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Editorial

Drug price reforms: the new F1–F2 bifurcation

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Key words: generic drugs, Pharmaceutical Benefits Scheme, reference pricing.

(Aust Prescr 2007;30:138–40)

Significant changes to the Pharmaceutical Benefits Scheme (PBS) are underway. The Australian Parliament recently passed the *National Health Amendment (Pharmaceutical Benefits Scheme) Act 2007*. At the core of this Act are new sections (85AB and 85AC) to the *National Health Act 1953*. These had the effect of dividing, from 1 August 2007, the PBS into two separate formularies – F1, which mostly contains single brand medicines, and F2, which mostly contains multiple brand, mainly generic, medicines (see box).

These complex changes aim to 'recognise the importance of world-class life-enhancing drugs to patients', protect patients from higher costs and get better value from market competition between medicines with multiple brands.[1] The changes may allow PBS and patient savings through lower priced generics, but their impact on the price of patented single-brand medicines is uncertain in our view. Chiefly this is because in future most new patented medicines will be listed in F1 with reduced reference pricing thereafter.

In Australia, overall pharmacy fees vary for products priced below the general patient co-payment ($30.70), and a Choice survey in August 2006 found a wide range in the prices pharmacies charge.[2] This was due to varied application of permissible fees under the Fourth Community Pharmacy Agreement. Australian prices for generic drugs were higher than in countries with larger markets or processes such as competitive tender. In Australia, the price a patient paid for a medicine below the general co-payment depended on the manufacturer's price, wholesale and pharmacy markups, and dispensing fees. Manufacturers could offer generic drugs to pharmacists at large discounts to the prices paid by the PBS. The government therefore considered that it had been paying too much for these medicines. In our view, this consideration unfortunately outweighed policy concerns about the importance of maintaining the full integrity of PBS reference pricing.[1,3]

PBS prices will now be influenced by which formulary a drug is in (Table 1). To add to the complexity, the criteria do not apply to single brand combination products, as they could have components in different formularies.

Drugs which are in F2 are categorised according to the size of the discounts to pharmacy as at 1 October 2006. When the discount was less than 25% the drug is in F2A. Drugs which were heavily discounted by more than 25% are in F2T. The suppliers of drugs in these categories will have to disclose to the Department of Health and Ageing the actual price at which they sell a brand to wholesalers or pharmacies. This requirement applies to new brands of F2A medicines from 1 August 2007 and to new brands of F2T medicines from 1 January 2011. The aim is to ensure that the PBS price is based on the actual supplier price to wholesalers or pharmacy.

A price reduction of 12.5% at the time of PBS listing of the first generic brand of a drug has been required since 2005, and will continue to apply. From 1 August 2008, there will be

F1 contains drugs with a single brand, however it does not contain those single brand drugs that are interchangeable on an individual patient basis with drugs that have multiple brands or single brand combination items.

F2 contains drugs with multiple brands and those single brand drugs that are interchangeable at the individual patient level with drugs that have multiple brands.

In this issue…

There are many balances in medicine. Debra Kennedy writes on balancing the use of antipsychotic drugs during pregnancy with the risk of congenital abnormalities, while Stephen Reddel describes how the benefits of immunosuppression for myasthenia gravis have to be balanced against the adverse effects.

Paul Komesaroff discusses the delicate balance between health professionals and the pharmaceutical industry. Sometimes this balance is upset and can result in promotional activity breaching the Medicines Australia Code of Conduct.

Governments have to balance health budgets and there have been recent reforms of the Pharmaceutical Benefits Scheme. Tom Faunce and Hans Lofgren give their view of the changes.

Table 1

Examples of drugs in the new Pharmaceutical Benefits Scheme formularies *

F1	F2A	F2T
atorvastatin	fluvastatin	simvastatin
bisoprolol	carvedilol	metoprolol
cefuroxime	cephazolin	cephalexin
celecoxib	ketoprofen	naproxen
doxorubicin (pegylated liposomal)	doxorubicin	–
levobunolol	betaxolol	timolol
olanzapine	clozapine	–
reboxetine	–	citalopram, fluvoxamine
salmeterol	–	salbutamol
ticarcillin with clavulanic acid	–	amoxycillin with clavulanic acid
zolmitriptan	sumatriptan	–
–	oxazepam	diazepam

* as at 2007 Sep 11

further compulsory price reductions for F2 drugs: a drop of 2% per year for three years for drugs in F2A, and a one-off price reduction of 25% for drugs in F2T (on 1 August 2008). There are no mandatory price cuts for drugs in F1. There will be compensation for wholesalers and pharmacists for the loss of income from statutory F2 price reductions. For example, from 1 August 2008 pharmacists will receive $1.50 each time they dispense a substitutable brand that costs the patient no more than the co-payment.

Many generic drugs are already priced below the general patient co-payment, and the price reductions to drugs in F2 are expected to result in more drugs falling under the co-payment. The Pharmacy Guild of Australia estimates that the price of more than 400 brands, below the general PBS co-payment, will fall.[4] Complete price and volume data will not be available for drugs once they fall below the general PBS co-payment. Although the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee (PBAC) receives some data, prescriptions for these drugs do not appear in official statistics of PBS expenditure.

The Minister for Health and Ageing has stated that the role of the PBAC, in assessing cost-effectiveness and cost minimisation and then advising the Minister on the listing of drugs on the PBS, is not affected by the legislation.[5] Yet the responsibilities of the PBAC will be formally extended to include advice to the Minister on exemptions from mandatory price reductions. It will also advise on whether drugs are 'interchangeable on an individual patient basis', a standard more uncertain than the previous, more evidence-based, 'equivalence' tests used to determine Therapeutic Group Premiums for reference pricing. Drugs appearing 'equivalent' on average effects measured in clinical trials, for example, may not be 'interchangeable' for an individual patient.[3] For example, while citalopram and escitalopram were in the same reference pricing group, escitalopram was initially included in F1 and citalopram was in F2T.[6]

The principle of reference pricing, that drugs with identical or similar clinical outcomes should have similar prices, is integral to the architecture of the PBS and the respect it has achieved internationally. In our view, the separation of listed drugs into two groups (F1 and F2), however this is implemented, weakens the role and fiscal benefits of referencing pricing in the PBS.

Although there will be reference pricing within F1, an effect of the changes is to insulate high priced single brand (patented) F1 drugs from price cuts and from the reference pricing that applied under previous PBS processes.[3] Once a new drug is listed on the PBS as F1, its price will not be linked to the price of any similar drug in F2. F1 drugs are not interchangeable at the individual patient level with drugs that have multiple brands, so the manufacturers may be able to retain their original PBS price until the listing of a bioequivalent brand satisfies the new standards for a shift to F2. Reductions in F2 drug prices will not affect F1 prices, even where the therapeutic effect of an F2 medicine is similar though not necessarily 'interchangeable at the individual patient level'.

It is our opinion that the creation of the F1 category will, over time, result in higher prices for some patented drugs than would have been the case under previous PBS arrangements. The government's rationale for this change appears to be that failure to make such changes could result in large 'special patient contributions' or the withdrawal of single-source products from the PBS.[5]

The government, Medicines Australia, the Consumers' Health Forum and several professional groups view the F1–F2 changes as a means of achieving lower prices and greater transparency in the generics market.[6] However, the expectation of price reductions flowing to consumers is premised on trust in effective competition among retail pharmacies. If direct benefits to

patients from lower generic medicines prices or government support for an Australian generics industry had been the primary policy objectives, then more broadly framed legislation could have included pharmacy rewards for meeting generic dispensing targets, an incentive period of market exclusivity for the first generic market entrant, and financial incentives for patients who elect to be dispensed a generic, or for patients whose doctors are prepared to prescribe generic drugs. The role of the patented pharmaceutical industry in promoting and framing these changes is also controversial[7], particularly if the new system allows price reductions to be deferred for some products.

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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.

Managing chronic obstructive pulmonary disease

Editor, – I wonder why alpha-1 antitrypsin deficiency was not mentioned in the article on 'Managing chronic obstructive pulmonary disease' (Aust Prescr 2007;30:59–63). There is worldwide evidence that this genetic problem is much more common than it was thought in the past. In fact the World Health Organization advises that everybody with chronic obstructive pulmonary disease should be tested for alpha-1 antitrypsin deficiency, especially since there is treatment for it, though no cure.

Michael A Kennedy
General practitioner, retired
Vaucluse, NSW

Professor Michael Abramson, Associate Professor Christine McDonald and Professor Nicholas Glasgow, authors of the article, comment:

We thank Dr Kennedy for drawing attention to the role of alpha-1 antitrypsin deficiency in chronic obstructive pulmonary disease (COPD). This genetic disorder is evidence for the elastase–antielastase hypothesis of emphysema. The prevalence of severe homozygous (ZZ) alpha-1 antitrypsin deficiency has been estimated at around 1/4,727 in European populations.[1] Although 75–85% of such individuals will develop emphysema, tobacco smoking is still the most important risk factor for COPD even in this group. Targeted screening suggests 1–4.5% of patients with COPD have underlying severe alpha-1 antitrypsin deficiency.[2] The index of suspicion should be high in younger patients with predominantly basal disease and a family history. The diagnosis can be made by measuring serum levels of alpha-1 trypsin. If they are reduced, genotyping should be performed. Whether people who are heterozygous (MZ, MS) are also at an increased risk of COPD remains controversial.

Although replacement therapy is available, trials conducted to date have been underpowered to confirm beneficial effects on the rate of decline in lung function or on survival. One placebo-controlled randomised trial suggested some reduction in the loss of lung tissue as assessed by CT scan.[3] Therapy involves intravenous administration of alpha-1 trypsin concentrate purified by fractionation of normal human plasma or recombinant alpha-1 trypsin. These products can restore alpha-1 trypsin levels above the protective threshold for some weeks. Replacement therapy is available through the Special Access Scheme. A national patient support group can be contacted at http://health.groups.yahoo.com/group/Alpha1-ANZ.

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A century of concern about complementary medicines

Editor, –The comment in *Australian Prescriber* (2007;30:91) draws unhelpful and misleading parallels between complementary medicines today and 'dangerous and useless medicines' available 100 years ago.

The author is right to point to the establishment of the Therapeutic Goods Administration (TGA) as an important landmark for the regulation of pharmaceuticals and complementary medicines. The Complementary Healthcare Council (CHC) fully supports a regulatory process that safeguards consumer interests. However, to suggest that complementary medicines as therapeutic goods are somehow compromised by false or misleading advertising or that barriers exist to understanding them because sponsors hide behind 'commercial-in-confidence' is inaccurate.

All advertisements for therapeutic goods are subject to the Therapeutic Goods, Trade Practices and other relevant laws. The Therapeutic Goods Advertising Code, which applies to advertisements directed to consumers and where sanctions apply for breaches, requires material to be truthful, balanced, not contain misleading or exaggerated claims, and all descriptions, claims and comparisons must be able to be substantiated.

With regard to 'commercial-in-confidence', it is hard to see how concerns regarding transparency would not equally apply to pharmaceutical companies. Companies responsible for marketing products are obliged to make available all evidence regarding claims in relation to their products, should they be asked to do so by the TGA.

What does concern the CHC, is the outdated attitudes demonstrated towards complementary medicines, despite repeated and compelling evidence demonstrating their health benefits. Let's imagine for one moment the implication for pregnant women globally, if folate supplementation in preventing neural tube defects had not become accepted mainstream practice.

Tony Lewis
Executive Director
Complementary Healthcare Council
Canberra

Dr JS Dowden, the author of the comment, responds:

There is Level 1 evidence to support the use of folate supplements by women planning pregnancy. It is doubtful that such strong evidence exists for many complementary products. Given the plethora of complementary medicines it is unlikely that the TGA has the resources to assess the evidence for many of these products. Evidence of a product's safety and efficacy should not be 'commercial-in-confidence' irrespective of whether it is a prescription or a non-prescription drug.

