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EDITORIAL

Outcomes of the Cochrane Airways Group International Conference

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Index words: asthma, systematic reviews, corticosteroids.

(Aust Prescr 2001;24:78–9)

The Cochrane Airways Group and the Commonwealth Department of Health and Aged Care held a meeting in Newcastle in March this year to discuss systematic reviews in asthma, and how these might be implemented to encourage good clinical practice.

Understanding best evidence is an essential part of good clinical practice. This can improve health when combined with an evaluation of the patient's clinical status and treatment preferences. The cornerstone of best evidence comes from systematic reviews of randomised controlled trials. The Cochrane Airways Group produces systematic reviews of treatment for asthma, chronic obstructive pulmonary disease, bronchiectasis, sleep disordered breathing, and pulmonary fibrosis. Asthma is a particularly topical area as the Commonwealth Department of Health and Aged Care has made it a national health priority.

The Cochrane Airways Group involves over 230 reviewers and 12 editors worldwide. This group has produced 47 systematic reviews on the treatment of asthma from the results of trials involving 37 525 patients.[1] A recent independent evaluation of systematic reviews in asthma confirmed the high quality of these reviews.[2]

In this issue...

Peter Gibson tells us how studying the evidence from clinical trials can guide the management of common conditions such as asthma.

There is limited evidence about the effectiveness of post-exposure prophylaxis, but Frank Bowden suggests when it is indicated after a needle-stick injury.

Warfarin is indicated in a growing number of patients, many of whom are elderly. Alex Gallus and colleagues advise us on how to minimise the risks of warfarin therapy in the community.

While Parkinson's disease is thought of as an older person's problem, Kay Messiter's case reminds us that it can affect younger people. Victor Fung and colleagues update us on the management of this condition.

Systematic reviews and guidelines

Guidelines for the management of asthma are typically consensus-based documents that are periodically updated. Asthma reviews from the Cochrane Airways Group are an important resource that can be used to update guidelines and enable the use of best evidence to strengthen recommendations. The meeting reviewed several guideline recommendations in the context of the results of recent Cochrane reviews. The results (see box) show that systematic reviews can improve asthma guidelines by identifying other treatment modalities, quantifying the benefit of a treatment, or resolving disagreement between guidelines.

Inhaled corticosteroids

Three main corticosteroids (beclomethasone, budesonide and fluticasone) are used in the treatment of asthma. These drugs can be given via several different devices across a dose range that varies 40-fold. Systematic review of 709 trials involving 2443 patients showed a significant benefit for beclomethasone over placebo, with an average improvement in FEV_1 of 340 mL. Fluticasone achieved the same benefit at 50% of the dose, suggesting increased potency. There was evidence of a dose-response effect with fluticasone, both for improvement in lung function and for increased oropharyngeal adverse effects.

These studies support the use of low doses of inhaled corticosteroid up to fluticasone 200 microgram/day, or beclomethasone/budesonide 400 microgram/day. The benefit of a higher dose is marginal and the adverse effect profile escalates. In Australia, the doses of inhaled corticosteroid used tend to be much higher. The reviews question this practice and reinforce the need to reduce the dose to the minimum needed to maintain asthma control.

Implementing recommendations from reviews

Systematic reviews seek to summarise the best available evidence. However, this alone does not necessarily ensure that clinical practice will change. The meeting examined the best ways to implement the results of a review or guideline recommendation in an Australian context, using the delivery of bronchodilator by nebuliser or by puffer/spacer as an example. A systematic review found that in acute asthma,

Cochrane systematic reviews can improve guidelines

Guideline recommendation	*Systematic review results*	*Impact of review*
Administer beta agonist by nebuliser	Delivery by puffer/spacer has similar efficacy to nebuliser[3]	Review identifies an alternative treatment modality
Administer oral corticosteroid	Reduces risk of hospitalisation by 60%, NNT* = 8[6,7]	Review quantifies benefit of treatment
Aminophylline • 2nd line therapy (UK guidelines) • use is uncertain (Australian guidelines)	Aminophylline of no additional benefit to beta agonist, but has increased adverse effects[8]	Review recommends against use of aminophylline (because of adverse effects)

* Number needed to treat

delivery of a beta agonist by puffer/spacer has similar (in adults) or improved (in children) efficacy with fewer adverse effects (in children) compared to delivery by nebuliser.[3] This contrasts with Australian practice where nebulisers are often used to give a beta agonist in acute asthma.

Two studies presented at the meeting detailed methods used to encourage the use of a puffer/spacer in acute asthma. Simply mailing the guideline with educational material had no impact on clinical practice. In both studies, a positive change in clinical practice was seen when a multifaceted intervention based upon available evidence was used.[4] The target audience needs to be defined, and the message tailored to the needs and interests of that audience. Successful interventions use several components including local adaptation of evidence-based guidelines that are widely disseminated to medical managers and implemented through respected opinion leaders, supported by interactive educational sessions delivered by peers, and reinforced by reminders at the point of prescribing. The best results have been obtained from a multifaceted intervention involving audit and feedback.[5] These studies show that it is possible to change clinical practice using the results of a systematic review to implement best evidence. However, even for a relatively simple intervention, a structured, evidence-based approach is required to ensure success.

Researching asthma outcomes

The large number of clinical trials reviewed by the Cochrane Airways Group provide an opportunity to examine the design of research studies. A key area is that of outcome measures in asthma. There are many outcomes used in asthma research, and each is reported in a variety of ways. For example, the lung function outcomes can be reported as end of study values, or change from baseline, and expressed either in absolute terms, as a percentage of the predicted value or as a percentage of the baseline value. The ability of these measures to detect change (sensitivity), and their reliability across studies has been examined using data from the systematic reviews of the Cochrane Airways Group. These results have shown that changes from baseline provide the most sensitive and reliable measures of response in asthma clinical trials, and FEV_1 appears to be the best measure of airway function. Morning and evening measurements of peak expiratory flow have equal utility to each other and perform better than measures of variability in peak flow.

Conclusion

The outcomes of the conference identified clear directions for improving the health of people with asthma. Guidelines based on systematic reviews can give clear recommendations and help standardise and improve the level of care delivered to people with asthma. Understanding the requirements for successful implementation of evidence-based guidelines will increase the likelihood of their success. Reducing corticosteroid doses and unnecessary nebuliser use in line with the recommendations of systematic reviews can minimise unnecessary drug dosing and costs, and possibly adverse effects. These outcomes also suggest opportunities for enhancing good clinical practice in asthma.

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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.

Cytochrome P450 drug interactions

Editor, – We are writing with respect to the article 'Cytochrome P450 drug interactions: are they clinically relevant?' by J. Martin and M. Fay (Aust Prescr 2001;24:10–2).

In this article, the authors state 'Some selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine, paroxetine and fluvoxamine) inhibit CYP2D6… The addition of fluoxetine, paroxetine or fluvoxamine (CYP2D6 inhibitors)…'.

These statements are not accurate in that fluvoxamine maleate has, to date, not been shown to be a significant inhibitor of CYP2D6 – *in vitro* or clinically.[1–7] The product information clearly states that 'Fluvoxamine has only a weak effect on CYP2D6, and it is therefore not likely that it will increase plasma concentrations of drugs metabolised by CYP2D6 to a clinically relevant effect'.

Pamela Noble
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Solvay Pharmaceuticals
Pymble, NSW

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Dr J. Martin and Dr M. Fay, authors of 'Cytochrome P450 drug interactions: are they clinically relevant?', comment:

It is prudent to be aware of the safety issues when prescribing fluvoxamine with other drugs that are metabolised by the cytochrome P450 system. Fluvoxamine, however, has only a weak inhibitory effect on CYP2D6 and we agree with Solvay Pharmaceuticals that this is unlikely to be as clinically significant as fluvoxamine's other well-documented drug interactions.

Editor, – It may be useful for readers to have some additional information about psychotropic drugs and cytochrome P450 enzymes (Aust Prescr 2001;24:10–2).

