or soaking solutions.

Alcoholic lotions have greater ovicidal activity[3], the creme rinses are less ovicidal than liquids and lotions[4] and shampoo formulations have low ovicidal activity and may not kill eggs.[5]

In theory, one application should kill all lice and eggs. However, *in vitro* studies[3,4] suggest that some eggs can survive and require a second application after seven days. Surviving eggs can cause reinfestation if not removed.

Everyone who has been in contact with the patient should be examined and treated if affected. It is also advisable to wash all clothes, head gear, towels, bed linen, combs and brushes as head lice can survive away from the human host for about three days and eggs can survive for up to 10 days.

Permethrin (3 phenoxybenzyl cis trans3(2,2-dichlorvinyl)-2,2 dimethyl cyclopropane carboxylate) is a synthetic pyrethroid. It acts on parasitic nerve cell membranes and has low mammalian toxicity, but incomplete ovicidal properties.[6] Patients apply permethrin to the hair for 10 minutes then wash

it off. As permethrin is not ovicidal, treatment may need to be repeated after a week.

Maldison is a moderately toxic organophosphate insecticide and a fast-acting ovicide which acts by non-reversibly blocking acetylcholine.[6] Patients apply maldison to their hair then wash it off after 12 hours.

Evidence of therapeutic efficacy

The most often quoted systematic review of the topical treatments for head lice[7] concludes that there is only sufficient evidence to support the efficacy of permethrin. However, a recent review by the Cochrane Collaboration could not make a recommendation about which treatment is best.[8]

Other therapy

A visit to the local pharmacy revealed naturally occurring substances including echinacea and melaleuca oil being marketed to treat head lice as well as an electronic lice comb. Reports supporting mechanical methods are anecdotal.[9]

Other anecdotal reports include the use of petrolatum used for its occlusion properties.[10]

Ivermectin is an antiparasitic agent used extensively in veterinary practice and more recently has been used in human medicine. The mode of action is via chloride ion channels in cell membranes, leading to an influx of negatively charged ions that block cellular action potentials and cause muscle paralysis. Much higher concentrations are required to affect neurological function in mammals than in parasites. Open studies on oral ivermectin, using a single 200 microgram/kg oral dose with or without a second dose at 10 days[11,12] suggest that further trials are warranted.

Resistance

In the UK resistance to permethrin is widespread. In Australia resistance to maldison has been reported.[13]

Safety and adverse effects

If used correctly the treatments have no major adverse effects. Patients may develop stinging or tingling of the skin, erythema of the scalp or red eyes. Maldison does not have the potential to cause a specific polyneuropathy as, unlike other organophosphates, it does not bind to the relevant target protein.[14]

Contacts

Parents are generally shocked when they discover that their children have head lice. It often becomes very difficult to trace contacts as parents do not wish to admit to their friends and family that their children have lice, because of the associated embarrassment and social stigma. On a practical level, whenever a school discovers even a few eggs, the whole class is treated and the recommendation from schools is often that the entire family also be treated.

Conclusion

Systematic review shows that only topical permethrin is efficacious for head lice. Clinical experience and information on the ovicidal properties of maldison suggests that further randomised controlled clinical trials are necessary to assess the efficacy of this alternative and cheaper insecticide. Immunosuppression may require the consideration of other medications and again appropriate clinical trials are needed.

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Self-test questions

The following statements are either true or false (answers on page 67)

7. Resistance to permethrin has made it ineffective against head lice in Australia.
8. Alcoholic lotion may have greater ovicidal activity than the shampoos used to treat head lice.

Australian Prescriber on the Internet

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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 Board believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Board is prepared to do this. Before new drugs are prescribed, the Board believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Orlistat

Xenical (Roche)

120 mg capsules

Approved indication: obesity

Australian Medicines Handbook Section 12.10

Patients with a body mass index (see box) of 30 or more can be difficult to treat. (See 'Obesity and its management' Aust Prescr 1999;22:12–6). These patients may benefit from orlistat in combination with a low calorie diet.

Orlistat inhibits lipase in the gut. This reduces the absorption of fat by approximately 30%. The decreased absorption of calories eventually leads to weight loss.