Despite the somewhat confusing regulatory system, there are plenty of complaints about the advertising of complementary medicines.[1] The usual sanction for an unacceptable advertisement seems to be a request for the advertisement to be withdrawn, but it is unclear how effectively this is enforced.[2]

Octavius Beale was concerned about the outrageous claims being made by medicines manufacturers in the early 20th century.[3] The number of justified complaints in 2007 suggests that there is still a problem.[1]

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Magnesium

Editor, – In the article on magnesium by Dr Wu and Dr Carter (Aust Prescr 2007;30:102–5) there is little attempt to address the issue of cramps and magnesium ingestion by the public. My clinical experience has been that every aged patient who has any problem with cramping, has either tried, or is on, oral magnesium usually from the supermarket or health store. This is often magnesium phosphate.

Could the authors comment on the issue of cramping and adults over the age of fifty years? Is there any evidence that lack of magnesium causes this, or that oral magnesium is of any benefit?

Chris Commens
Dermatologist
Pennant Hills, NSW

Dr J Wu and Dr A Carter, authors of the article, comment:

In response to Professor Commens, a literature search performed in consultation with our pharmacology unit failed to raise any conclusive evidence that magnesium phosphate is useful in preventing cramps in the elderly. This is not to say that biochemically proven hypomagnesaemia would not respond to supplementation, in the same way as hypocalcaemia or hypokalaemia would require calcium or potassium supplementation respectively.

Top 10 drugs

These tables show the top 10 subsidised drugs in 2006–07. The tables do not include private prescriptions.

Table 1

Top 10 drugs supplied by DDD*/1000 pop/day †

Drug	PBS/RPBS ‡
1. atorvastatin	131.799
2. simvastatin	58.072
3. ramipril	30.451
4. perindopril	21.681
5. aspirin	18.01
6. omeprazole	17.996
7. frusemide	17.984
8. irbesartan	17.28
9. salbutamol	17.116
10. esomeprazole	16.802

Table 2

Top 10 drugs by prescription counts †

Drug	PBS/RPBS ‡
1. atorvastatin	10 000 495
2. simvastatin	6 231 212
3. esomeprazole	4 428 530
4. omeprazole	3 882 359
5. paracetamol	3 754 140
6. perindopril	3 633 536
7. atenolol	3 217 151
8. irbesartan	2 989 359
9. pantoprazole	2 922 724
10. metformin hydrochloride	2 822 776

Table 3

Top 10 drugs by cost to Government †

Drug	Cost to Government ($A)	DDD/1000/day PBS/RPBS ‡	Prescriptions PBS/RPBS ‡
1. atorvastatin	562 234 406	131.799	10 000 495
2. simvastatin	309 227 367	58.072	6 231 212
3. clopidogrel	179 983 732	9.219	2 404 361
4. esomeprazole	161 102 420	16.802	4 428 530
5. olanzapine	157 471 533	3.073	775 475
6. salmeterol and fluticasone	157 239 113	– §	2 789 814
7. omeprazole	114 030 881	17.996	3 882 359
8. pravastatin	93 389 809	13.537	1 870 879
9. venlafaxine	93 329 210	11.987	2 318 531
10. tiotropium bromide	91 223 529	5.289	1 303 682

* 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.

† Based on date of supply

‡ PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

§ Combination drugs do not have a DDD allocated

Source: Drug Utilisation Sub-Committee (DUSC) Drug Utilisation Database, as at 11 October 2007.

NPS RADAR December 2007

Strontium ranelate: The PBS listing for the osteoporosis drug strontium ranelate has been extended to allow treatment of postmenopausal women without an existing fracture and a bone mineral density T-score ≤ –3.0 (primary prevention). The latest issue of *NPS RADAR* describes the place in therapy of strontium relative to other anti-resorptive agents.

It also contains information on:

- the listing of the anticonvulsant drug topiramate as an alternative treatment for migraine prevention, for adults unable to tolerate beta blockers or pizotifen
- updated safety information for the glitazones – rosiglitazone and pioglitazone.

See the complete reviews at www.npsradar.org.au

Drugs for the doctor's bag

Andrew Baird, General Practitioner, Brighton, Victoria

Summary

The doctor's bag should contain drugs for medical emergencies that may occur in the community. Most of these drugs are provided under the Pharmaceutical Benefits Scheme and can be ordered free of charge through a pharmacist. General practice accreditation now requires that clinics have appropriate emergency drugs as well as oxygen and a bag-valve-mask system. Practices should also have an up-to-date logbook detailing the emergency drug stocks and a system for checking that the drugs have not expired.

Key words: medical emergencies, Pharmaceutical Benefits Scheme.

(Aust Prescr 2007;30:143–6)

Introduction

Traditionally the doctor's bag contains drugs and equipment for managing medical emergencies that present in the clinic or in the community.[1,2,3] The frequency and type of emergencies that occur depend on the location and nature of the practice. With the increasing availability of skilled Mobile Intensive Care Ambulance (MICA) paramedics as 'first responders', many general practitioners have become less involved in managing emergencies. However, in rural and remote areas the doctor will often be the 'first responder' and may be working with volunteer ambulance crews.

What to carry

Doctors should consider the medical emergencies that they may encounter in their practice and select appropriate drugs for their doctor's bag (Table 1). Many of these drugs are provided under the Pharmaceutical Benefits Scheme (PBS) as Emergency drug (Doctor's bag) supplies.[4] Most of them are injectable. However, there are some non-injectable drugs which are useful in emergencies, such as soluble aspirin, glyceryl trinitrate (sublingual spray) and salbutamol aerosol.

Doctors can submit a monthly order form* to a pharmacist for the supply of PBS doctor's bag emergency drugs at no cost. Some PBS drugs are supplied as paired alternatives. These include hydrocortisone or dexamethasone and metoclopramide or prochlorperazine. A group practice can have all of these drugs available if doctors agree to order one or other item in each pair. A drug can only be requested if the doctor holds less than the maximum quantity provided under the PBS, or to replace date-expired drugs.

Some drugs which are useful for emergencies are not provided under the PBS (Table 1). Doctors may obtain these as private items by submitting a written order to a pharmacist. These drugs include:

- oral drugs such as aspirin, analgesics, diazepam, antibiotics, prednisolone
- non-steroidal anti-inflammatory drugs (NSAIDs) for rectal or intramuscular use
- glucose 50%
- ceftriaxone
- midazolam
- ergometrine.

It is also useful to carry at least one 1 L bag of normal saline, and a supply of normal saline and water for injections.

Current practice guidelines

Emergency drugs available through the PBS sometimes differ from those recommended by Australian treatment guidelines. For example, the use of parenteral chlorpromazine is not recommended by the Therapeutic Guidelines because it can cause serious hypotension. Instead, oral preparations of risperidone, olanzapine or haloperidol are recommended for behavioural emergencies if oral diazepam is not effective.[5] Only injectable forms of diazepam and haloperidol are provided as emergency drugs by the PBS.

Lignocaine is a PBS doctor's bag item. However, other treatments for sustained ventricular tachycardia may be preferred.[5]

Precautions with emergency drugs

With sedating drugs, there is a risk of death from respiratory depression, especially when given intravenously. It is therefore important to keep the patient under observation after administration of these drugs.

Pethidine is no longer supplied as a doctor's bag item.[6] Instead, an injectable form of tramadol is now available through the PBS. Tramadol should not be used in patients taking a serotonergic antidepressant because of the risk of serotonin syndrome.

Doctors should be aware that ketorolac should not be given to patients with renal impairment.

* Order forms are obtainable from Medicare Australia, phone 13 22 90.

Table 1

Useful drugs for the doctor's bag

Drug (form)	Indications	Contraindications	Cautions
Adrenaline (1 mg in 1 mL injection)	Cardiac arrest, anaphylaxis[7]	None in cardiac arrest or anaphylaxis	May cause arrhythmia and myocardial or cerebrovascular ischaemia
† Aspirin, soluble, 300 mg tablet	Acute coronary syndrome, migraine	Peptic ulcer, bleeding disorders	None
Atropine sulfate (600 microgram in 1 mL injection)	Bradycardia, asystole	None in cardiac arrest or hypotensive bradycardia	May cause tachycardia, confusion and nausea
Benztropine mesylate (2 mg in 2 mL injection)	Acute dystonic reactions	Children < 3 years	May cause tachycardia and confusion
Benzylpenicillin (600 mg or 3 g of powder)	Severe infections (meningococcaemia, pneumonia, septicaemia)	Allergy	None
† Ceftriaxone (2 g powder)	Severe infections (meningococcaemia, pneumonia, septicaemia)	Allergy	None
Dexamethasone sodium phosphate (4 mg in 1 mL injection)	Acute allergic reactions (anaphylaxis, severe asthma), severe croup, acute Addisonian crisis. Palliative care emergencies[8]	None in emergency	None
Diazepam (10 mg in 2 mL injection)	Acute anxiety, convulsions (can be given rectally)	Cardiorespiratory failure, CNS depression	May cause drowsiness, confusion and respiratory depression
Dihydroergotamine mesylate (1 mg in 1 mL injection)	Migraine	Hemiplegic migraine, use of sumatriptan	Vasospasm syndromes can occur but are rare
Diphtheria and tetanus vaccine (0.5 mL injection)	Tetanus and diphtheria prophylaxis following injury	Children < 8 years	May cause pain and swelling locally and fever and malaise
† Ergometrine maleate (500 microgram in 1 mL)	Postpartum haemorrhage and incomplete abortion	Threatened abortion, severe hypertension	May cause hypertension, headache and nausea
Frusemide (20 mg in 2 mL injection)	Acute pulmonary oedema	Sulfonamide allergy	None
Glucagon hydrochloride (1 mg in 1 mL injection)	Hypoglycaemia	None	None
† Glucose 50% (500 mg/mL in 50 mL)	Hypoglycaemia	Diabetic coma	May cause phlebitis
Glyceryl trinitrate (400 microgram dose per spray)	Acute coronary syndrome, angina, acute pulmonary oedema	Cardiogenic shock (SBP < 90 mmHg)	May cause headache and hypotension
Haloperidol (5 mg in 1 mL injection)	Acute psychosis, acute mania, nausea and vomiting	Cardiovascular collapse and CNS depression	May cause extrapyramidal symptoms, confusion and hypotension
Hydrocortisone sodium succinate (100 mg or 250 mg in 2 mL injection)	Anaphylaxis, severe asthma	None in emergency	None

Drug (form)	Indications	Contraindications	Cautions
† Ketorolac (10 mg in 1 mL injection)	Pain	Renal impairment, anticoagulation, asthma, treatment with probenecid	May cause nausea
Metoclopramide hydrochloride (10 mg in 2 mL injection)	Nausea and vomiting, migraine	Acute complete bowel obstruction	Extrapyramidal symptoms with increased risk of dystonic reactions in children
† Midazolam (5 mg in 1 mL or 15 mg in 3 mL injection)	Convulsions, severe agitation	Cardiorespiratory failure and CNS depression	May cause drowsiness, confusion and respiratory depression
Morphine sulphate (15 mg or 30 mg in 1 mL injection)	Severe pain, acute coronary syndrome, acute pulmonary oedema	Respiratory or CNS depression. Avoid using in infants.	May cause sedation, nausea and vomiting
Naloxone hydrochloride (2 mg in 5 mL)	Opioid-induced respiratory depression	None	People with opioid dependence may experience acute withdrawal syndrome
Procaine penicillin (1.5 g for injection)	Severe infections (meningococcaemia, pneumonia, septicaemia)	Allergy	None
Prochlorperazine (12.5 mg in 1 mL)	Nausea and vomiting, vertigo	Circulatory collapse and CNS depression	May cause drowsiness and extrapyramidal symptoms
Promethazine hydrochloride (50 mg in 2 mL injection)	Nausea and vomiting, allergic reactions	Children < 2 years (except on advice)	May cause drowsiness
Salbutamol sulfate (inhaler 100 microgram/ dose or nebuliser solution 2.5 mg or 5 mg in 2.5 mL)	Asthma, bronchospasm	None	May cause tachycardia or tremor
Tramadol hydrochloride (100 mg in 2 mL injection)	Pain	Children, treatment with serotonergic antidepressants or MAOIs, respiratory or CNS depression	May cause nausea, vomiting and dizziness
Verapamil hydrochloride (5 mg in 2 mL injection)	Supraventricular tachycardia	Cardiogenic shock, heart block, hypotension, use of beta blockers and some SSRIs	May cause nausea, heart block, bradycardia and hypotension

† Not supplied under PBS doctor's bag emergency drugs

CNS central nervous system
SBP systolic blood pressure
MAOI monoamine oxidase inhibitor
SSRI selective serotonin reuptake inhibitor

Oxygen

Oxygen cylinders can be rented and refilled from a medical gas supplier (for example BOC (British Oxygen Corporation)). A 490 L (size C) will last for 55 minutes at 8 L/min. Use high-flow oxygen with caution in patients at high risk of carbon dioxide retention.