Fluvoxamine seems not to significantly inhibit 2D6 as it has no effect on the O-demethylation ratio of dextromethorphan at a steady state dose of 100 mg/day. However, fluvoxamine potently inhibits cytochrome P450 1A2 and most patients treated with even low doses of 100 mg/day will reach population minimums for CYP1A2 activity (i.e. become poor metabolisers). Other potent inhibitors of 1A2 are mexiletine, lidocaine, and (weaker) tocainide, and also flavones – a class of dietary phytochemicals found at high concentrations in tofu.

Cytochrome P450 1A2 metabolises many structurally related psychotropic drugs – for instance all the quaternary tricyclic antidepressants (clomipramine, amitriptyline, doxepin, dothiepin, but not nortriptyline) and also many neuroleptics like clozapine, olanzapine, chlorpromazine and structurally related drugs. Their metabolism is also induced by cigarette smoking which may have significant clinical consequences.

Besides nefazodone, fluoxetine (via its metabolite norfluoxetine, which can have a half-life of up to 14 days) is also an inhibitor of cytochrome P450 3A4 and may thus, *inter alia*, inhibit ergotamine metabolism and precipitate ergotism.

It is incorrectly stated in the article that serotonin syndrome can be precipitated by combining tricyclic antidepressants and selective serotonin reuptake inhibitors.

Ken Gillman
Honorary Senior Lecturer
James Cook University
PsychoTropical Research Unit
Townsville, Qld.

Dr J. Martin and Dr M. Fay, authors of 'Cytochrome P450 drug interactions: are they clinically relevant?', comment:

The letter from Dr Gillman gives some interesting information on potential cytochrome P450 interactions with psychotropic drugs. However our brief was to focus on clinically significant drug interactions only, and we tried to use only reports from the literature that indicated clinical significance. The aim of the article was to provide a few general rules to help clinicians identify potential drug interactions, rather than provide an exhaustive list.

However, there are several points in this letter which we would like to comment on. Firstly fluoxetine, although having an active and long half-life metabolite, is unlikely to have much clinically relevant inhibition of CYP3A4. The evidence comes from *in vivo* studies with terfenadine and midazolam (CYP3A4 substrates) which showed no increase in plasma concentrations of these with the addition of fluoxetine, and no change in cognitive state when added to midazolam. *In vitro*, fluoxetine has one hundred times less CYP3A4 inhibition than ketoconazole.

Secondly, serotonin syndrome can be precipitated by giving a selective serotonin reuptake inhibitor to a patient already on a tricyclic antidepressant. Concentrations of amitriptyline, clomipramine, imipramine and maprotoline have been shown to increase up to five fold with the addition of both fluoxetine

and fluvoxamine. This is associated with anticholinergic, serotonergic and adrenergic adverse effects.

Editor, – In the article on cytochrome P450 drug interactions (Aust Prescr 2001;24:10–2) there is mention of the inductive capacity of St John's wort on the CYP3A4 enzyme. In view of the high first-pass effect on oestradiol and the intermediate effect on ethinyloestradiol, is it possible for pill failure, breakthrough bleeding and postmenopausal bleeding to occur when St John's wort is used by women on the oral contraceptive or hormone replacement therapy?

James Brodribb

Obstetrician and Gynaecologist

Hobart

Dr J. Martin and Dr M. Fay, authors of 'Cytochrome P450 drug interactions: are they clinically relevant?', comment:

We agree with Dr Brodribb that there is likely to be quite a significant drug interaction with St John's wort (CYP3A4 inducer) and oestrogen/progesterone (CYP3A4 substrates) combinations. However, we were unable to find case reports of this in the literature, unlike the interactions with St John's wort and other 3A4 substrates. However, because of the likelihood of a significant interaction we would discourage St John's wort from being used by patients taking the contraceptive pill or hormone replacement therapy. We would also encourage the reporting of any suspected drug interaction.

Activities to improve hospital prescribing

Editor, – As a director of pharmacy in an Australian public hospital, it was naturally with some interest that I read the recent discussion of activities to improve hospital prescribing (Aust Prescr 2001;24:29–31). Jonathan Dartnell correctly points out that much prescribing in hospitals is undertaken for acutely unwell patients by relatively inexperienced prescribers, and that factors such as rapid staff turnover and poor information systems can exacerbate the problems caused by these factors. It was particularly disappointing, therefore, to discover that the discussion fails to address the important roles played by hospital-based pharmacists in advancing the quality of prescribing.

Advanced clinical pharmacy services are widely established in our hospitals, and make a substantial contribution to the quality of prescribing in these institutions (and the wider community). A properly resourced clinical pharmacy service allows experienced pharmacists with specialist expertise to work alongside hospital-based prescribers to improve outcomes for patients through activities such as drug therapy monitoring, or screening for adverse drug reactions and interactions. Despite Dr Dartnell's assertion that there is little information available about drug use in our hospitals, pharmacy departments around Australia maintain active drug utilisation evaluation programs, providing a sound basis for locally targeted educational strategies, and underpinning audit and feedback activity that can make a real difference to prescribing patterns. In contrast to confrontational approaches such as the enforcement of prescribing restrictions, a co-operative approach that brings together doctors, nurses and pharmacists in a multidisciplinary effort to improve prescribing has a durable and positive effect upon prescribing practices.

Neglecting recognition of the role of skilled clinical pharmacy practitioners in influencing prescribing is a curious omission from a discussion focused upon ways to improve drug use in hospitals. Simply providing information (such as prescribing guidelines) is not enough. Without the sustained contribution of clinical pharmacists as a way to influence prescribing in hospitals, and the substantial contribution that these practitioners make to averting drug-related harm, health care in Australia would be a great deal less safe, and in all probability, much more expensive. Appropriate recognition of this contribution by funding agencies and hospital administrators is long overdue.

Chris Alderman

Associate Professor

Quality Use of Medicines and Pharmacy Research Centre

University of South Australia

Adelaide

Dr Jonathan Dartnell, author of 'Activities to improve hospital prescribing', comments:

I agree that pharmacists are essential contributors in improving hospital drug use, as are patients, doctors, nurses, quality improvement teams, clinical pharmacologists, clinical epidemiologists, behavioural scientists and administrators. I deliberately avoided defining the roles of any of the players apart from doctors as their contributions can, and do, change depending on the availability of personnel and resources in any given setting. While we would wish otherwise, clinical pharmacy services are variably established, implemented and supported. In some hospitals advanced clinical pharmacy services are routine, in other hospitals basic clinical pharmacy is not available.

In the examples cited in my article, pharmacists were key players providing academic detailing, developing and implementing guidelines, auditing and providing feedback. This was in the context of multidisciplinary programs, such as drug usage evaluation (DUE) programs. I recognise their importance and strongly support them, but most hospitals do not have DUE programs and those that exist are not necessarily based in pharmacy departments.

A major constraint in conducting DUE is the limited drug use data that are available without resorting to manually intensive methods. The few electronic data that are available are not linked to prescribers, patients and indications, and as these data are not standardised, inter-hospital aggregations and comparisons are difficult. Community prescribing data has its own limitations but national data are available.

Electronic prescribing in hospitals

Editor, – Hugo Stephenson makes some very good points in his editorial, 'Electronic prescribing in hospitals: the road ahead' (Aust Prescr 2001;24:2–3). There is clearly a need for hospitals to implement electronic strategies to reduce adverse events, improve the quality of patient care through decision-support tools and facilitate the continuum of care between hospitals and the community.

The Austin and Repatriation Medical Centre (A&RMC), Melbourne, is in the process of implementing a fully integrated, web-based electronic health system, including electronic prescribing and administration. Features of the system will include use of mobile computing for bedside prescribing/recording and clinical decision support. We plan to pilot the electronic prescribing and administration software in November 2001 with roll-out to the Medical Centre during 2002.