Two placebo-controlled trials have assessed the effect of orlistat on several hundred patients.[1,2] The patients were given a diet which contained fewer calories than their daily energy needs. They took orlistat or placebo for a year then were re-randomised and switched to a diet designed to maintain their weight. The patients were followed up for a further year. During the first year of the trials the patients in one study lost an average of 10.3 kg with orlistat and 6.1 kg with placebo.[1] In the second study the mean weight losses were 8.7 kg and 5.8 kg.[2] During the second year of the trials patients who had been re-randomised to placebo put weight back on. Those who had continued on orlistat regained less weight. Some of the patients switched from placebo to orlistat lost a small amount of weight (0.9 kg).[1]

The recommended dose is 120 mg with each main meal. Very little of the dose is absorbed. The effect of orlistat on faecal fat can be seen within two days. Some metabolism may take place within the wall of the gut, but most of the drug is excreted unchanged in the faeces.

As orlistat reduces fat absorption most patients develop adverse effects including fatty stools, loose stools, faecal urgency, flatulence and incontinence. Most of the approximately 9% of patients who discontinued treatment because of adverse effects did so because of gastrointestinal problems.

Although orlistat reduces cholesterol concentrations, it also reduces the absorption of fat-soluble vitamins. Reduced vitamin K absorption could alter the control of patients taking warfarin. In the clinical trials no deficiencies developed so vitamin supplements may not be needed.

Orlistat increases the plasma concentration of pravastatin, but does not alter the pharmacokinetics of digoxin, glibenclamide or phenytoin. Acarbose, which acts on intestinal glucosidase enzymes, should not be prescribed with orlistat as the potential for interactions has not been studied.

Pooled data have revealed more cases of breast cancer in women taking orlistat than in those taking a placebo. The clinical relevance of this observation is uncertain, as is the effect of exposing the colonic mucosa to large amounts of fat.

The clinical trials show that orlistat will enable patients to lose approximately 4 kg more than they would by dieting. This difference is reduced when the patient is given a eucaloric (weight-maintaining) diet. Continuing a hypocaloric diet for two years is the subject of more research. The drug is likely to be even less effective if the patient does not change their lifestyle. One approach is to stop orlistat if the patient has not lost 5% of their weight after 12 weeks of treatment.

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$$\text{Body mass index} = \frac{\text{weight in kilograms}}{(\text{height in metres})^2}$$

Quetiapine fumarate

Seroquel (AstraZeneca)

25 mg, 100 mg and 200 mg tablets

Approved indication: schizophrenia

Australian Medicines Handbook Section 18.2.2

Quetiapine is one of the 'new antipsychotics'.[1] It acts by antagonising neurotransmitters at several receptors. The affinity of quetiapine for dopamine receptors (D_2) is relatively low compared to its affinity for $5HT_2$ receptors. It also has little affinity for cholinergic receptors.

Patients take quetiapine twice a day. For the first four days of treatment the dose is increased each day. It is then adjusted according to the patient's response.

Each dose is rapidly absorbed and widely distributed. Quetiapine is extensively metabolised by the liver and then excreted in the urine and faeces. Cytochrome P450 (CYP 3A4) is probably primarily responsible for the metabolism. Extra caution is needed if quetiapine is given with inhibitors of this enzyme including some antidepressants. The clearance of quetiapine will be increased by drugs such as phenytoin which induce hepatic enzymes. Hepatic or renal impairment will reduce the clearance of quetiapine. Although its half-life is seven hours, quetiapine occupies the $5HT_2$ and D_2 receptors for up to 12 hours.

Quetiapine can cause postural hypotension so it should be used with caution in patients with cardiovascular disease. Other common adverse effects are somnolence, dry mouth, constipation, dizziness and altered liver function. Quetiapine may mildly prolong the QT_c interval so caution is needed if it is prescribed with other drugs which have this effect. In the USA patients are advised to have their eyes checked every six months because cataracts developed in some animal studies. This precaution is not included in the Australian product information.

Short-term studies have found quetiapine to be as effective as chlorpromazine and haloperidol, but it has a lower incidence of dystonia. In a comparison with risperidone, quetiapine was effective for the treatment of exacerbations of schizophrenia. Approximately 33% of the patients taking quetiapine and 38% of those taking risperidone had at least a 40% reduction in their positive and negative symptom scores. The long-term effectiveness of quetiapine requires further study.