Storage of drugs

Drugs must be stored in a locked bag or a locked cupboard at below 25° C. Doctor's bags should not be left in cars where the temperature will easily exceed 25° C on even a mild day. Diphtheria and tetanus vaccine is stored in a refrigerator.

A register is required to log drugs received and drugs used (including the recipient's name). Schedule 8 drugs (opioids) must be stored in a locked, fixed, steel safe, although ampoules may be put in a locked bag for use away from the clinic. A separate book (available from the Royal Australian College of General Practitioners) is required to log Schedule 8 drugs that are received and used.

General practice accreditation

To meet accreditation standards, general practices must have oxygen, a bag-valve-mask system, and appropriate emergency drugs. All general practitioners must have access to a doctor's bag (which may be shared between two or more general practitioners). There should be a system for checking emergency drug stocks and expiry dates – for example, a monthly inventory by a practice nurse. Doctor's bags should have a sharps container, disposable gloves, and dressing packs. Safety intravenous cannulas and needleless systems reduce the risk of needlestick injury.[3]

Conclusion

Appropriate drugs in the doctor's bag are an essential part of general practice. The contents of the bag will be tailored to suit the needs of each practice.

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Conflict of interest: none declared

Dental notes

Prepared by Dr M McCullough of the Australian Dental Association

Drugs for the doctor's bag

Dentists do not need to stock as many emergency drugs as general practitioners, however we are required to have fully equipped and well maintained emergency equipment in our surgery.

As stated in the recently published Therapeutic Guidelines: Oral and Dental[1], the minimum requirements for emergency situations in the dental surgery are oxygen, a disposable airway, and adrenaline. For dental practices performing more extensive procedures, or with an increased proportion of medically compromised patients, then more equipment and medications are required.

Medical emergencies in dental surgeries are uncommon so there is a risk that medications will expire before they are needed. It is incumbent on dentists to ensure that the drugs in their emergency equipment are not out of date. Ideally, there should be a system for checking emergency drug stocks and expiry dates, perhaps by a monthly inventory. Many dental practices probably already have such an inventory and it can be easily foreseen that such documentation may well become part of any potential practice audit.

Emergency drugs are not available under the Pharmaceutical Benefits Scheme for dentists and must be purchased at full cost. This anomaly should be redressed.

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Evaluation of adrenocortical function in adults

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Summary

Cushing's syndrome is caused by increased concentrations of cortisol. Most cases can be detected by measuring the free cortisol in a urine sample collected over 24 hours. In Cushing's syndrome the increased secretion of cortisol is not reduced during a dexamethasone suppression test. Addison's disease is caused by a decreased secretion of cortisol that does not respond to an injection of synthetic adrenocorticotrophic hormone. Concentrations of adrenocorticotrophic hormone are raised in primary, and low or normal in secondary adrenal insufficiency. Some patients with hypertension have primary aldosteronism. They have a high ratio of aldosterone to plasma renin activity. When investigating adrenal function it is important to consider the patient's diet and drugs as well as the timing of the sample.

Key words: Addison's disease, aldosterone, Conn's syndrome, cortisol, Cushing's syndrome.

(Aust Prescr 2007;30:147–9)

Introduction

The adrenal cortex consists of three functionally separate layers. The outer zona glomerulosa produces aldosterone under the stimulatory control of the renin-angiotensin system and potassium. Aldosterone increases sodium reabsorption and potassium excretion in the kidney and gut. The zona fasciculata produces cortisol under the control of pituitary adrenocorticotrophic hormone (ACTH). ACTH is principally regulated by hypothalamic corticotrophin-releasing hormone. The secretion of ACTH responds to a diurnal rhythm, stress and negative feedback from circulating cortisol. Cortisol regulates metabolism, and during stress it restrains and redirects the immune system and accentuates cardiovascular responses. The inner zona reticularis produces the adrenal androgens dehydroepiandrosterone and androstenedione.

Clinical evaluation determines which tests of adrenal function are needed. The principles of testing include:

- using basal hormone concentrations for screening
- using suppression or stimulation tests to definitively diagnose hormone excess or deficiency
- measuring trophic hormones to diagnose the site of endocrine lesions (for example, measuring ACTH to distinguish an adrenal from a pituitary lesion in hypocortisolism).

Testing for hypercortisolism (Cushing's syndrome)

Mild Cushing's syndrome is notoriously difficult to diagnose, but early diagnosis avoids disability and reduces mortality. Cortisol concentrations increase in Cushing's syndrome, but there are two major confounders. One is that some patients have increased cortisol production rates that remain within the statistically normal range. Furthermore, this overproduction may be intermittent or cyclic. Secondly, some individuals may have transient hypercortisolism and features consistent with early Cushing's syndrome, but without the progressive catabolic effects. These individuals have 'pseudo-Cushing's'. In some cases this is associated with alcohol abuse or depression. No single test is infallible in Cushing's syndrome and values close to the limits of normal must be regarded with suspicion.[1]

Screening tests for Cushing's syndrome

Most cases can be readily diagnosed by an elevation of the free cortisol in a 24-hour collection of urine, however in up to 15% of new cases the result may be normal. The dexamethasone suppression test also has a substantial false positive and false negative rate. The diagnosis can be made with plasma cortisol, but the blood sample has to be taken at midnight and this is often impractical. A midnight value less than 120 nmol/L virtually excludes Cushing's syndrome.

Urinary free cortisol

Over 24 hours the free cortisol provides an integrated assessment of cortisol secretion. This avoids the pitfalls of blood tests including circadian rhythm, pulsatile cortisol release and altered levels of corticosteroid-binding globulin. However,

urine volumes above four litres per day may result in false positive tests.

Cortisol excretion rates vary diurnally but urine creatinine excretion does not. Hence, it is not possible to correct an incomplete or over-collection with the 24-hour urine creatinine. Urinary creatinine is useful in determining if the urine collection was adequate, for example a low 24-hour urine creatinine in a large person may suggest under-collection. In addition, in sequential measurements the 24-hour urine creatinine should not vary by more than 10%.

False positive results can occur in patients with high urine volumes, chronic alcoholism, depression, idiopathic pseudo-Cushing's, or serious illness. False negatives may occur in patients with early or mild Cushing's syndrome, or in those with cyclic hypercortisolism which occurs in 10% or more of cases depending on how cyclic is defined.

Midnight plasma cortisol

Cortisol peaks around the time of waking, decreases rapidly through the morning and reaches a nadir around midnight. Most patients with Cushing's syndrome have early morning plasma cortisol concentrations within or slightly above the normal range. In contrast, midnight plasma cortisol concentrations are almost always high (greater than 207 nmol/L).

Midnight salivary cortisol

Salivary cortisol concentrations reflect plasma free cortisol, but appropriate assay-specific normative values must be used for its interpretation. Internationally, cut-offs have ranged widely. We have found a cut-off of 13 nmol/L to reliably distinguish Cushing's from non-Cushing's patients.

Low-dose dexamethasone suppression testing

A low dose of dexamethasone should suppress plasma cortisol. This is commonly used as a screening test for Cushing's syndrome. Dexamethasone, 1 mg orally, is given at 11 pm and plasma cortisol is measured at 8–9 am the next day to see if it has been suppressed. The dexamethasone suppression test has been variously validated in the past, often with inappropriate controls, such as normal volunteers. Low cut-off values (50 nmol/L or less) tend to over-diagnose, while high cut-off values (140 nmol/L or above) tend to miss cases of Cushing's syndrome. False positive results can occur in acute illness, depression, anxiety, alcoholism, high oestrogen states and with drugs that accelerate dexamethasone metabolism. If a low dose does not suppress cortisol, a high-dose dexamethasone suppression test is indicated.

Testing for primary hypoadrenalism (Addison's disease) and ACTH deficiency

Hypoadrenalism may be caused by abnormalities in the adrenal gland or a lack of ACTH. Adrenal suppression is also an adverse effect of corticosteroids.

Although fatigue is a key symptom of hypoadrenalism, most fatigued people have normal adrenal function. There is no single cheap and convenient test for evaluating hypoadrenalism.[2] Testing includes an ACTH stimulation test, and measurements of sodium, potassium, ACTH, plasma cortisol, aldosterone and renin activity.

Plasma cortisol

An early morning plasma cortisol, measured within one hour of waking, below 200 nmol/L strongly suggests adrenal insufficiency. Conversely, a plasma cortisol greater than 500 nmol/L excludes the diagnosis and obviates the need for an ACTH stimulation test. Intermediate cortisol concentrations may require investigation with an ACTH stimulation test.

ACTH stimulation testing

In most cases of suspected hypoadrenalism, a stimulation test is needed to diagnose cortisol deficiency. A normal response to intravenous ACTH (250 microgram) is a cortisol peak value at either 30 or 60 minutes of greater than 500 nmol/L. The previously recommended additional criterion of a cortisol increment greater than 200 nmol/L rarely contributes to the diagnosis.

There are cases of missed adrenal insufficiency after a normal ACTH test. The reproducibility of testing is imperfect. The test has not been validated against clinical end points, but has been validated against the now rarely used insulin hypoglycaemia test.

Plasma ACTH

Measurement of plasma ACTH helps localise the cause of adrenal insufficiency – adrenal (primary or Addison's) versus pituitary (secondary) or hypothalamic (tertiary). In primary adrenal insufficiency, plasma ACTH is greatly elevated due to a lack of the negative feedback of cortisol on the hypothalamic-pituitary axis. In secondary or tertiary adrenal insufficiency, ACTH is low or inappropriately normal.

Corticotrophin-releasing hormone test

The use of corticotrophin-releasing hormone to test ACTH and cortisol reserve directly assesses pituitary and adrenal function. Other than minor flushing, corticotrophin-releasing hormone (1 microgram/kg intravenously) rarely produces adverse effects. The test is expensive and corticotrophin-releasing hormone is not widely available.

Testing for primary aldosteronism

Conn's syndrome is hypertension and hypokalaemia due to an aldosterone-secreting adrenal tumour, however many cases are normokalaemic. Screening for primary aldosteronism may be indicated in patients with hypertension who have spontaneous or thiazide-induced hypokalaemia.[3]

Plasma aldosterone concentration:plasma renin activity ratio

A mid-morning blood sample is taken from a seated patient. In primary aldosteronism, the plasma renin activity is reduced

and the plasma aldosterone concentrations are high, resulting in a plasma aldosterone concentration (pmol/L):plasma renin activity (ng/mL/hr) ratio of greater than 700. A false positive may occur with low aldosterone concentrations if the plasma renin activity is very low, for example in patients taking a high salt diet. Hence, an elevated ratio may not suggest primary aldosteronism if the plasma aldosterone concentration is less than 270 nmol/L.