Our impression from evaluation of prescribing software used in general practice is that the software would require significant modification for the hospital environment. In addition, there are scalability issues that would need to be overcome for general practice software to perform well over a hospital network.

Initial funding for implementation of the electronic health system at the A&RMC was provided by the Department of Human Services, Victoria. However, further funding will be required to complete the project.

If hospitals are to implement electronic prescribing and administration and realise the benefits of such a system, funding must be provided, as it has been for general practice.

Rosie McKew

Pharmacy Business Manager

Team Leader, Electronic Prescribing and Administration Project Team

Austin & Repatriation Medical Centre

Melbourne

Electronic prescribing in general practice

Editor, – I am writing to express my concern over the amount of errors I have seen with computer-generated prescriptions. The most alarming example I saw recently was a prescription for fluvastatin which was meant to be Fluvax [influenza vaccine]. Aside from this I have also encountered numerous prescriptions with incorrect dosages (e.g. 14 nocte for Rulide [roxithromycin] 300 mg) and many examples of incorrect strengths (e.g. Adalat [nifedipine] 60 mg instead of 30 mg). There are also a huge number of prescriptions printed out as private when they clearly are not.

Nearly all of these mistakes can easily be picked up by the doctor with a quick check of the script they have just printed out and simply require a quick handwritten correction. Computer-generated prescriptions are certainly an enormous improvement over their handwritten counterparts, however improvements can still be made with a tiny amount of effort.

Chris Morris

Pharmacist

Gold Coast, Qld.

Rh D immunoglobulin

Editor, – Further to my article on the shortage of Rhesus D immunoglobulin (Aust Prescr 2000;23:36–8), a mini-dose of Rh D was marketed in May 2001. This has the dosage of 250 IU and should be offered to every Rh D negative woman with no preformed anti-D antibodies, for problems in the first twelve weeks of gestation. The indications usually include miscarriage, termination of pregnancy, ectopic pregnancy and chorionic villous sampling. The 250 IU dose is sufficient to prevent immunisation by a fetomaternal haemorrhage of 2.5 mL of red blood cells (5 mL of whole blood).

The introduction of the mini-dose is a significant achievement as currently a larger than necessary dose is being used for these first trimester indications. This will therefore allow a more efficient usage of the limited amount of anti-D. A communication plan is being developed.

Mark Dean

Assistant Director

Australian Red Cross Blood Service – NSW

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Direct to consumer advertising

Editor, – It has become apparent in the last couple of years that many pharmaceutical companies are providing a broader spectrum of services to general practitioners and their patients. Examples include educational activities, clinical audits and patient education services.

One large multinational company states on its advertising material that it has two current databases of patient-based information containing (as at December 2000) over 22 000 and 9000 entries. These patients have been enrolled, usually by their general practitioners, often via the software utilised by the general practitioner, to receive patient educational material from the company. This material relates to particular diagnoses where the company's product has been prescribed.

Direct to consumer advertising would appear to be looming on the horizon. This would provide far easier access for the marketing and sale of pharmaceutical products, bypassing the current appropriate systems that are in place – systems such as advertising in professional journals, and distribution of pharmaceuticals through appropriate outlets.

In this case, the consumer is usually a patient. A patient often has an illness. This illness may be physical, emotional, spiritual, mental, or a combination of some or all. Consequently, it is not unreasonable to assume that the patient is vulnerable, due to disability, fear, anxiety, lack of appropriate information, etc.

Pharmaceutical companies are primarily businesses, and not benevolent societies. To succeed in today's environment a business usually has to be profit-driven, and responsible to its shareholders. Advertising plays a major role in this successful profile.

If my crystal ball gazing is correct, and direct to consumer advertising is in the pipeline, then pharmaceutical companies would be wise to prepare themselves in advance. This would make commercial sense. Data collection would have to be part of this strategy. If this does occur, then the normal gatekeeping provided by general practitioners and pharmacists will be bypassed to a large degree, and the costs of pharmaceuticals to society would presumably increase considerably.

Scott Bell

Rural and Remote Locum

Tas.

Drug interactions with oral hypoglycaemic drugs

Gillian M. Shenfield, Professor in Clinical Pharmacology, Department of Clinical Pharmacology, Royal North Shore Hospital, Sydney

SYNOPSIS

Oral hypoglycaemic drugs may interact with other drugs. Pharmacodynamic interactions occur with medications that alter blood glucose and may require the dose of the oral hypoglycaemic drug to be altered. Pharmacokinetic interactions vary with the drug group. Sulfonylureas and repaglinide are metabolised in the liver. Their plasma concentrations and activity can be reduced by drugs which induce hepatic enzymes and increased by hepatic enzyme inhibitors. Metformin is renally excreted and may have increased toxicity with drugs that impair renal function. Acarbose is only slightly absorbed across the gut and has few significant interactions. Significant interactions with the thiazolidinediones have not yet been reported, but pioglitazone is known to induce cytochrome P450 3A4.

Index words: diabetes, pharmacokinetics, lactic acidosis.

(Aust Prescr 2001;24:83–5)

Introduction

The sulfonylureas and metformin (a biguanide) have been the mainstay of drug treatment for type 2 diabetes. Recently three new types of drugs have become available; acarbose (an alphaglucosidase inhibitor), repaglinide (a meglitinide) and the 'glitazones' (thiazolidinediones) (Table 1). Drugs from one or more groups are frequently used in combination and have additive effects in lowering blood glucose. The exception to this rule is that repaglinide should not be used with the sulfonylureas since they act through the same final common pathway.

Table 1

Oral hypoglycaemic drugs in Australia

Class	*Drug*
Sulfonylureas	Chlorpropamide Glibenclamide Gliclazide Glimepiride Glipizide Tolbutamide
Biguanides	Metformin
α Glucosidase inhibitors	Acarbose
Meglitinides	Repaglinide
Thiazolidinediones	Pioglitazone* Rosiglitazone

* Approved but not marketed

All of the oral hypoglycaemic drugs have the potential to interact with other medications and if the result is hypoglycaemia or hyperglycaemia the consequences can be serious. The interactions may be pharmacodynamic (another drug independently raises or lowers blood glucose) or pharmacokinetic (another drug alters the absorption, metabolism or excretion of the hypoglycaemic drug). Both mechanisms may have the effect of changing the apparent efficacy of the hypoglycaemic drugs. Pharmacokinetic interactions may also exacerbate other adverse effects of oral hypoglycaemic drugs.

Pharmacodynamic interactions

Interactions of this type apply to all classes of hypoglycaemic drugs.

Medications which may raise blood glucose

Any drug that has the potential to raise blood glucose may produce apparent inefficacy of an oral hypoglycaemic drug. Medications which are commonly reported to increase glucose concentrations are listed in Table 2 with their probable causative mechanisms. In some cases, for example high dose corticosteroids, the patient may need insulin to control their blood glucose until the steroids are ceased.

Stopping a drug which causes hyperglycaemia may produce a significant fall in blood glucose. This may require a parallel reduction in the dose of a hypoglycaemic drug.

Table 2

Some medications that can raise blood glucose

Drug	*Probable mechanism*
Clonidine	Adrenergic action
Clozapine	? Impairs insulin secretion
Corticosteroids	Oppose insulin action
Diuretics (especially thiazides)	Oppose insulin action
Nicotinic acid	? Opposes insulin action
Nifedipine (but not other calcium antagonists)	Delays insulin action
Oral contraceptive hormones	Oppose insulin action
Phenytoin	Blocks insulin secretion
Phenothiazines	Not known
Sugar-containing syrups (e.g. antibiotics/cough mixtures)	Increased glucose intake

Note: Clinical relevance of some effects is uncertain

Table 3

Some medications that may lower blood glucose

Drug	*Suggested mechanism*
ACE inhibitors	Increase insulin action
Alcohol	Inhibits hepatic glucose production and release
Fibrates	Not known
Monoamine oxidase inhibitors	Not known
Quinine (? quinidine)	Increases insulin secretion
Salicylates (large dose)	Not known

Note: Clinical relevance of some effects is uncertain

Table 4

Potential interactions between sulfonylureas or repaglinide and drugs which alter hepatic enzymes

Inducers of metabolism (reduce concentration of hypoglycaemic drug)	*Inhibitors of metabolism (increase concentration of hypoglycaemic drug)*
Phenytoin	Allopurinol*
Phenobarbitone	Chloramphenicol
Rifabutin	Cimetidine*
Rifampicin	Erythromycin 'Azole' antifungals

* Repaglinide concentrations not increased

Medications which may lower blood glucose

Some drugs can lower blood glucose, but the mechanisms of action are not well understood (Table 3). Taking one of these drugs with a hypoglycaemic drug might cause clinically significant hypoglycaemia. The patient may need a lower dose or even have to cease the oral hypoglycaemic drug. Conversely stopping a drug with the potential to lower blood glucose might produce relative inefficacy of a hypoglycaemic drug and create a need for an increased dose.