A Cochrane review has found that quetiapine causes no more extrapyramidal effects than placebo and may be more effective. However, the review concludes that more studies are needed before quetiapine can be recommended. Many of the studies in the review had high dropout rates (48–61%) which make the results difficult to interpret.[2]

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Quinupristin/dalfopristin

Synercid IV (Rhone-Poulenc Rorer)

vials containing 500 mg for reconstitution

Approved indication: specified infections

Australian Medicines Handbook Section 5.1.13

Overuse of antibiotics has contributed to the development of resistant organisms. There is an urgent need for new treatments for the vancomycin-resistant enterococci which have recently emerged. The streptogramin antibiotics may have a role.

Quinupristin and dalfopristin are derived from the pristinamycins. The combination of the two drugs acts synergistically to inhibit bacterial protein synthesis. This makes the combination bactericidal. It is mainly effective against Gram-positive aerobic bacteria.

After infusion over an hour the combination is rapidly metabolised. These metabolites contribute to the antimicrobial actions. Most of the combination and its metabolites are excreted in the faeces.

Although many bacteria are susceptible to quinupristin and dalfopristin, the combination should be reserved for the treatment of vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* (MRSA). As the combination often has to be used in an emergency where no other treatment is available, the efficacy of the combination is difficult to evaluate. In one case control study the mortality was lower in the control group, but fewer patients given the combination died as a result of vancomycin-resistant infection.[1] In general, treatment of infections due to MRSA will have a higher success rate.

Approximately 11% of patients have to discontinue treatment because of reactions at the infusion site. They commonly experience pain, inflammation and oedema. To try to reduce these reactions the intravenous line should be flushed with 5% glucose. Flushing with heparin or saline is not recommended as the quinupristin/dalfopristin combination is incompatible with saline.

Systemic adverse reactions caused 6% of patients to stop treatment. These reactions include arthralgia, myalgia, nausea, vomiting and rashes. Liver function may also be affected.

The quinupristin/dalfopristin combination inhibits the enzyme cytochrome CYP 3A4. It can therefore inhibit the metabolism of drugs such as midazolam and nifedipine.

While this new product may help some patients with severe infections, it is important not to overlook the basic principles of management. For example, surgical debridement and the removal of infected devices such as catheters may be essential for successful treatment.[2]

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2. Lai KK. Treatment of vancomycin-resistant *Enterococcus faecium* infections. Arch Intern Med 1996;156:2579–84.

Tamsulosin hydrochloride

Flomax (CSL)

400 microgram modified-release capsules

Approved indication: benign prostatic hypertrophy

Australian Medicines Handbook Section 13.2.1

$Alpha_1$ adrenoceptor antagonists, such as prazosin and terazosin, can be used to treat the symptoms of benign prostatic hypertrophy.[1] They act by reducing smooth muscle tone in the prostate and bladder neck. Tamsulosin acts in the same way, but is claimed to be more selective for the $alpha_1$ adrenoceptors in the prostate.

The once-daily dose is absorbed slowly. Although food reduces the bioavailability, it is recommended that the dose is taken 30 minutes after breakfast. Most of the drug is metabolised by the liver and the metabolites are excreted in the urine.

In placebo-controlled trials tamsulosin improved the maximum urine flow rates. A comparison of tamsulosin with alfuzosin (a non-selective $alpha_1$ adrenoceptor antagonist), found that both drugs increased maximum flow rate by 1.6 mL/second.[2] Similar results were seen in a comparison with terazosin.[3]

Blocking the $alpha_1$ adrenoceptors reduces the blood pressure, but hypotension is not a frequent problem with tamsulosin. Symptoms, such as dizziness, suggestive of low blood pressure occurred in 9.2% of the tamsulosin group and 10.5% of the

alfuzosin group.[2] In the placebo-controlled studies, the only adverse event which occurred significantly more with tamsulosin was abnormal ejaculation. This affected almost 7% of the men taking tamsulosin.

Overall, tamsulosin is as effective as other drugs in its class, but may have fewer adverse effects. This may be an advantage if tamsulosin does not cost more than its competitors.