Serum potassium should be measured simultaneously as a low serum potassium will reduce the plasma aldosterone concentration and indicate a requirement to replace potassium before testing again. Antihypertensive drugs, except for hydralazine, prazosin and verapamil, can also interfere with the plasma aldosterone concentration:plasma renin activity ratio. Diuretics and aldosterone receptor blockers such as spironolactone need to be stopped for six weeks before testing. Beta blockers suppress the plasma renin activity but they can be stopped for 24–48 hours before testing. The effects of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists are generally minor, but in a patient treated with these drugs a detectable plasma renin activity level or a low plasma aldosterone concentration:plasma renin activity ratio does not exclude the diagnosis of primary aldosteronism. Dihydropyridine calcium antagonists such as nifedipine and amlodipine can reduce the plasma aldosterone concentration in patients with an aldosterone secreting adenoma. Renal impairment may elevate the ratio as increased potassium elevates aldosterone secretion while salt and water retention suppresses the plasma renin activity.

Confirming primary hyperaldosteronism

Confirmatory testing aims to demonstrate aldosterone secretory autonomy, using measurements of plasma or urine aldosterone under salt loading conditions, with or without fludrocortisone. The final step is to determine if one or both adrenals are the source of aldosterone, generally requiring adrenal vein sampling.

Adrenal incidentaloma

An unanticipated adrenal mass (incidentaloma) is found in approximately 4% of upper abdominal computed CT scans. Clinical, imaging and biochemical evaluation is necessary to exclude malignancy and hormone excess.[4] The risk of adrenocortical cancer is very low, but adrenal metastases are common and need to be considered in patients with a history of cancer.

Conclusion

Disorders of adrenocortical function are uncommon and the symptoms often non-specific. Application of a small number of biochemical screening tests can separate those patients who do not have a disorder of adrenal function from those who require specialised assessment and more complex testing.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 167)

1. Most patients with primary hyperaldosteronism have hyperkalaemia.
2. A normal 24-hour urine free cortisol excludes Cushing's syndrome.

Therapeutic Advice and Information Service (TAIS)

A telephone service for health professionals Telephone 1300 138 677 (local call charge)

The National Prescribing Service Therapeutic Advice and Information Service (TAIS) is a national telephone service for general practitioners, community pharmacists and other health professionals. For the cost of a local call, TAIS provides independent drug and therapeutics information on topics such as new drugs, use of drugs for unlicensed indications, interactions between drugs, foods or complemetary therapies, adverse effects, and the safety of drugs in pregnancy and lactation.

Contact: Office hours Monday to Friday, except national public holidays

Telephone: 1300 138 677 (local call charge)
Fax: (03) 9459 4546
Email: tais@nps.org.au
Mail: Austin Health Drug Information
Pharmacy Department
Austin Hospital
145 Studley Road
HEIDELBERG VIC 3084

For non-urgent enquiries you can also use the TAIS online enquiry form on the NPS website.

Relationships between health professionals and industry: maintaining a delicate balance

Paul A Komesaroff, Professor of Medicine, Director, Centre for the Study of Ethics in Medicine and Society, Monash University Department of Medicine, Alfred Hospital, Melbourne, and Ethics Convener, Royal Australasian College of Physicians

Summary

The power and influence of the pharmaceutical industry has raised concerns among health professionals and the wider community and led to calls for increased regulation. Overwhelming evidence that advertising, contact with company representatives, gift giving, sponsorship of meetings and other forms of promotion influence prescribing behaviour, has drawn particular attention to drug promotion. In answer to these concerns a range of responses has developed, including rules set by government, processes for the review and management of research, industry codes of conduct, community responses, and guidelines generated by practitioner associations. The various forms of regulation taken together strike a delicate balance that aims to protect the interests of the community and individual patients, foster research and the development of new products, maintain public confidence in pharmaceuticals and medicine, and facilitate ethical decision making among the various participants. Although guidelines for health professionals provide some advice, they cannot cover all situations where conflicts and dualities may arise in practice.

Key words: drug promotion, drug regulation, ethics.

(Aust Prescr 2007;30:150–3)

Introduction

Despite improvements achieved in the management of complex medical conditions in recent years and widespread and increasing use of pharmaceuticals, the pharmaceutical industry has been increasingly portrayed in both the academic literature and the popular media in an unfavourable light. While it may be true that the industry's negative reputation is not completely justified, it is not difficult to understand the source of the concerns.

General practitioners and other health professionals such as pharmacists are frequently visited by representatives of pharmaceutical companies. The purpose of these visits is to promote the company's drugs and to build a relationship. In dealing with such encounters, situations may arise where there is an ethical dilemma or conflict of interest. It is important for health professionals to be aware of these and to respond appropriately.

Drug promotion

In Australia the primary targets of drug promotion are doctors, who may be provided with gifts, offers of travel, and other inducements to prescribe.[1] More subtle promotion may include educational activities, drug samples and drug familiarisation schemes, and support for the practice such as providing a nurse to collect data.

Even though doctors generally deny that they are influenced by such approaches[2,3], there is overwhelming evidence that advertising influences prescribing behaviour. Physicians who attend pharmaceutical events are more likely to use the products of the sponsors, even in the absence of reliable and credible evidence in their favour.[4,5] Promotional activities in general lead to increased prescribing of drugs, acceptance of commercial rather than scientific views, a propensity to engage in non-rational prescribing behaviour[6,7,8], and biases in favour of a company's drugs.[9,10]

While research undertaken by industry is often rigorous and well conducted, it may be driven by commercial imperatives leading to biased presentation and interpretation of results.[11,12] Protocols and methodologies may reflect and support intended outcomes rather than disinterested inquiry.[13]

Perhaps of even greater concern is the well documented fact that industry interests substantially influence the social agenda relating to the understanding of health and disease, sexuality, body image and lifestyles.[14,15]

What is special about drug promotion?

Concern about the role and influence of the pharmaceutical industry is heightened because of the special features of medicines compared to other commercial products. The consumers of medications are often extremely vulnerable, for the obvious reason that their health may be at stake in using a product. Decisions about what drugs to use are often taken

not by them alone but by their medical practitioners, whose interests are not always identical to those of their patients.

For prescription drugs, medical practitioners have great influence and are charged with the responsibility of balancing patients' needs and the public interest. They have knowledge and expertise to assess the scientific evidence, and access to the specific contextual details of medical need in particular cases.

For over-the-counter products, pharmacists advise patients and directly benefit from making a sale. They may also be offered incentives to stock particular brands.

The ongoing debates about the role and power of the drug industry in the popular media[16,17,18] have no doubt influenced community attitudes, although it is difficult to determine just what impact these may have had. While some consumer groups have expressed suspicion and hostility to the industry, other groups have emphasised the importance of improved co-operation and development of active collaborations.[19] Public scepticism may help to control doctors' dealings with industry, but may also damage the doctor–patient relationship.

Physicians need to be aware of the evidence about the impact of advertising on behaviour and community perceptions. While bans on the provision of information by drug companies are inappropriate, high levels of critical awareness, supported by educational programs, are needed by clinicians.

In many countries, including Australia, the purchase of medications is heavily subsidised from public funds. The prescriber therefore does not directly bear the cost of their decisions.

Conflicts of interests

One of the key requirements of a health professional involved in interactions with industry is to be able to distinguish dualities and conflicts of interests. A duality exists where there are two or more social roles that overlap, each of which is associated with a moral imperative. A conflict exists where these imperatives are contradictory and threaten to compromise the primary goal of one of them.

A duality of interest would exist when a general practitioner involved in research is considering recruiting their own patients for a study, or when a doctor considers accepting travel assistance from a pharmaceutical company to attend a meeting with undisputed scientific content at a pleasant resort location. The principles for responding to a duality are straightforward. It needs to be identified and disclosed publicly to the relevant community. This community should decide whether it constitutes a conflict and, if so, this needs to be managed, usually by disengaging the two conflicting roles.

Sometimes this process of disengagement is straightforward – for example, if researchers propose to include their own patients in a research project they should in general not approach the patient themselves but leave the consent process to third parties. On other occasions, such as where a researcher has direct pecuniary interests in a product being tested, more elaborate mechanisms, such as an arm's length committee or divestment of shareholdings, may be necessary.

Regulation of drug promotion

In response to the real or perceived risks associated with the pharmaceutical industry's influence and power, an array of formal and informal mechanisms for regulating the industry has developed. These include rules set by government, industry codes of conduct, guidelines generated by practitioner associations, processes for the review and management of research, and community responses. Together, they seek to ensure a wide range of goals, including protection of the interests of the community and individual patients, responsiveness to specific clinical contexts, fostering of research and development of new products, maintenance of public confidence in pharmaceuticals and medicine, facilitation of ethical decision making among the various participants, and enhancement of options and freedom to act.

Government

Although government regulation undoubtedly plays a key role, it is a blunt instrument that may not be able to provide specific guidance for all circumstances that occur in a clinical setting. Statutory regulatory regimes are also cumbersome and bureaucratic and require elaborate and expensive systems of enforcement.

Industry

The industry itself has developed a code of conduct, which is administered through the industry peak body, Medicines Australia.[20] This Code has been criticised, for example, on the basis that membership of Medicines Australia, and thus allegiance to its policies, is voluntary and does not include all manufacturers. Areas of concern, such as the collection and control of data, are omitted altogether. Enforcement of the Code is incomplete and mostly relies on complaints. Sanctions for breaches are generally modest.[21] Nonetheless, it is believed that the Code represents a substantial achievement and that it has contributed to significant change in the commercial behaviour of the pharmaceutical industry in Australia. For example, a recent amendment to the Code now requires pharmaceutical companies to publicly disclose the cost of events organised for doctors.

Guidelines for health professionals

A number of professional associations have developed guidelines about the ethical relationships between health professionals and the pharmaceutical industry.[22,23] Among these are the Royal Australasian College of Physicians (RACP)[24], the Royal Australian College of General Practitioners (RACGP)[25], and the Pharmaceutical Society of Australia.[26]

RACP recommendations

These guidelines seek to demonstrate how dualities may be managed in specific circumstances that arise in common practice. They recommend that gifts should be rejected, even items of trivial value. In general, acceptance of travel expenses is discouraged. However, where a practitioner is making a formal contribution to a meeting it may be acceptable for the organising committee to offer assistance with travel and other costs.

For scientific meetings or professional development events, it is important that programs are developed by committees at arm's length from sponsors and that sponsorship is not negotiated on the basis of conditions relating to speakers or content.

The RACP guidelines cover many issues regarding research, including design of experiments, management and interpretation of data, and publication of results, which raise the possibility of conflicts of interests. Researchers have special responsibilities to ensure that the conduct and outcomes of research are not influenced by pecuniary or non-pecuniary interests and that the public can have full confidence in the integrity of any data that are disseminated.

RACGP recommendations

The RACGP makes similar recommendations to general practitioners but is more relaxed about doctors accepting gifts. A gift may be accepted but the patient should be the primary beneficiary and the gift should be related to the general practitioner's work. So, for instance, gifts such as a stethoscope or a textbook are acceptable, whereas gifts of a holiday, frequent flyer points, a computer or cash payments are not acceptable.

The guidelines also recommend that if a general practitioner is involved in postmarketing surveillance studies, they should make it clear to the patient that the patient's welfare is not dependent on participation in the study and they can withdraw at any time and start an alternative treatment if they wish.

The Pharmaceutical Society of Australia Code

Although very brief, the Code obligates pharmacists to avoid situations that may present a conflict of interest. Accepting inappropriate gifts is also contrary to the Code.