Beta blockers can mask the warning signs of hypoglycaemia, and the non-selective drugs may impair the normal recovery reaction to hypoglycaemia. There is little evidence that they actually induce hypoglycaemia.

Pharmacokinetic interactions

These need to be considered separately for each drug class as the body handles the drugs in very different ways and the potential sites for interactions are different.

Sulfonylureas

All drugs in this class are partially or totally metabolised by the liver. Chlorpropamide is the only member of the class with substantial renal excretion, but is now rarely used. It is excreted much more rapidly in alkaline urine so its half-life and duration of action are reduced with excessive ingestion of alkalis. Antacids may increase the absorption of all the sulfonylureas and hence produce higher peak concentrations of the drugs and a risk of temporary hypoglycaemia.

Chlorpropamide has an additional interaction with alcohol which can produce significant facial flushing. This has been reported with very high doses of tolbutamide, but not with the other drugs in this group.

Sulfonylureas are highly protein bound drugs and may be displaced from blood protein binding sites by drugs such as the non-steroidal anti-inflammatory drugs. This can cause a short-term increase in free (unbound) sulfonylurea and hence temporary hypoglycaemia.

The majority of significant interactions with sulfonylureas are due to the induction or inhibition of cytochrome P450 enzymes in the liver. Table 4 lists the common interacting drugs and the resultant clinical outcomes. Although dicoumerol interacts with tolbutamide it is not used in Australia and there are no significant interactions reported for warfarin or phenindione.

Repaglinide

This is the only drug of its class currently available in Australia. It has been in use for too short a time for the full spectrum of its potential interactions to have emerged. Like the sulfonylureas it is metabolised by a liver enzyme (cytochrome P450 3A4) and is potentially subject to many of the interactions listed in Table 4.

Metformin

Metformin is the only biguanide available in Australia. It is not metabolised at all but is completely excreted in urine. Metformin may therefore accumulate and cause lactic acidosis if other medications have induced renal failure. Examples include contrast media, cyclosporin and aminoglycosides. Metformin should therefore be stopped before, and for 48 hours after, contrast radiography.

Metformin is excreted by the renal tubules and this process can be inhibited by cimetidine, but not the other H_2 receptor antagonists. This interaction causes retention of metformin and increases the risk of lactic acidosis.

Acarbose

Acarbose inhibits alpha glucosidase in the gut wall. This reduces the release of glucose from carbohydrate and hence the amount of glucose available for absorption. The drug itself is only absorbed to a minor extent and any interactions relate to interference with its access to the gut lining. In general these interactions would be likely to reduce its efficacy and this has been reported with charcoal and digestive enzyme preparations. In addition neomycin may increase the unpleasant gastrointestinal adverse effects of acarbose.

Thiazolidinediones

So far three drugs in this group have been marketed but troglitazone has been withdrawn worldwide because of unacceptable hepatotoxicity. Troglitazone also induced cytochrome P450 3A4 and interacted with a number of drugs including cyclosporin and oral contraceptives. So far rosiglitazone and pioglitazone have not shown any significant interactions either in specific studies or in early clinical use. Pioglitazone is known to induce cytochrome P450 3A4 and it

is possible that interactions with it and with rosiglitazone will become apparent over the next few years.

Conclusion

Interactions with oral hypoglycaemic agents are important because the outcomes, particularly hypoglycaemia, are serious. As with all interactions the times of high risk are when a second drug is started or stopped or has its dose changed. Regular co-prescription of the same dose of another drug is not likely to cause major problems.

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Self-test questions

The following statements are either true or false (answers)

1. Drug interactions with metformin are due to induction or inhibition of hepatic enzymes.
2. Patients with diabetes may need to increase the dose of their oral hypoglycaemic drug when they start a course of corticosteroids.

Book review

Therapeutic Guidelines: Antibiotic. Version 11. North Melbourne: Therapeutic Guidelines Limited; 2000. 317 pages.
Price $31.90 (students $25.30) + $7.15 postage

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Therapeutic Guidelines: Antibiotic was first published in 1978. Since the early 1990s a reasonably up-to-date version of this book has been one of my most used sources of reference when consulting. While my usage of this book was previously limited to a few favourite chapters, the opportunity to review this book has provided the impetus to read it in much more detail. As I expected, given the expertise that has contributed to this book, it appears to be a very useful book for busy clinicians.

I have mainly considered the book from the general practitioner viewpoint and have structured my review to address its presentation, organisation and content.

Presentation

The book is presented in its familiar pink cover and has a wonderful historical 'discovery of antibiotics' graphic on the front. The book seems to be getting a little thicker and the font a little smaller over the years, but in the current version I do not find either feature a major problem. I did wonder if the smaller font size might be problematic for readers with a degree of visual impairment.

Organisation

The slightly different colours of the various sections of the book facilitate quick access to the content. Future editions would benefit from variation in the colour of the appendices, too.

One other aspect for comment is the listing of drug alternatives. The 'Key information…' section of the book contains the statement 'several drugs are given as alternatives in a list, they are listed alphabetically or in order of preference'. This is confusing, and one or the other scheme should be used throughout.

Content

Aspects of the book I found particularly useful were:

- the inclusion of statements about the strength of evidence for drug and non-drug therapies
- the introductory chapter 'Principles of antimicrobial use', provides a valuable overview of the basic good practice that will minimise emerging drug resistance
- 'Getting to know your drugs' is a very useful refresher and overview of antimicrobial categories, mechanisms of action, effectiveness and risks
- in the chapters particularly relevant to general practice: (eye, gastrointestinal, genital tract, intra-abdominal, oral and dental, respiratory and skin infections) the topic coverage extends from common minor to more complicated, yet still not uncommon, infections
- the chapter 'Prophylaxis: medical' has a number of useful recommendations including post needle-stick injury prophylaxis
- 'Antimicrobials and food' answers questions patients often ask about
- the appendices 'Pregnancy and breastfeeding' and 'Paediatric doses' are both useful quick references.

While a few of the chapters and appendices are less useful for day-to-day general practice, they are helpful for keeping up to date with inpatient treatments and as a source of information for general practitioners caring for patients in hospital.

Overall I found Version 11 to be a practical, concise and informative book. Despite a few minor imperfections in the organisation and presentation of the book I would recommend it highly to the busy general practitioner. In addition, because of its breadth of cover and summarised format, it is likely to be of value to specialist clinicians outside their area of expertise, clinicians in training and medical students.

Managing warfarin therapy in the community

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SYNOPSIS

Warfarin is the most widely used oral anticoagulant in Australia. Although it can prevent thrombosis, it can cause life-threatening haemorrhages. Patients taking warfarin should have their INR measured regularly. More frequent tests are needed when patients start, stop or alter the dose of their other medications. Educating the patients about warfarin helps them to take their treatment correctly. They should report any abnormal bleeding and have their INR measured. A very high INR is an indication for admission to hospital to have the effects of warfarin controlled.

Index words: anticoagulation, coagulation, thrombosis.