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NEW FORMULATIONS

Beclomethasone dipropionate

Qvar (3M Pharmaceuticals)

inhaler and autohaler delivering 50 microgram or 100 microgram per inhalation

Approved indication: asthma prophylaxis

Australian Medicines Handbook Section 19.2

This new formulation delivers beclomethasone dipropionate using a propellant which does not contain chlorofluorocarbons. In addition, the beclomethasone is in solution rather than in suspension. As a result, this formulation produces much smaller droplets than the particles produced by conventional inhalers. This results in a bigger dose being deposited in the lungs.

Lower doses of this formulation are needed to produce the same effects as a conventional inhaler. A patient currently inhaling a total daily dose of 400 microgram of beclomethasone will probably need only 200 microgram of the new formulation. As the delivery devices only provide half the dose per inhalation as that delivered by conventional puffers, a patient will take the same number of puffs as they currently do with inhalers delivering 100 microgram per inhalation.

Follitropin beta

Puregon (Organon)

vials containing 50 IU/0.5 mL, 100 IU/0.5 mL, 150 IU/0.5 mL and 200 IU/0.5 mL solution for injection

Haemophilus influenzae type b

Liquid PedvaxHIB (CSL)

7.5 microgram vials

Mycophenolate mofetil

CellCept (Roche)

500 mg powder for infusion

NEW STRENGTHS

Cabergoline

Cabaser (Pharmacia & Upjohn)

1 mg, 2 mg and 4 mg tablets

Interferon beta-1a (rch)

Rebif (Serono)

22 microgram and 44 microgram pre-filled syringes

Epoetin alfa

Eprex (Janssen-Cilag)

vials containing 40 000 IU/mL

Ganciclovir

Cymevene (Roche)

500 mg capsules

NEW COMBINATIONS

Dipyridamole/aspirin

Asantin SR (Boehringer Ingelheim)

sustained-release capsules containing 200 mg dipyridamole and 25 mg aspirin

Haemophilus influenzae type b/hepatitis B

Comvax (CSL)

0.5 mL single dose vials containing 7.5 microgram Haemophilus influenzae type b and 5 microgram hepatitis B surface antigen

NEW PROPRIETARY BRANDS

Amoxycillin trihydrate

DBL Amoxycillin (Faulding)

250 mg and 500 mg capsules

Amoxycillin/clavulanic acid

Ausclav products (Sigma)

tablets, and powder for syrup

Clozapine

SBPA Clozapine (SBPA)

25 mg and 100 mg tablets

Fluoxetine hydrochloride

Lovan Liquid (Alphapharm)

20 mg/5 mL

SBPA Fluoxetine (SBPA)
20 mg capsules

Moclobemide

Arima (Alphapharm)

300 mg tablets

Ranitidine hydrochloride

Ausran (Sigma)

150 mg and 300 mg tablets

The painting on the cover

Australian Prescriber's international readership is growing. To identify the journal as distinctively Australian, the cover features an Australian Aboriginal painting. Jennifer Summerfield, the Aboriginal artist, lives in the centre of Australia, and created the painting in 1998 for National Medicines Week. The central icon is of a gathering of people sitting around a fire, talking. Jennifer's story follows:

I'm Jennifer Summerfield. I am a Pitjantjatjara woman. I live at Umuwa on the Anangu Pitjantjatjara Lands in the north west of South Australia. I work as an Anangu Health Worker for Nganampa Health Council. I am the artist who did the painting for National Medicines Week.

This painting is about using medicine properly, especially for older people. Store your tablets in a cool place or in your bag away from kids and other old people. Take your medication at the right time with the pictures of the sun showing in the morning, at midday and in the evening. Don't throw your medicines on the ground. If you don't take your tablets you may be blind or never walk again. This is what the painting is about.

The older people in the middle of the painting are keeping their medicine safe in a bag. The people in each corner have not taken their medicines and have become blind or crippled. There is the sun to tell them to take their medicine, in the morning, at midday and in the evening. People at the middle top of the painting are taking their medicines. People down the bottom of the painting sometimes take their medicine and sometimes throw it away. Then young kids can find that medicine and take it and become sick. The two black paintings show that when people don't take their medicine properly, they die. Around the outside of the painting are a few bush medicines.

Answers to self-test questions

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

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