Conclusion

Opinions differ and controversies continue about the influence of the pharmaceutical industry and the proper responses to it. The system of regulation that has evolved in Australia is complex and heterogeneous, incorporating components from government, industry, community and the professions. Although each would on its own be insufficient, together these elements constitute a delicately balanced equilibrium that goes at least some way towards ensuring that the diverse tasks and goals set by the various stakeholders are addressed and acknowledged. Whether the balance should shift more in the direction of regulation, whether a more punitive approach would be more or less effective, how best to maintain both economic incentives and public responsibility – or even if it is possible to do so – remains uncertain.

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Conflict of interest: none declared

Dental notes

Prepared by Dr M McCullough of the Australian Dental Association

Relationships between health professionals and industry: maintaining a delicate balance

The level of prescribing that occurs in the average dental practice is not usually such that it attracts the attention of pharmaceutical companies' marketing departments. However, we are large consumers of restorative materials, medicaments and other products. We rely on a good working relationship with dental supply companies who not only offer access to these products, but are also often involved in research related to them. It is most likely that dentists are not aware of the influence that advertising, 'special offers', personal visits by company representatives, endorsements and trade shows have on our purchasing habits.

What dental practitioners purchase or prescribe should always be done on the basis of available scientific evidence with patients' interest utmost in our minds. In fact, in the majority of practices it is not the dentists who purchase these items, but rather the practice manager on the advice of the dentist, advice that may not be consistently available. Situations of conflict and duality of interest may well be relatively common in the dental profession, and these should be acknowledged and dealt with in an open manner. Currently, the Australian Dental Association is developing a policy to advise its members where these conflicts and dualities of interests arise.

Medicines Australia Code of Conduct: breaches

Medicines Australia has a Code of Conduct to guide the promotion of prescription drugs by pharmaceutical companies in Australia. A new edition of the Code has recently been approved.[1] Complaints are considered by the Code of Conduct Committee and the results are published in its annual report. The report for 2006–07 is available on the Medicines Australia website.[2]

This year's report contains detailed information about 41 complaints. In fourteen cases no breach of the Code was found. Table 1 shows the 27 complaints in which at least one breach of the Code was found. As usual, most of the complaints were made by rival pharmaceutical companies, but 12 were made by health professionals.

Most of the breaches were for using misleading information in promotional material. Some of the larger fines were imposed on companies that had allowed the public to be exposed to their promotions. Two complaints related to a company which sponsored the national conference of a patient support

group. An article, originally drafted for health professionals, but published in Reader's Digest, clearly breached the Code. Another breach, identified by several complaints, was offering a 'money-back guarantee' to patients being treated for erectile dysfunction.

The information in the report reveals some of the sophisticated strategies companies can use. One company had used a public relations consultant to manage a campaign about a medicine which had yet to be approved in Australia. This included sponsoring a journalist to attend an overseas conference about the drug. Issuing a media release on an unapproved drug was considered to be promotional activity which breached the Code.

The Committee had to grapple with what constitutes excessive hospitality. One company was fined for providing a function that was not 'simple or modest', while a function at the Crown Towers in Melbourne was ruled to be 'not extravagant'. Perhaps the new requirement for companies to disclose the cost of their promotional functions will help the Code of Conduct Committee decide what is appropriate.

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The story of one complaint

John S Dowden, Editor

An advertising campaign for vardenafil encouraged men with erection difficulties to seek treatment. The advertisement included the product logo and the name of the company. The imagery, of an upright banana, was also used in the advertising to health professionals. As part of this parallel campaign, doctors and pharmacists were informed that the company would offer a money-back guarantee to patients.

I made a complaint to Medicines Australia as I believed that the advertising to the public would stimulate demand for a particular product and the money-back guarantee could be seen as an inducement. Complaints were also made by two pharmacists and the Australian Consumers' Association.

The Code of Conduct Committee considered my complaint within a month and sent me its decision within six weeks. The ruling was in an extract of the minutes of the Committee's meeting. This showed that there had been a severe breach of the Code of Conduct, but I was asked to keep the ruling confidential in case there was an appeal. As there was no appeal the complaint was finalised and details appear in the Code of Conduct Annual Report.[1]

The Code of Conduct Committee considered that the advertising campaign could have breached nine sections of the Code, however only one breach was confirmed. A majority of the Committee considered that the campaign brought discredit to the industry. This was not because the banana images were in poor taste, but because a money-back guarantee was considered to decrease the value of prescription medicines.

The Code of Conduct Committee did not fine the company for the severe breach, but ordered it to immediately cease the promotion offering the money-back guarantee. Corrective letters had to be sent to all health professionals who received the promotion and corrective advertisements had to be placed in health professional journals which had published advertisements about the money-back guarantee.

Reference

1. Medicines Australia Code of Conduct Annual Report 2006/2007. Canberra: Medicines Australia; 2007. http://www.medicinesaustralia.com.au [cited 2007 Nov 12]

Table 1

Breaches of the Code of Conduct July 2006 – June 2007

Company	Drug		Sanction imposed by Code of Conduct Committee
	brand name	generic name	
Abbott Australasia	Lucrin	leuprorelin	Withdraw material Corrective letter $10 000 fine
Alcon Laboratories	DuoTrav	timolol maleate/ travoprost	Cease program $10 000 fine
Allergan Australia	Lumigan	bimatoprost	Withdraw material Corrective letter $15 000 fine

AstraZeneca	Crestor	rosuvastatin	Withdraw promotional materials Corrective letter $75 000 fine reduced on appeal to $40 000
	Nexium	esomeprazole	Withdraw materials $75 000 fine
Bayer Healthcare	Levitra (four complaints)	vardenafil	Withdraw money-back guarantee offer Corrective letters Corrective advertisement
Boehringer Ingelheim	Buscopan	hyoscine	Withdraw material $25 000 fine reduced on appeal to $10 000
	Mobic	meloxicam	Withdraw materials Corrective letter $25 000 fine
CSL Limited	Biostate	factor VIII	$5000 fine dropped on appeal
	Behaviour of company representative		Withdraw training material $15 000 fine
GlaxoSmithKline Australia	Rotarix	rotavirus vaccine	Withdraw materials Corrective letter $25 000 fine
	Tykerb	lapatinib	Provide no media releases until medicine registered $40 000 fine
Janssen-Cilag	Pariet	rabeprazole	Withdraw material $100 000 fine
	Pariet	rabeprazole	Withdraw material Other sanctions covered in previous breach
Merck Sharp & Dohme	Fosamax Plus	alendronate	Withdraw materials
Octapharma	Octanate	factor VIII	Withdraw materials Corrective letter $100 000 fine reduced on appeal to $10 000
Pfizer Australia	Celebrex	celecoxib	Withdraw materials $100 000 fine
	Celebrex	celecoxib	Article not to be published again for general public $100 000 fine
	Xalacom	latanoprost/ timolol maleate	Withdraw material Corrective letter $50 000 fine
Roche Products	Hospitality		$75 000 fine
Sanofi-Aventis	Stilnox	zolpidem	Withdraw materials $5000 fine
Schering	Betaferon	interferon beta-1b	Withdraw materials Corrective letters $150 000 fine
	Betaferon	interferon beta-1b	Withdraw materials Letter to Multiple Sclerosis Society $100 000 fine
	Angeliq	drospirenone/ oestradiol	Cease distribution of trade packs

Treatment of myasthenia gravis

Stephen W Reddel, Sydney Neurology, Brain and Mind Research Institute, The University of Sydney, and Departments of Neurology and Molecular Medicine, Concord Repatriation General Hospital, Sydney

Summary

Myasthenia gravis is a syndrome of weakness and fatigue due to dysfunction of the neuromuscular junction. It is an antibody-mediated autoimmune condition with a range of moderately effective treatments. Occasionally patients go into remission spontaneously, but most require treatment. Mild disease, such as that confined to the ocular muscles, can often be treated with pyridostigmine alone. More significant or generalised weakness requires immunosuppression, principally with prednisone and azathioprine. The response to immunosuppression is slow, ranging from several months to 1–2 years for a full response. Short-term use of antibody-based therapy such as plasma exchange or intravenous immunoglobulin is warranted for more severely affected patients. Thymectomy offers the hope of drug-free remission but as yet remains unproven. Treatment-related morbidity is considerable, but partly preventable.

Key words: azathioprine, immunosuppression, prednisone, pyridostigmine, thymectomy.

(Aust Prescr 2007;30:156–60)

Introduction

Myasthenia gravis is an autoimmune disease which causes muscular weakness due to dysfunction of the neuromuscular junction (Fig. 1). Autoantibodies directed against antigenic proteins on the postsynaptic side of the neuromuscular junction result in both blockade of transmission and damage to the postsynaptic structure. As a result the motor neuron is unable to 'talk' to the muscle fibre and weakness results. The known antigens to which the autoantibodies bind are the acetylcholine receptor and, less commonly, muscle-specific tyrosine kinase.

The prevalence of myasthenia gravis is about 1 in 10 000. The gender ratio is approximately equal, with a peak incidence of onset in the 20s for women and the 60s for men. Around 10% of patients with a positive acetylcholine receptor antibody test have an associated thymoma.

Diagnosis

There are a range of diagnostic tests for myasthenia gravis. These include dynamic tests for measuring muscle weakness (for example, response to edrophonium or ice pack), electrical tests such as repetitive stimulation or single fibre electromyography, and measurement of antibodies to acetylcholine receptor and to muscle-specific tyrosine kinase.

Clinical manifestations

Myasthenia gravis affects some regional muscles more than others. Most commonly the orbital muscles are affected first, with either diplopia or ptosis. However, myasthenia gravis may first affect the bulbar muscles (speech and swallowing), the neck muscles (head drops) and proximal or rarely distal limb or respiratory muscles. Involvement is fairly symmetrical except in the eyes. Symptoms may get worse towards the end of the day or after a few minutes of continuous use – for instance speech may become slurred over a few minutes. More severe myasthenia gravis affects multiple muscular regions and may be sufficiently severe to cause respiratory failure and death if untreated.

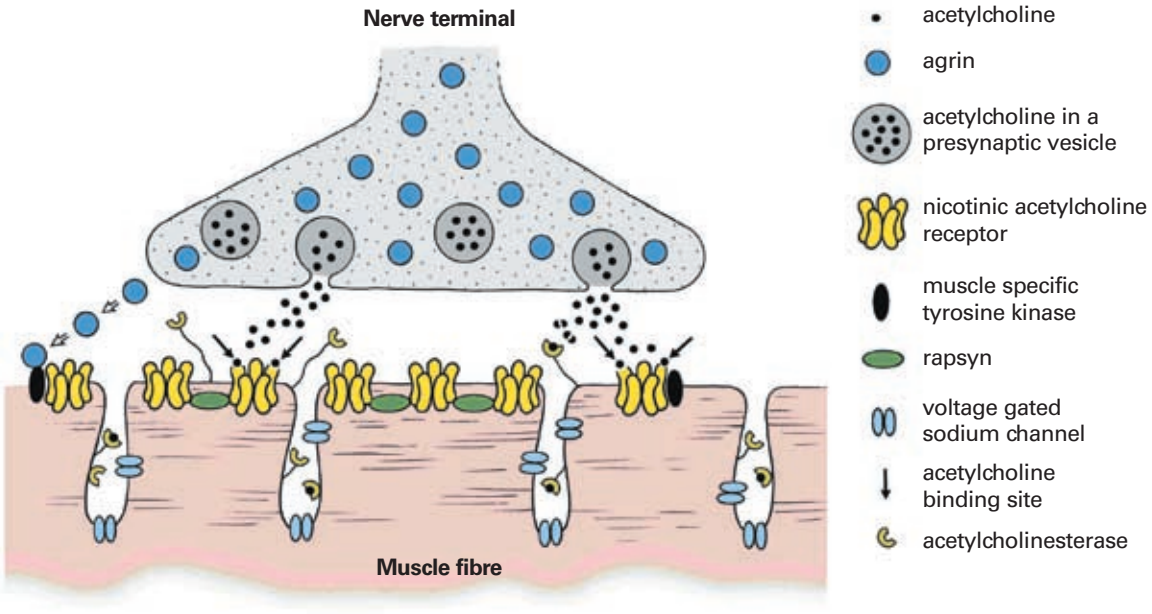
Natural history of myasthenia gravis

Generally, myasthenia gravis is a persistent disease requiring chronic treatment. Fluctuations over the long term are the norm. Some patients go into long-term remission spontaneously – approximately 15–25% after five years for those presenting with generalised disease and somewhat more for those presenting with ocular disease only. Late relapse after sustained remission also occurs, the longest reported example being after 32 years. It should be noted that the neuromuscular junction can be reformed, unlike many parts of the nervous system. Muscle strength that has been affected by myasthenia gravis for a long time often recovers with treatment. This means that the intensity of treatment for myasthenia gravis can be modulated to the current severity of the disease.