(Aust Prescr 2001;24:86–9)

Introduction

Warfarin is one of the commonest causes of death related to prescription drugs, but when used appropriately it is one of the most beneficial drugs. As the population ages and more trials show its benefits, more and older patients will be started on warfarin. Its pharmacology is complicated and many factors need to be considered in the optimal management of each patient.

Risks and benefits of warfarin

There are many indications for warfarin therapy (Table 1). The decision to start warfarin depends on an assessment of each patient's balance between the harmful effects and the benefits of anticoagulation.

The major adverse effect of warfarin is an increased bleeding tendency and many factors can increase the risk (Table 2).[1] A patient's risk of bleeding is greatest in the first few months after starting warfarin. Bleeding complications occur in 3–10% of patients on warfarin per year, but most bleeds are minor. Although the bleeding risk increases as the INR (International Normalised Ratio) increases, 50% of bleeding episodes occur while the INR is less than 4.0.

Age is one of the strongest risk factors for bleeding. In one study, the annual risk of major bleeding was 2.9% for patients older than 70 years, while no major bleeds occurred in patients under

Table 1

The common indications for warfarin therapy

Supported with good evidence

- prosthetic valve replacement
- deep vein thrombosis within the last three months
- pulmonary embolism within the last six months
- recurrent deep vein thrombosis or pulmonary embolism
- atrial fibrillation associated with valvular heart disease
- atrial fibrillation without structural heart disease in patients >50 years old
- embolic stroke

Supported but limited evidence

- congestive heart failure or dilated cardiomyopathy

Little or no supporting evidence

- non-embolic cerebrovascular disease
- peripheral vascular disease

Table 2

Risk factors for major bleeding in patients on warfarin

Marked increase in risk

- age >70 years old
- bleeding disorder
- gastrointestinal haemorrhage within the last 18 months
- previous stroke
- liver disease
- history of falls

Moderate increase in risk

- age 60–70 years
- chronic renal failure
- change in interacting medications (see Table 4)
- change in, or poor, nutrition
- first three months of warfarin therapy
- large fluctuations in INR

50 years old.[2] Bleeding in this report was called 'major' if it was fatal, was intracranial, retroperitoneal or involved a joint, required surgery, led to a haemoglobin fall of 2 g/dL or more, and/or required the transfusion of two or more units of blood.

Warfarin in pregnancy is teratogenic and causes peripartum bleeding in mother and child, so it is generally contraindicated in pregnancy. There may be a place for mid-trimester warfarin in pregnant women with prosthetic heart valves, but this choice should be made only after a full discussion of the implications with the patient. Unfractionated heparin and low molecular weight heparin are alternatives that do not cross the placenta.

Patient education

Patients who have a poor understanding of the indications and potential adverse effects are more likely to be non-compliant than those who receive education about warfarin.[3] Patients should be encouraged to:

- report any signs of bleeding while on warfarin
- have more frequent measurements of their INR when starting or stopping other medications, either prescribed or complementary
- keep a written record of INR results and warfarin dosage
- remain with one or other of the currently available brands of warfarin (Coumadin or Marevan), as these have not been formally shown to be bioequivalent and are therefore not interchangeable.

Booklets aimed at patient education are available from all pharmacies. These are a useful supplement to the doctor's advice.

Women of childbearing age should be informed of the potential dangers of warfarin in pregnancy. Pre-conception counselling is needed for women on long-term treatment.

Trials of patient-based self-monitoring and dose-adjustment of warfarin therapy are under way, but currently this cannot be recommended.

Starting warfarin therapy

Patients with acute thromboembolic events, such as deep vein thrombosis, pulmonary embolism or embolic stroke, should be given heparin or low molecular weight heparin when starting warfarin. The heparin or low molecular weight heparin can be ceased after a minimum period of five days of combined therapy with warfarin and after the INR has been in the therapeutic range for 48 hours. Patients at less immediate risk, such as patients in stable atrial fibrillation without embolic events, may be safely started on warfarin without concurrent heparin.

Several trials have shown that low dose induction regimens cause fewer episodes of over-anticoagulation, with only minimal delay in the time to achieve the target INR. One protocol, validated specifically in elderly patients, is given in Table 3.[4] Loading regimens of 5 mg warfarin per day in all patients have also been reported.[5] Previously, a modified Fennerty's protocol, using loading doses of 10 mg, 10 mg and 5 mg on the first three days, has been the most commonly used nomogram for starting warfarin. However, this protocol can lead to significant over-anticoagulation, particularly in the elderly.[4] With all induction protocols, a baseline INR is measured before starting warfarin, and the INR is measured each day until doses are stabilised.

Maintaining warfarin therapy

The target INR varies for different clinical situations.[6] For patients with mechanical prosthetic heart valves, the target INR is usually 2.5–3.5. For almost all other conditions, including deep vein thrombosis and pulmonary embolism, atrial fibrillation and tissue valve replacements, the target INR is usually 2.0–3.0. Patients with recurrent thromboembolic events while anticoagulated, and patients with cancer or antiphospholipid syndrome may benefit from a higher INR, but this approach should be undertaken with specialist advice.

The frequency of monitoring INR once the dose is stabilised should be determined by the clinical situation. Initially, patients will require a few tests each week, but this can be gradually decreased to once a week or once a fortnight if the INR is stable. Patients who have a very stable INR, no interacting medications and low bleeding risk, may only need to have a test once every four to six weeks.

Many hospitals have anticoagulation clinics for managing patients on warfarin, although most patients can be safely managed in the community. However, clinical trials suggest that patients managed at an anticoagulant clinic spend more time with a therapeutic INR and have a lower rate of major haemorrhage, compared to 'best usual care'.[7] Patients most likely to benefit from anticoagulation clinics include those with comorbidities, those with unstable INRs and those very sensitive to warfarin (requiring daily doses of 1 mg or less).

Table 3

A dosage schedule for starting warfarin therapy, validated in elderly patients

Day	*INR*	*Warfarin dose*
1	<1.4	10 mg
2	<1.8	5 mg
	1.8–2.0	1 mg
	>2.0	Hold
3	<2.0	5 mg
	2.0–2.5	4 mg
	2.6–2.9	3 mg
	3.0–3.2	2 mg
	3.3–3.5	1 mg
	>3.5	Hold
4	<1.4	10 mg
	1.4–1.5	7 mg
	1.6–1.7	6 mg
	1.8–1.9	5 mg
	2.0–2.3	4 mg
	2.4–3.0	3 mg
	3.1–3.2	2 mg
	3.3–3.5	1 mg
	>3.5	Hold

Dose adjustment after day 4 depends on clinical judgement based on the pattern of INR.
The table is slightly modified from the table in reference 4.

Table 4

Some of the important interactions of warfarin

Increased effect of warfarin (↑INR)	*Decreased effect of warfarin (↓INR)*	*Potentiate bleeding risk because of antiplatelet effect*	*Potentiate bleeding risk by effects on gastric mucosa*
Medications			
• Antibiotics (sulfonamides, erythromycin and other macrolides, metronidazole) • Antifungals (itraconazole, fluconazole, ketoconazole) • Amiodarone • Selective serotonin reuptake inhibitors (especially fluvoxamine, fluoxetine) • Cimetidine • Propylthiouracil • Quinine and quinidine • COX-2 inhibitors (celecoxib, rofecoxib)	• Antiepileptics (carbamazepine, phenytoin, barbiturates) • Rifampicin, rifabutin • Cholestyramine	• Aspirin • Non-steroidal anti-inflammatory drugs (except COX-2 inhibitors) • Clopidogrel • Dipyridamole • Tirofiban	• Aspirin • Non-steroidal anti-inflammatory drugs
Herbal medicines			
• Dong quai • Garlic • Papaya • St John's wort	• Ginseng		

Interactions with warfarin

Warfarin is particularly prone to interactions with other drugs, herbal medicines[8] and dietary factors (Table 4). Some interactions involve the cytochrome P450 system in the liver. Many interactions are unpredictable, so the INR should be tested more frequently after starting a new medication and similarly when stopping a medication or changing the dose. It takes about five days for enzyme induction to take place, so that an INR measured about one week after a change in medication should reflect any interaction. In one study, recent antibiotic use was the second greatest risk factor (after age) for over-anticoagulation.[9]

Alcohol in small to moderate amounts probably has little effect on warfarin metabolism. In heavy drinkers, however, factors such as increased falls, alcohol-induced gastritis, poor diet and poor compliance potentiate the risk of bleeding.