Over time, patients with clinically isolated ocular myasthenia gravis often progress to generalised myasthenia gravis. Treatment with corticosteroids can reduce the likelihood of progression, and control both ocular and generalised weakness completely in many cases. It is not known if this alters the natural history or the need for long-term treatment. It is therefore unclear whether treatment should be commenced for ocular disease or just 'as required' to control symptoms that

Fig. 1

Normal muscular junction



In the normal neuromuscular junction, acetylcholine released from the nerve terminal following a nerve action potential, binds to the acetylcholine receptor on the postsynaptic muscle, triggering a muscle action potential propagated by the voltage gated sodium channel. Acetylcholinesterase scavenges and breaks down unbound acetylcholine. In a separate pathway, neural agrin binds muscle specific tyrosine kinase initiating clustering of phosphorylated rapsyn and acetylcholine receptors, stabilising the postsynaptic structure opposite the nerve.

In myasthenia gravis caused by antibodies to the acetylcholine receptor, there is blockade of the binding site for acetylcholine, cross-linking of the acetylcholine receptor with subsequent internalisation and reduction in its surface expression, and initiation of complement and cellular inflammatory cascades with damage to the post- and presynaptic structures. The molecular physiology of myasthenia gravis mediated by antibodies to muscle specific tyrosine kinase has not been established.

are causing sufficient disability to justify the adverse effects of treatment. Long-standing ocular misalignment may not recover despite generalised remission.

Treatment

The diagnosis must be confirmed before treatment, because the mainstay of treatment for most patients is immunosuppression. Treatments to prevent the adverse effects of immunosuppression should be started simultaneously with the therapy (see Table 1). There is no robust evidence that long-term treatment actually cures the condition, so some patients choose to avoid the adverse effects of immunosuppressive therapy and accept degrees of weakness. Coping without treatment is not always the safest strategy as patients with significant weakness, particularly in the bulbar musculature, are at risk of ventilatory failure or of needing intensive care following an intercurrent respiratory infection. Immunosuppressive treatment is therefore strongly recommended for control of significant bulbar weakness.

Initial treatment is usually with pyridostigmine, followed by prednisone and azathioprine if the response is incomplete. A combination of approaches is often useful to cover deficiencies in each available drug.

Immunosuppression produces a very slow response, often taking many months to 1–2 years.[1,2] An unrealistic expectation of a speedy response is often a problem for both the patient and the doctor.

There are four main approaches to treatment, each with very different durations of effect, requirements, consequences and adverse effects.

Improve neuromuscular transmission by inhibiting acetylcholinesterase

Drugs that inhibit acetylcholinesterase include pyridostigmine, edrophonium (used only for testing) and neostigmine (for intravenous use in intensive care units only). These drugs take effect within minutes and last for hours. Although they are without long-term adverse effects, the efficacy of all

Table 1

Prophylaxis of the complications of immunosuppression

Osteoporosis prevention	Measure bone density before treatment and yearly while on treatment. Start calcium and vitamin D supplements. Bisphosphonates may reduce bone loss associated with the chronic use of glucocorticoids.
Cardiovascular risk	Risk factor modification should be standard and includes advice to stop smoking, start an exercise program and manage hypertension.
Peptic ulcer prevention	Helicobacter screening and prophylactic treatment with proton pump inhibitors or H_2 antagonists seems appropriate for those with a past history of previous ulceration or concordant use of non-steroidal anti-inflammatory drugs.
Infection prophylaxis	Use of inactivated vaccines such as influenza is recommended. Live vaccines are contraindicated. A chest X-ray should be performed prior to treatment. More specific testing for tuberculosis may be indicated depending on history and chest X-ray results.
Malignancy prevention	Skin cancer rates are increased in patients using azathioprine. A full yearly dermatological survey is recommended. Exhort sun protection and cancer surveillance. Regular cervical smears are recommended. Eye protection may also limit cataract development.

acetylcholinesterase inhibitors is limited. As a sole drug they are not enough for most patients with generalised myasthenia gravis.

Pyridostigmine

Pyridostigmine is the first-line treatment for myasthenia gravis. It is a reversible inhibitor of acetylcholinesterase so increases acetylcholine stimulation of the remaining acetylcholine receptors. If there are insufficient acetylcholine receptors remaining to trigger a muscle action potential, extra acetylcholine from the action of the drug is not going to help. The underlying autoimmune state is not altered. It is often sufficient for ptosis alone, but not for diplopia or generalised myasthenia gravis. Benefit is often not sustained, possibly due to counterproductive upregulation of acetylcholinesterase and downregulation of acetylcholine receptors. The dose required is variable, as is gastrointestinal tolerance. One approach is to start at 10 mg three times a day and titrate up to 60 mg 4–6 times daily. A 180 mg 'timespan' preparation is available for nocturnal symptoms. In practice a degree of patient control of dosing and 'when required' use is often helpful.

Doses less than 480 mg daily rarely produce depolarising crisis. Increasing weakness after an increase in the pyridostigmine dose (when high doses are already being given) suggests deteriorating disease and/or a depolarising crisis. This may require treatments such as plasma exchange and a reduction in pyridostigmine dose. The presence of gastrointestinal adverse effects and fasciculations, clinically or on electromyogram, might suggest depolarising crisis. The patient must be hospitalised and the dose of pyridostigmine reduced while they are carefully monitored. Lack of improvement with edrophonium (which has a very short half-life) indicates that further pyridostigmine will not be useful.

Immunosuppression

The principal drugs used to suppress the immune system in myasthenia gravis are prednisone (a glucocorticoid) and azathioprine. The response to these treatments can take weeks to many months, with the maximal effect taking months to years.[1,2]

Prednisone

Prednisone or another corticosteroid is the primary immunosuppressant used in myasthenia gravis. Sustained improvement or remission can be achieved while patients remain on treatment. A typical course for generalised myasthenia gravis would use 1 mg/kg prednisone daily (0.5 mg/kg for ocular myasthenia gravis) until clinical control is achieved and then weaning either directly or by initial conversion to alternate daily dosage, with the determination of a maintenance dose by trial and error during a slow withdrawal of medication over many months. Deterioration in myasthenia gravis can occur in the first few weeks of treatment so the dose is often increased slowly. The mean time to maximal effect of prednisone in myasthenia gravis is six months – much longer than most expect.

Azathioprine

Azathioprine is used as a steroid sparing drug and additional immunosuppressant with prednisone. In a randomised trial, after three years of treatment, 63% of patients with myasthenia gravis taking azathioprine were off all prednisone, versus 20% taking placebo, but no effect was seen in the first year.[2] Compared to the metabolic consequences of continued corticosteroids, the problems of azathioprine seem significantly less. However, the long-term consequences do include an increased risk of skin cancers and a small possible increase in the risk of haematological malignancies. About one-fifth

of patients cannot take azathioprine due to rash, hepatitis, myelosuppression, nausea or vomiting, but this is usually evident within two weeks to two months. Some doctors routinely use azathioprine for patients with generalised myasthenia gravis still requiring more than 10 mg prednisone per day at six months, or if severe disease is obvious earlier.

Other drugs

If not using azathioprine, other steroid-sparing drugs used include mycophenolate mofetil, cyclosporin, methotrexate and cyclophosphamide. Experience with these drugs is generally derived from retrospective series. None of these have proven efficacy in randomised trials except for cyclophosphamide, and choice of drug depends on age and competency of the patient plus local experience of the physician. In practice they are frequently used with apparent success, but like azathioprine the response is often slow.

Mycophenolate mofetil is a pharmacologically similar alternative to azathioprine but two recent randomised controlled trials failed to demonstrate benefit in myasthenia gravis.* The duration of both trials was less than a year. As it works in the same pathway as azathioprine this may have been inadequate and it remains widely used.

Rituximab, a monoclonal antibody specific to CD20 (on B cells), or bone marrow ablation with autologous transplant are treatments of last resort.

Remove or block autoantibodies

Plasma exchange removes autoantibodies and intravenous immunoglobulin is thought to block autoantibodies. These treatments take effect within days, but only last weeks before treatment needs to be repeated. They have a key role in stabilising severe myasthenia gravis and in preparation for surgery, or in pregnancy.

Plasma exchange is expensive and only available in major hospitals. It requires good intravenous or alternatively central catheter access, but a central line increases the risk of infection. Intravenous immunoglobulin, a purified blood product, is also very expensive and is in limited supply. Its mode of action remains unclear.

Thymectomy

Thymectomy has a possible immunomodulatory role in the absence of thymoma. Results of a global randomised trial are awaited.† The effect of a thymectomy appears to take years. Non-randomised retrospective data suggest there is an increased complete remission rate from thymectomy when it is performed within 2–3 years of the onset of disease. This treatment involves major surgery with midline sternotomy, although minimally invasive approaches are becoming available. Other than surgical complications there are no known long-term adverse effects.

Thymectomy for thymoma does not on average improve myasthenia gravis, but is required to remove the tumour.

Drugs that worsen myasthenia gravis

Neuromuscular blocking drugs used for intubation and muscle relaxation in surgery cause profound deterioration in myasthenia gravis with marked prolongation and severity of neuromuscular dysfunction. The diagnosis of myasthenia gravis should be considered if patients fail to breathe spontaneously or are weak after an anaesthetic.

Aminoglycosides such as gentamicin partially block the neuromuscular junction and dramatically worsen myasthenia gravis. Beta blockers have a generally mild adverse effect (adrenergic stimulus is mildly beneficial for myasthenia gravis) and the need to use them should be carefully considered. Anticholinergics of all types logically have a deleterious effect on the neuromuscular junction. In practice a muscarinic anticholinergic such as propantheline is sometimes used to control the adverse effects of pyridostigmine on the gut. Many other drugs have been cited as provoking deterioration in myasthenia gravis or have myasthenia gravis listed as a contraindication to use in the product information. This includes tetracyclines and quinolones, which in practice are only occasionally problematic. Sedatives such as narcotics and benzodiazepines have no direct effect on the neuromuscular junction but obviously are contraindicated if hypercapnia or respiratory failure are a risk.

Conclusion

Myasthenia gravis is a readily treatable condition and many patients can expect to have little disability. It should be acknowledged that of the residual disability, a considerable amount comes from the treatment. Attempts to re-establish immune tolerance of the acetylcholine receptor to cure the condition have not yet borne fruit. No revolution in treatment is expected in the near future.

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* http://www.aspreva.com/clinical_trials.php#mg

† http://clinicaltrials.gov/ct/show/NCT00294658

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Stephen Reddel is an investigator of the United States National Institutes of Health (NIH) randomised clinical thymectomy trial currently underway. The NIH has paid for a trial workshop including travel. He has also received a consultancy fee from Aspreva, marketing company of mycophenolate mofetil for use in autoimmune diseases.

Self-test questions

The following statements are either true or false (answers on page 167)

3. In patients with myasthenia gravis, the maximum response to therapy is seen within six months of starting azathioprine.
4. Myasthenia gravis may be exacerbated when a patient starts prednisone.

Dental notes

Prepared by Dr M McCullough of the Australian Dental Association

Treatment of myasthenia gravis

The prevalence of myasthenia gravis (about 1 in 10 000 people) is such that every dentist will probably treat more than one patient with the condition during their career. Changes in tongue and facial muscle strength can often be the first sign of myasthenia gravis. These changes may impact on oral hygiene and the ability to wear dentures. Postural changes and the potential for the patient's medication to interact with drugs given by the dentist means that patients with myasthenia gravis have specific needs during dental treatment.

A review of the dental literature recommended that, depending on the severity of disease, patients should have multiple, short, early morning appointments, perhaps preceded by oral anticholinesterase drugs, to take advantage of their early morning muscle strength.[1] Factors related to dental treatment that are likely to worsen myasthenia gravis should be avoided, such as stressful protracted procedures, the use of ester-linked local anaesthetics (not available in Australia) and the use of antibiotics that have some muscle relaxing properties (erythromycin, gentamicin, neomycin and clindamycin).[1] The use of these drugs, as well as the use of benzodiazepines, sedation and general anaesthesia, has been reported to worsen muscle weakness and should only be undertaken after consultation with the patient's physician. To avoid complications, dentists should therefore have good communication not only with the patient, but also with the treating physician.

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Patient support organisation

Australian Myasthenic Association in NSW

The Australian Myasthenic Association in NSW was set up to support sufferers of myasthenia gravis and their carers. It has members from all over Australia and overseas.

The website contains useful information about myasthenia gravis, its causes, symptoms, diagnosis, treatments and history. There are links to a range of patient support resources such as newsletters, chat facilities, events, patient experiences and practical lifestyle advice. A membership fee entitles members to receive the association's newsletters and goes towards funding events and other costs.

Website: www.myasthenia.org.au
Email: info@myasthenia.org.au
Phone: (02) 4283 2815
Address: 108 Bantry Bay Road
FRENCHS FOREST NSW 2086

Myasthenia gravis: a patient's perspective

Mark Latham was the United Nations representative in the Cape Verde Islands. He was 56 years old when he developed myasthenia gravis in 1998.

AP: *What were the first symptoms you had?*

ML: I had some back pain due to all the packing and unpacking I do on my travels, but then I began to feel weaker. The orthopaedic opinion was that I had a disc problem and I was advised to rest in bed.

During this period of bed rest I noticed my arms were weak. It was difficult to hold a book to read. Over the next few weeks I experienced some difficulty chewing and swallowing.

AP: *How was the diagnosis made?*

ML: I had to travel to the UN headquarters in New York, but I was so weak I had to do the whole journey on a stretcher. When I got to the USA I was taken by ambulance to the emergency department of a large city hospital. My wife suggested that I had a neurological problem so a neurologist was called to see me. He quickly diagnosed myasthenia gravis and confirmed this by giving me an injection which promptly improved how I felt.

AP: *How did you feel about the diagnosis?*

ML: Myasthenia gravis did not mean anything to me, but I was glad that somebody now knew what was wrong with me.

AP: *What treatment were you given?*

ML: I was given prednisone and pyridostigmine. Within a week I was walking, but then I began to feel worse. I then collapsed. I was paralysed and only able to move my wrist and head. It was hard to breathe. I was admitted to intensive care and had three hours of plasmapheresis every other day for seven sessions. This had to be done through a femoral tap.

Azathioprine was added to my treatment and I gradually improved. Being able to sit up and turn myself over in bed were big achievements. While I was in New York I had my thymus removed.

AP: *How were you able to get around?*

ML: I lost a lot of muscle so I had to learn to walk again. When I was discharged from hospital I was in a wheelchair. I stayed in a hotel for a month and just had to practise walking up and down the corridor, first with a frame and then with a stick. I had physiotherapy three times a week.

Going out of the hotel was difficult. I could not lift my feet over the smallest step and I fell over several times. When I went to hospital by taxi I was unable to get out of my seat.

AP: *Were you able to work?*

ML: When I returned to the Cape Verde Islands I waited a month to build up my strength before resuming work.

Back at work I found that I was easily fatigued. I could only sit in meetings for an hour. Having a chair with a high back helped to support my head.

AP: *Have you had any relapses?*

ML: About six months after returning to the Cape Verde Islands I started feeling increasingly weak particularly in the legs and neck. My eyelids started to droop and my breathing became laboured.

This time I was treated in Oxford, England. By the time I got there my eyelids were completely closed and breathing was very difficult. My eyes stayed shut for six weeks. The pyridostigmine and azathioprine were continued and the prednisone was increased. I also had plasmapheresis and I gradually recovered.

I retired to Sydney in 2000 and had one recurrence of weakness in 2002 when I experienced double vision. This was managed with plasmapheresis.

AP: *Have you had any side effects from your treatment?*

ML: The pyridostigmine gives me nausea and a headache. I had to have cataracts removed from both eyes as a result of the prednisone. I have also had a few skin cancers removed and now take mycophenolate in place of azathioprine.

AP: *How are you managing now?*

ML: My weakness can vary from day to day. On some days I can walk five kilometres, on others I can barely manage one kilometre. I am unable to run.

I am able to drive again, but manual transmission was a problem. In a traffic jam my left leg ran out of strength and I was unable to move the clutch pedal. I now drive an automatic.

The main problem now is fatiguability. I've retired, so the fatigue is manageable and does not interfere with my lifestyle.

Antipsychotic drugs in pregnancy and breastfeeding

Debra Kennedy, Director, MotherSafe, Royal Hospital for Women, and Conjoint Lecturer, School of Women's and Children's Health, University of New South Wales, Sydney

Summary

There are limited data on the safety of antipsychotic drugs in pregnancy and breastfeeding. Reports of congenital abnormalities in the babies of women taking typical antipsychotics are uncommon, although chlorpromazine may cause symptoms in the neonate. No increased risk with atypical antipsychotics has yet emerged. If women can be managed with a low dose of a single antipsychotic drug the benefits of breastfeeding are likely to outweigh the risk of harmful effects.

Key words: chlorpromazine, olanzapine.

(Aust Prescr 2007;30:162–3)

Introduction

The lifetime prevalence of schizophrenia is 0.5–1%. The peak incidence in women is during their childbearing years, but treatment can reduce fertility. The older antipsychotic drugs increase prolactin, resulting in significantly lower fertility rates than with the atypical antipsychotic drugs. The newer antipsychotics are also being used increasingly to treat other psychiatric disorders such as major depression and bipolar disorder. Many women with well-controlled psychiatric disease are therefore now able to contemplate pregnancy, but they have concerns about the effect of treatment on their offspring. Addressing these concerns is difficult because of a lack of data.

Typical antipsychotic drugs

Studies examining the use of the older antipsychotic drugs in pregnancy have not shown a significantly increased risk of birth defects above the baseline rate of 3% in the general population.[1] There have been reports of two infants exposed to haloperidol with isolated limb defects, but they were also exposed to other drugs and thus there is no clear causal relationship with haloperidol. In contrast, there have been several larger studies which have not shown an increased risk of birth defects. Babies exposed to haloperidol and chlorpromazine *in utero* may show extrapyramidal abnormalities, similar to those seen in adults, for weeks after birth. Other suspected withdrawal symptoms following intrauterine exposure to chlorpromazine have included paralytic ileus, necrotising enterocolitis, fever, cyanotic spells and transient heart block.

Long-term follow-up studies of children have been reassuring. While these drugs probably still have their place in the treatment of acutely psychotic patients, they have largely been superseded by the atypical antipsychotics for long-term therapy.[2,3]

Flupenthixol and the depot preparation zuclopenthixol are thioxanthene major tranquillisers. There are minimal human data apart from some case reports of normal outcomes following use in pregnancy. Like the older antipsychotic drugs they have been shown to affect fertility via dopamine and prolactin pathways.

Lactation

Chlorpromazine and haloperidol are excreted in human milk in small amounts. In one report, three breastfed infants exposed to haloperidol and chlorpromazine showed developmental regression which was not seen in infants exposed to trifluoperazine alone, suggesting that use of a single antipsychotic drug poses less of a risk to a breastfed infant. No adverse effects were reported in four infants exposed to flupenthixol via breast milk.

Atypical antipsychotic drugs

One study followed up over 150 cases of exposure to atypical antipsychotic drugs (olanzapine, risperidone, quetiapine and clozapine) in the first trimester of pregnancy. There were no differences in any of the pregnancy outcomes of interest, apart from low birth weight, which could not be explained by the study's authors. The rate of malformations in the exposed group was no greater than in the control group.[4]

Animal studies have not shown an increased risk of malformations with clozapine. Although human pregnancy data are relatively limited, there does not appear to be a significant increase in the incidence of birth defects or other adverse outcomes. There is one case report of a child with possible delayed speech acquisition following clozapine use during pregnancy and lactation.[5] No other long-term neurodevelopmental follow-up data are available.

Concerns have been raised that olanzapine in particular tends to be associated with significant weight gain. During pregnancy this could be associated with an increased incidence

of outcomes, including increased rates for birth defects such as neural tube defects and an increased risk of obstetric complications. Theoretical concerns about a relative folate deficiency have prompted some experts to suggest that women planning pregnancy while taking olanzapine should take 5 mg folate rather than the usual 0.5 mg to try and reduce the risk of neurodevelopmental disabilities.[6]

Lactation

Limited information shows that maternal doses of olanzapine up to 20 mg/day produce low levels in milk and undetectable levels in breastfed infants. Generally, short-term adverse effects have not occurred, and sedation has not been reported. Limited long-term follow-up of infants exposed to olanzapine has been reassuring, particularly with monotherapy.

Conclusion

The potentially harmful effects of taking an antipsychotic drug in pregnancy have to be balanced against the harm of untreated psychotic illness. Data are limited, particularly for the atypical antipsychotic drugs, but there are no clear associations with specific congenital abnormalities.

The benefits of breastfeeding are likely to outweigh the potential harm of medication. Women who wish to breastfeed should be managed with a single antipsychotic drug if possible. All antipsychotic drugs are sedating and have relatively long half-lives, so babies should be observed for lethargy, sedation and appropriate developmental milestones particularly if multiple antipsychotic drugs are used.

Note: A national register of antipsychotic medication in pregnancy has been developed. For information phone (03) 9076 6988 or email H.Gilbert@alfred.org.au

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Conflict of interest: none declared

New drugs

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

Abatacept

Orencia (Bristol-Myers Squibb)

vials containing 250 mg lyophilised powder

Approved indication: rheumatoid arthritis

Australian Medicines Handbook section 15.2

The primary goal of treatment for rheumatoid arthritis is to preserve and restore physical function as well as modify the disease process and slow down the development of joint damage. In Australia, methotrexate is initially used to manage the disease. It is often given with other disease-modifying antirheumatic drugs (DMARDs) for moderate to severe disease (Aust Prescr 2003;26:36–40). If these drugs are not effective or not tolerated, biological agents such as tumour necrosis factor (TNF) inhibitors may be considered.

Abatacept, a genetically-engineered protein, is a biological drug for rheumatoid arthritis which is designed to suppress T cell-mediated inflammatory reactions. It is made up of the extracellular part of the human cytotoxic lymphocyte-associated antigen (CTLA-4) linked to a fragment of human immunoglobulin G. Abatacept works by binding to two signal molecules (CD80 and CD86) on antigen-presenting cells, thereby preventing them from activating T cells.

Abatacept should be given as a 30-minute intravenous infusion. The dose is dependent on the patient's body weight. The infusion should be repeated at two and four weeks and then every four weeks after that. Following multiple 10 mg/kg intravenous infusions of abatacept, the serum concentration reaches a steady state after 60 days. The mean half-life is approximately 13 days in patients with rheumatoid arthritis, and clearance increases with body weight.