The amount of vitamin K in the diet partly determines the sensitivity to warfarin. A diet high in vitamin K reduces the response. This is important to consider in situations when diet changes, such as during illness, travel, fad diets, hospitalisation and postoperatively. Foods high in vitamin K include green tea, turnips, avocados, brussel sprouts, broccoli and green leafy vegetables (e.g. lettuce, cabbage). It takes a very large daily intake of 'greens' to influence the INR. In any case, a consistently sustained diet will minimise this potential source of fluctuating results.

Table 5

A protocol for managing over-anticoagulation[9]

No bleeding	
INR 4–5.9	Withhold warfarin and measure INR next day
INR 6–9	Vitamin K 1–2.5 mg subcutaneously or orally*
	Recheck INR next day
INR >9	Hospitalise
	Vitamin K 5 mg IV or subcutaneously*
	Fresh frozen plasma 2 Units. This may be given with a factor II, VII, IX concentrate †
	Recheck INR after 6–8 hours and then daily for 3 days
Moderate or severe bleeding	
INR >1.5	Vitamin K 5–10 mg intravenously
	Fresh frozen plasma 2 Units immediately
	Recheck INR after 6–8 hours and then daily for 3 days (may need further vitamin K if INR rises)

* The intravenous preparation may be given orally or subcutaneously with safety and efficacy. Not all community pharmacies have the intravenous formulation of vitamin K and it may be worth keeping a supply in the practice rooms. (Avoid intramuscular injections of vitamin K to prevent local injection site bleeding which also reduces bioavailability.)

† Fresh frozen plasma and concentrates of clotting factors are blood products and may carry a small risk of viral contamination.

Management of over-anticoagulation

Over-anticoagulation increases the risk of haemorrhage. The first step in managing this problem is to identify the cause. Common causes include starting or stopping an interacting medication, deteriorating liver function, and patient error (such as taking the wrong dose or confusing different strength tablets). Many of these causes are preventable.

The approach to a raised INR should be individualised, paying attention to the indication for the warfarin, the patient's risk of bleeding and whether it is safe to continue therapy at all. Some patients need to be admitted to hospital, while others just need to miss a dose of warfarin.

Guidelines for managing over-anticoagulation (Table 5) are based on the recently published recommendations from the Australasian Society of Thrombosis and Haemostasis.[10] The half-life of vitamin K is shorter than that of warfarin, so the INR may rebound 24–48 hours after giving vitamin K. The intravenous preparation of vitamin K can be administered orally or subcutaneously with equal efficacy, and these routes are usually safer and more convenient in patients who are not actively bleeding.

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Self-test questions

The following statements are either true or false (answers)

3. The risk of warfarin causing bleeding is the same in all age groups.
4. The INR of a patient taking warfarin may be altered by a change in diet.

Medicinal mishap

Hidden haemorrhage with warfarin

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Case

A 78-year-old man presented to hospital because his right leg felt clumsy and weak. On assessment he had slightly reduced muscle power and appeared to have suffered a right hemiparesis. Over the next four hours, his right side became weaker, although he was still able to flex and extend his right hip against gravity. His ECG showed that he was in sinus rhythm with a heart rate of 70 beats/minute. He was started on warfarin therapy as we presumed that he had a 'stroke in evolution'.

After 10 days of warfarin therapy, the man noticed that his weak right leg was 'twitching' and he felt generally unwell. He complained of cramps in his right leg which made the whole leg 'jump off the bed', involuntarily. A few hours later, he became hypotensive but remained conscious. Clinical examination revealed that he had developed painful spontaneous contractions of his right hip flexors (positive psoas sign). The INR at this time was 2.7.

A CT scan of the abdomen showed a large haemorrhage in the retroperitoneal space and surrounding the right psoas muscle. Anticoagulation was stopped, and clotting factors and vitamin K used to reverse the anticoagulant status. The man's symptoms gradually settled and with a short intensive rehabilitation program, he made a good functional recovery.

Comment

Occult bleeding due to warfarin therapy can present in many ways and requires a high index of clinical suspicion for prompt diagnosis. It can also occur when the INR is in the therapeutic range, especially in older people, although the risk of bleeding is clearly higher when the INR exceeds the specified upper limit. Haemorrhage into the retroperitoneal space does not cause classic abdominal signs such as peritonism. A positive psoas sign is caused by conditions which irritate the psoas muscle. Tenderness may also be elicited by stretching the psoas muscle by hip extension. Apart from haematoma, other causes of a positive psoas sign include appendicitis and retroperitoneal abscess.

ABNORMAL LABORATORY RESULTS

Drug screens

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SYNOPSIS

The two types of drug screens are rapid tests and specific assays. Rapid tests are for a restricted range of substances (usually just drugs of abuse) and have limited sensitivity and specificity. When there are important medicolegal considerations, the results must be confirmed by more specific assays. Specific assays are labour-intensive tests that can detect most drugs but take much longer to perform. They are required where the concentration of the drug may lead to specific interventions (such as in certain overdoses). Conversely, even the most comprehensive negative screen cannot entirely rule out drug ingestion as some substances are difficult to detect. The knowledge of the laboratory staff should be utilised when ordering and interpreting the tests.

Index words: diagnostic tests, drug abuse, poisoning, therapeutic drug monitoring.

(Aust Prescr 2001;24:90–1)

Introduction

'Drug screens' are simply tests for a range of drugs or other substances. They have a wide variety of uses and almost any bodily fluid can be screened. Routine use of drug screens does not improve clinical outcomes, but selective use may assist patient management and occasionally yield an unexpected diagnosis.

Types of drug screens

There are two main types of drug screens. Immunoassays screen for a limited range of selected substances. These assays are relatively quick and some can even be performed at the bedside. They are commonly used to detect drugs of abuse or to test for commonly ingested substances in overdose. There may be cross reactivity with some chemically related substances and the test cannot detect uncommon or unsuspected drugs. Different brands of immunoassays have different problems with sensitivity and specificity. These problems should be outlined in the product information of the assays.

The second form of drug screening involves chromatography with or without mass spectrometry. This can detect most substances that are present in significant concentrations. Testing is relatively expensive and is heavily dependent on the skill and experience of the laboratory staff. Unless only specific substances are of interest, the turnaround time varies from days to weeks, so these tests are less likely to influence the acute management of a patient.

Screening tests most commonly use urine, but serum can also be used. In forensic studies, vitreous humour, pleural effusions, hair, bone or nails may be screened. Saliva, breath, sweat and breast milk can also be screened when looking for drugs of abuse.

Indications for screening

Overall, screening is most frequently used in medicolegal situations. These include determining cause of death, detecting performance-enhancing drugs in athletes, and detecting drug abuse in the workplace, drug and alcohol rehabilitation programs or psychiatric patients. In most cases, detecting a drug, in any concentration, gives sufficient information.

In acute poisoning and other toxicological screening the drug concentration may be important so screening the urine may not be the appropriate investigation. Drug screens of the urine do not reveal the amount of drug or the time it was taken because the urinary concentration correlates poorly with serum concentrations. Detecting the presence of a drug does not tell you if it is at a toxic concentration or explain the clinical status of the patient. In these circumstances, serum may be a better body fluid to screen. This is particularly so for substances such as paracetamol, salicylates, anticonvulsants, alcohol, ethylene glycol, methanol, lithium and theophylline as their concentrations determine the treatment. In these situations specific assays are usually more appropriate than a 'drug screen'. Paracetamol is so commonly taken in overdose that a routine specific assay in unconscious patients is generally warranted. However, routine specific assays for other substances are not indicated unless there are signs or biochemical changes that raise suspicion of their ingestion. Quantitative screening for drugs is also important in patients with suspected brain death.

Performing drug screening

To optimise the usefulness and the cost-effectiveness of drug screens there are several important factors. These include selection of a screening test appropriate to the patient, correct collection of samples, communication with the laboratory and follow-up tests where appropriate.

Selection of an appropriate screen

The most common clinical reason for requesting a drug screen is suspected ingestion of an unknown substance or substances. Examples include suspicions of overdose (e.g. coma, seizures, acidosis), malingering or child abuse (e.g. unexplained

hypoglycaemia or ataxia), or illicit drug abuse (e.g. psychosis, mood swings). Where possible, the drug screen should relate to the patient's clinical presentation. For example, a patient with severe acidosis may be suspected of taking a number of substances. However, most immunoassay techniques do not detect many of the drugs and poisons that lead to acidosis. They are designed to detect only commonly used drugs of abuse and drugs that lead to coma, such as alcohol, benzodiazepines, opiates, amphetamines, tricyclic antidepressants, LSD, cocaine and marijuana. A 'negative' drug screen of the urine in a patient with acidosis would be largely unhelpful or misleading. Specific screening of the serum for ethylene glycol, methanol and salicylates, and chromatography to detect other unusual substances may be quicker and much more useful investigations.

In many cases drug screens are done for legal or quasi-legal purposes and the screen must accurately detect substances relevant to that purpose (for example, drugs that might impair driving). Testing for other substances is irrelevant.

Communication with the laboratory

Most laboratories performing drug screens do large numbers of tests for non-clinical reasons. If you anticipate that the drug screen may alter your clinical management it is important to discuss the case with the laboratory. A history of the drugs the patient is known to take will help the laboratory to identify the substances you are not concerned about. Knowing which specific substances are suspected on clinical grounds helps the laboratory to tell you whether or not it can identify such substances, for how long they can be detected after ingestion and whether serum or urine is preferred. The laboratory may also alter the methods used to prepare the sample to maximise the sensitivity of the testing for those substances.

Collection of sample and follow-up tests (medicolegal cases)

Correct and explicit identification of the patient and sample, prevention of tampering during collection and a secure chain of custody are very important in medicolegal cases. If the result has important medicolegal implications the accuracy of the result should be confirmed by using a more specific and accurate method such as gas or liquid chromatography and mass spectrometry. Depending on the drug involved these tests are done on the same specimen or a different specimen.

Results

False positives

The most common cause of false positive results in clinical settings is the therapeutic use of barbiturates, benzodiazepines and/or opiates for sedation, anaesthetic induction or analgesia. Many immunoassays do not differentiate between drugs in these classes and may cross react with related therapeutic substances. For example codeine (and poppy seeds) may lead to positive opiate reactions, and decongestants such as pseudoephedrine and phenylpropanolamine may lead to positive amphetamine reactions. Only discussion with the laboratory and further specific testing can clarify such results.

False negatives

False negatives can relate to the time of sampling (too soon or too late), the body fluid tested or the method used. Immunoassays test for a restricted range of chemically related substances. Even within pharmacological drug classes they may not detect substances that have identical effects but an unrelated chemical structure. For example, most immunoassays for opiates do not detect the structurally unrelated methadone, dextromethorphan or pethidine. Metals (e.g. mercury, arsenic) are not detected by the commonly used drug screens and require specific tests. Some toxic substances (insulin, succinylcholine, potassium) cannot be detected by any method, as any avid reader of crime fiction knows.

Other problems of interpretation

The detection of one substance does not exclude the presence of others which cannot be detected by the same method. Drugs with similar chemical structures, but different toxicities, may give the same result. For example, within the drugs in the amphetamine class (methamphetamine, MDMA, PMA, fenfluramine and pseudoephedrine) there is a non-overlapping spectrum of peripheral and central nervous system stimulant effects and serotoninergic effects which lead to quite different toxicological syndromes. Failure to appreciate that some positive immunoassay screens for amphetamines could indicate ingestion of any or all of these drugs may lead to inappropriate management.

Conclusion

Drug screens are a useful clinical tool if you are selective in their use, have realistic expectations of their sensitivity and specificity, and discuss the clinical setting and suspected drugs with the laboratory staff. Otherwise you may be better off disposing of the urine in the traditional and less expensive manner.

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Self-test questions

The following statements are either true or false (answers)

5. A drug screen for amphetamines may be positive in someone taking pseudoephedrine.
6. When testing for a specific drug, immunoassay is a more accurate method than chromatography.

Drugs for Parkinson's disease

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SYNOPSIS

Levodopa is the most effective drug available for treating the motor symptoms of idiopathic Parkinson's disease. It is usually combined with a peripheral dopa decarboxylase inhibitor. Early treatment with dopamine agonists can reduce the risk of developing dyskinesia. Dopamine agonists and catechol-O-methyltransferase inhibitors can significantly reduce motor fluctuations. Amantadine reduces the severity of dyskinesia in some patients. No treatment has been proven to delay disease progression.

Index words: amantadine, dopamine, entacapone, levodopa, selegiline.

(Aust Prescr 2001;24:92–5)

Introduction

Motor dysfunction in idiopathic Parkinson's disease is caused predominantly by degeneration of dopamine-producing neurons in the substantia nigra of the midbrain. Symptomatic treatment of idiopathic Parkinson's disease is therefore aimed at restoring dopaminergic stimulation of the striatal neurons which are involved in controlling movement. These striatal neurons are preserved in idiopathic Parkinson's disease, but degenerate in the atypical parkinsonian syndromes, which explains their variable and usually poor response to therapy.

Mechanism of action of available drugs

The major classes of drugs currently available for the treatment of idiopathic Parkinson's disease are shown in Table 1. Many aim to increase dopamine in the brain, by increasing its production or altering its metabolism (Fig. 1).

Levodopa

Levodopa is absorbed from the small intestine and transported into the brain where it is converted to dopamine. (Dopamine cannot cross the blood-brain barrier.) Levodopa has a short plasma half-life of about one hour. Early in Parkinson's disease, levodopa has a long duration of action (lasting days) which is independent of plasma concentration, but as the disease progresses, the duration of the effect reduces. The short-duration effect is strongly linked to plasma concentration and lasts, at most, hours.

Slow-release preparations are gradually absorbed, resulting in more sustained plasma concentrations. They have reduced bioavailability; higher doses are required to match the benefit of an equivalent strength of a standard preparation. Rapid release preparations are taken in liquid form to enhance passage through the stomach and absorption from the small intestine.

Levodopa commonly causes nausea, especially when treatment begins. This nausea results from the conversion of levodopa to dopamine which stimulates the dopamine receptors in the area postrema ('vomiting centre') in the brainstem, a structure which lies outside the blood-brain barrier. The nausea is minimised by introducing levodopa slowly, starting with a low dose, taking it with food and giving it in combination with a peripheral dopa decarboxylase inhibitor such as carbidopa or benserazide. A minimum daily dose of 75 mg is necessary to adequately inhibit the production of dopamine outside the blood-brain barrier. Metoclopramide and prochlorperazine should be avoided as they are dopamine antagonists and make parkinsonism worse. If an antiemetic is required, domperidone 10–20 mg three times daily is the drug of choice as it is a dopamine antagonist which does not cross the blood-brain barrier.

Dopamine agonists

The oral dopamine agonists directly stimulate striatal neurons. They have a longer plasma half-life than levodopa, and thus provide a more continuous dopaminergic stimulation. In the doses tolerated by most patients, they usually do not provide the same degree of motor improvement as levodopa. They do not work if levodopa has failed to benefit the patient. The efficacy of the available dopamine agonists is similar. Equivalent daily doses of bromocriptine, pergolide and cabergoline are 10 mg, 1 mg and 1 mg respectively.