When given as a monotherapy to patients with severe active rheumatoid arthritis, more patients responded to abatacept (10 mg/kg) than to placebo. After 85 days, a 20% clinical improvement (based on the criteria of the American College of Rheumatology) was observed in 53% of patients on abatacept compared with 31% on placebo.[1] This study was primarily a dose-finding trial and so there were only 32 patients in the abatacept 10 mg/kg group.

Abatacept appears to be efficacious when given in combination with other DMARDs.[2,3,4,5,6] In a trial of patients with active disease despite methotrexate, 652 patients were randomised to also receive abatacept or placebo. After a year, 73% of patients given abatacept had a 20% clinical improvement compared to only 40% of those given placebo. There was slower radiological progression of joint damage in the abatacept group.[4]

In another trial patients who had not responded to anti-TNF therapy received either abatacept or placebo with another DMARD. More patients in the abatacept group than in the control group had a 20% improvement (50% vs 20% of patients after six months). However, reduced progression of joint damage was not established in these patients.[5]

Infusion-related reactions, such as dizziness and headache, are common with abatacept. In a one-year safety trial of 1441 patients, serious infections were more frequent with abatacept than with placebo (2.9% vs 1.9%). Pneumonia was the most common type of serious infection. In patients receiving other biological drugs as well as abatacept, the rate of serious infections increased to 5.8%. Overall, the incidence of neoplasms was similar with abatacept compared to placebo (3.5%). However, this rate increased to 6.8% in patients who were also taking other biological drugs. In patients with chronic obstructive pulmonary disease, there were more adverse events with abatacept than with placebo.[7]

As abatacept inhibits T cell activation, it may affect a patient's ability to fight infections or malignancies. Caution is needed when treating patients who have a history of recurrent infections and patients should be checked for latent tuberculosis infections and viral hepatitis before starting treatment. Live vaccines should be avoided.

Abatacept in combination with methotrexate is indicated for patients with moderate to severe rheumatoid arthritis who have had an inadequate response or intolerance to other DMARDs. Non-biological DMARDs can be used with abatacept, however, it should not be given with biological drugs such as adalimumab, anakinra, etanercept and infliximab.

As rare but potentially fatal adverse effects can occur with abatacept, longer-term safety studies are needed. It is not known how abatacept compares with other treatments for rheumatoid arthritis as there do not appear to be any comparative studies.

T T T manufacturer provided clinical evaluation

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Exenatide

Byetta (Eli Lilly)

250 microgram/mL in 1.2 mL and 2.4 mL pre-filled pen injectors

Approved indication: type 2 diabetes

Australian Medicines Handbook section 10.1.4

An oral dose of glucose causes more insulin secretion than the same dose given intravenously. This is because glucose in the gut stimulates the release of hormones called incretins which increase insulin secretion. As this action would have a favourable effect in diabetes researchers have tried to develop drugs with a similar action.

One of the incretins is a glucagon-like peptide (GLP-1). The venom of a lizard *(Heloderma suspectum)* contains a peptide with a similar structure and this led to the development of exenatide, an injectable synthetic peptide that acts as a GLP-1 agonist.

Unlike GLP-1, exenatide is not rapidly inactivated. Instead it is cleared by the kidneys at a rate which enables twice-daily dosing. Plasma concentrations peak two hours after a subcutaneous injection so exenatide should be injected before morning and evening meals.

Postprandial and fasting glucose concentrations are reduced by exenatide. It also moderates glucagon secretion, slows gastric emptying and decreases appetite.

A 28-day study investigated different regimens of exenatide in patients being treated for type 2 diabetes. Compared to the 28 patients randomised to receive placebo, the 81 patients injecting exenatide had significantly greater reductions in glycated haemoglobin (HbA1c).[1]

A longer-term study looked at adding exenatide to the treatment of patients whose diabetes was not controlled by the maximum dose of sulfonylureas. Placebo injections were given to 123 patients, while 125 injected exenatide 5 microgram and 129 injected 10 microgram. All injections were given twice daily. At the start of the study the HbA1c averaged 8.6%. In the 30th week of the trial this had fallen by 0.46% with exenatide 5 microgram and by 0.86% with 10 microgram. In the placebo group HbA1c increased.[2]

A similar study compared the two doses of exenatide with placebo in 336 patients taking at least 1.5 g metformin daily. After 30 weeks HbA1c had declined by 0.4% with 5 microgram exenatide, 0.78% with 10 microgram, while it had increased in the placebo group.[3]

Another 30-week study enrolled patients who were already taking metformin and the maximum dose of a sulfonylurea. There were 247 patients who injected a placebo twice daily, 245 who injected exenatide 5 microgram and 241 who injected 10 microgram. At the end of the study, HbA1c had declined by 0.6% with exenatide 5 microgram, 0.8% with 10 microgram and had increased with placebo.[4]

Exenatide has also been studied in patients whose diabetes has not been controlled by a thiazolidinedione with or without metformin. A group of 121 patients injected exenatide and 112 injected a placebo twice daily. After 16 weeks the HbA1c had decreased by 0.89% with exenatide 10 microgram and increased by 0.09% in the placebo group.[5]

After the placebo-controlled trials, 668 patients who had taken exenatide continued using it in open-label extension studies. A total of 314 patients completed a further 52 weeks of treatment. The reduction in HbA1c seen at the end of the placebo-controlled studies was maintained.[6]

In the medium-term placebo-controlled studies, more patients dropped out of the exenatide groups because of adverse effects.[2,3,4,5] In the trial adding exenatide to a thiazolidinedione, 16% of the patients withdrew because of adverse effects compared with only 2% of the patients who added a placebo.[5] A common problem with exenatide is nausea. It affects more than 40% of patients some of whom will vomit. Diarrhoea and dyspepsia are also more frequent than with placebo. There is an increased frequency of hypoglycaemia when exenatide is added to regimens containing a sulfonylurea. The dose of sulfonylurea may need to be reduced.

The exenatide molecule is not identical to human GLP-1. Some patients will develop antibodies against exenatide. Hypersensitivity reactions may occur and it is possible that high antibody titres could reduce the efficacy of exenatide.

During the 30-week trials, patients randomised to take exenatide lost 1–3 kg in weight.[2,3,4] This continued in the open-label extension studies.

Exenatide's role in therapy is unclear. If optimum therapy with oral hypoglycaemic drugs does not control a patient's type 2 diabetes, introducing insulin is the next step. Although exenatide appears to have a similar effect on HbA1c to once-daily insulin glargine[7] or twice-daily insulin aspart[8] in open-label studies, it causes more adverse effects. In the comparison with insulin glargine, 19.4% of the 282 patients injecting exenatide dropped out, compared with 9.7% of the 267 patients injecting insulin.[7] In the comparison with insulin aspart the corresponding figures were 21.3% of the 253 patients injecting exenatide and 10.1% of the 248 patients injecting insulin.[8] Gastrointestinal adverse reactions were common with exenatide and contributed to these withdrawals.

In Europe there is a risk management plan to monitor for safety concerns such as pancreatitis and anti-exenatide antibodies. Long-term outcomes with exenatide are currently unknown.

As it is relatively expensive, the use of exenatide may be limited to obese patients with insulin resistance, but this will require further study. At present, the Australian approval is for adjunctive therapy in patients who are not achieving adequate glycaemic control with metformin, a sulfonylurea, or both.

☒ manufacturer declined to supply data

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Telbivudine

Sebivo (Novartis)

600 mg tablets

Approved indication: chronic hepatitis B

Australian Medicines Handbook section 5.3

Worldwide, hepatitis B is the most common form of viral hepatitis. Some people who are infected develop chronic hepatitis B which may lead to serious liver disease such as cirrhosis and hepatocellular carcinoma. Chronic hepatitis B infection is usually diagnosed by detecting viral antigens and their corresponding antibodies, and viral DNA in serum.[1] Current drugs used to treat chronic hepatitis B include interferons and nucleotide/nucleoside analogues (lamivudine, adefovir and entecavir).

Telbivudine is a synthetic thymidine analogue which inhibits the replication of hepatitis B virus by binding to its DNA polymerase and causing DNA chain termination. It is indicated for chronic hepatitis B (irrespective of whether the patient has the hepatitis B e antigen (HBeAg) or not) in patients who have compensated liver disease, evidence of viral replication and liver inflammation and who have not previously been treated with another nucleoside analogue such as lamivudine.

Following oral administration of telbivudine (600 mg), peak plasma concentrations occur within 1–4 hours. Telbivudine has an overall terminal half-life of around 42 hours and is eliminated mainly unchanged in urine. Patients with impaired renal function may need a dose interval adjustment.

In a phase I placebo-controlled trial, the safety, antiviral activity and pharmacokinetics of telbivudine were assessed in 43 adults with HBeAg-positive chronic hepatitis B. Patients were given one of six different daily doses of telbivudine for four weeks and were followed up for 12 weeks after treatment. The antiviral activity of telbivudine, measured by quantifying serum viral DNA (using the polymerase chain reaction), appeared to be higher at doses of 400 mg or above.[2]

A subsequent phase II trial compared the safety and efficacy of telbivudine (400 or 600 mg/day) and lamivudine (100 mg/day) alone or in combination, in 104 patients with HBeAg-positive chronic hepatitis B. At week 52, there was no detectable viral DNA in 61% of patients on telbivudine monotherapy compared to 32% of patients on lamivudine monotherapy ($p<0.05$). Likewise, a greater proportion of patients taking telbivudine monotherapy had improved liver function (normalisation of alanine transferase) compared to those taking lamivudine monotherapy (86% vs 63%, $p<0.05$). Combination treatments with telbivudine were no more effective than telbivudine alone.[3]

Results of a two-year multicentre phase III trial comparing telbivudine (600 mg/day) and lamivudine (100 mg/day) are currently unpublished. This trial included approximately 1300 patients with HBeAg-positive or -negative chronic hepatitis B. Interim results suggest that viral suppression was greater in patients treated with telbivudine than in those treated with lamivudine. Improvements in liver function were not statistically different between the two treatments.

The efficacy of telbivudine has also been compared to adefovir in an open-label trial of 136 HBeAg-positive patients. After a year of treatment, there seemed to be greater viral suppression with telbivudine than with adefovir.[4]

In the phase II and III trials, genetic evidence of viral resistance was found following viral breakthrough in some patients.[3] In *in vitro* studies, some viral strains that showed resistance to other nucleotide/nucleoside analogues, such as lamivudine or adefovir, also had reduced susceptibility to telbivudine.

The safety profiles of telbivudine and lamivudine were comparable in the phase III trial, with muscle-related symptoms being the most common treatment-emergent clinical adverse events, occurring in 2% of all patients. Creatine kinase elevations occurred in 9% of telbuvidine-treated patients and 3% of lamivudine-treated patients.

Telbivudine comes with a warning about the risk of myopathy. Patients taking telbivudine should therefore be advised to report any unexplained muscle aches, pain, tenderness or weakness. Treatment should be stopped if myopathy is diagnosed.

Health professionals should also be aware that discontinuing telbivudine treatment may lead to severe acute exacerbations of hepatitis B infection. Hepatic function should be monitored for a minimum of several months once therapy has been stopped. When monitoring hepatic function in patients taking telbivudine, check for flares in alanine transferase.

Telbivudine offers a new therapy for patients diagnosed with chronic hepatitis B infection. While telbivudine seems to be effective at reducing viral loads, we do not know if viral resistance will become a problem. It is not known if this drug will reduce the long-term complications associated with chronic hepatitis B.

T manufacturer declined to supply data

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The T-score (T) is explained in 'Two-way transparency', Vol 28 No 4, 2005 (Aust Prescr 2005;28:103).

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

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

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