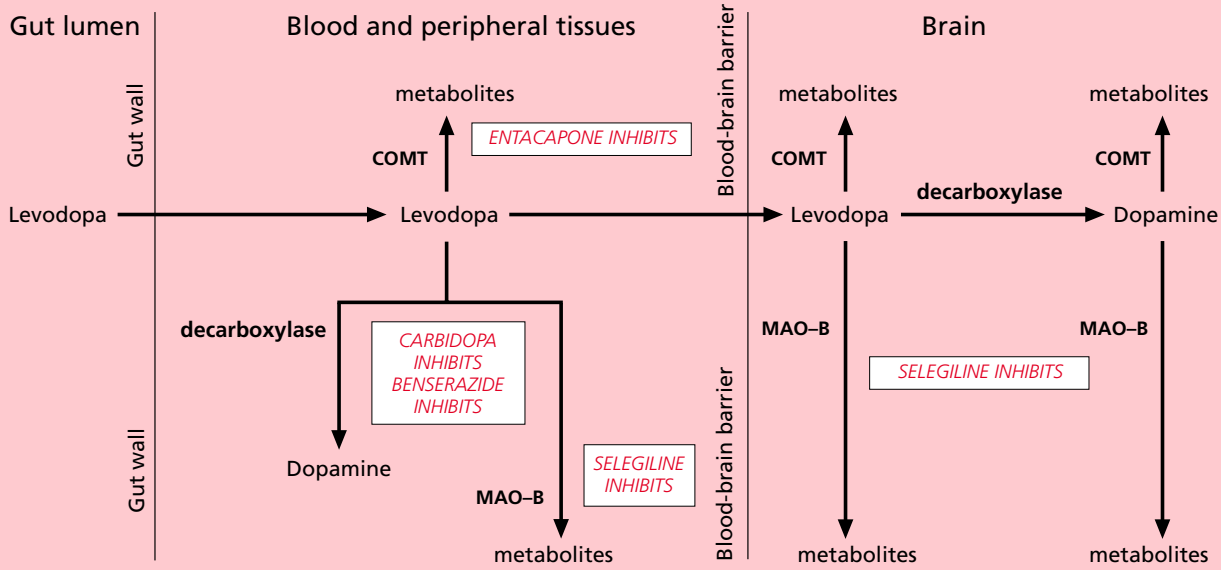
Table 1

The major classes of drugs currently available for the treatment of Parkinson's disease

Levodopa preparations	Standard release	Levodopa/benserazide Levodopa/carbidopa
	Slow release	Levodopa/benserazide Levodopa/carbidopa
	Rapid release	Levodopa/benserazide
Dopamine agonists	Ergot	Bromocriptine Cabergoline Pergolide
	Non-ergot	Pramipexole Ropinerole Apomorphine
Catechol-O-methyltransferase inhibitors		Entacapone Tolcapone
Monoamine oxidase B inhibitors		Selegiline
Other	NMDA antagonist	Amantadine
	Anticholinergics	Benzhexol Benztropine Biperiden Orphenedrine Procyclidine

Fig. 1

Drugs affecting the metabolism of levodopa



Enzymes in bold
COMT = catechol-O-methyltransferase
MAO-B = monoamine oxidase B
Drugs which alter metabolism in boxed red italics

The newer agonists are probably better tolerated than bromocriptine, although there have been few comparative studies.[1] The long half-life of cabergoline (65 hours) allows a once daily dosage, whereas the shorter half-life of bromocriptine and pergolide can make it easier to tailor therapy. Pramipexole and ropinirole are non-ergoline derived preparations which are not available on the Pharmaceutical Benefits Scheme in Australia but are used extensively overseas.

Dopamine agonists commonly cause nausea and postural hypotension, and must be introduced slowly over a few weeks. Some patients require the use of domperidone when starting treatment to reduce the peripheral adverse effects. Dopamine agonists should be avoided in all patients with hallucinations or cognitive impairment because of the risk of confusion and prolonged delirium. Ergoline-derived dopamine agonists (bromocriptine, cabergoline and pergolide) can cause pulmonary and retroperitoneal fibrosis and other ergot adverse effects such as digital vasospasm and erythromelalgia. The fibrosis is reversible if diagnosed early. Patients should be monitored with regular chest auscultation and measurement of the erythrocyte sedimentation rate, although even with these measures detection can be difficult. Patients treated with pramipexole and ropinirole, can experience 'sleep attacks' severe enough to cause motor vehicle accidents.

Apomorphine is a short-acting dopamine agonist which is given by subcutaneous injection. It is used as 'rescue' medication (where a dose of levodopa has failed to take effect) for severe fluctuations in younger patients because of its rapid and reliable onset of action within 5–10 minutes. Patients need to be admitted to a specialised clinic or hospital in order to establish the effective dose and to be educated about its administration. Apomorphine is a potent emetic so patients must be pre-treated with domperidone 20 mg three times daily orally for at least 48 hours before the first injection. Domperidone should be continued for at least a few weeks once regular intermittent treatment has commenced. The dose can then be tapered slowly as tolerance to the emetic effects of apomorphine (but not its anti-parkinsonian action) usually develops.

Catechol-O-methyltransferase (COMT) inhibitors

If dopa decarboxylase is inhibited, peripheral levodopa is predominantly metabolised by catechol-O-methyltransferase (COMT). COMT inhibitors prolong the plasma half-life of levodopa and therefore reduce motor fluctuations. Dopaminergic adverse effects can result, including increased peak-dose dyskinesia and confusion. Class-related adverse effects include urine discoloration, diarrhoea and abdominal pain.

Entacapone has a short half-life (90 minutes) and must be taken concurrently with each dose of levodopa. It does not have a central effect as it does not cross the blood-brain barrier. Tolcapone has a longer half-life but has been withdrawn in Australia because of rare severe or fatal hepatic toxicity. It can be obtained under the restricted conditions of the Special Access Scheme.

Monoamine oxidase B inhibitors

Levodopa and dopamine are metabolised in the brain by monoamine oxidase B (MAO-B) and COMT. Selegiline selectively inhibits MAO-B and prolongs the duration of effect of levodopa. It also provides mild symptomatic benefit when used as monotherapy. The most common significant adverse effect is confusion or delirium. Patients should be warned about the possibility of a tyramine-induced

hypertension if a selective monoamine oxidase A inhibitor (e.g. the antidepressant moclobemide) is also prescribed.

Anticholinergics

Although anticholinergics were the mainstay of treatment prior to the advent of dopaminergic drugs, their current role is limited because of their relative lack of efficacy and the frequent occurrence of unacceptable adverse effects such as memory impairment, confusion and psychosis, dry mouth, difficulty with micturition and constipation. Anticholinergics can occasionally be of benefit when tremor is prominent and poorly responsive to dopaminergic therapy. Withdrawal of long-term therapy with anticholinergics can be difficult and should be done slowly to avoid precipitating a cholinergic crisis.

An approach to the treatment of Parkinson's disease

No treatment can arrest or slow neurodegeneration in Parkinson's disease. The aim is to relieve symptoms and avoid the complications of therapy.

Early Parkinson's disease

Many studies have shown that early treatment with dopamine agonists reduces the incidence of dyskinesia.[1] Fewer motor fluctuations were shown in some but not all of the studies. We recommend a dopamine agonist as the first treatment in younger patients (under 50 years old) who have mild disease and no cognitive deficit. It is necessary to add levodopa within 1–5 years in most patients. In more severe disease, treatment begins with levodopa but a dopamine agonist may be added to keep the daily dose of levodopa in the lower range (300–600 mg) if there is no cognitive deficit. Dopamine agonists are used infrequently and with caution in patients more than 70 years old because of the risk of neuropsychiatric adverse effects and postural hypotension. They are contraindicated in the presence of dementia.

Isolated resting tremor is rarely disabling, but if it interferes with function it can usually be managed with levodopa. When this is ineffective at low to moderate doses, the addition of an anticholinergic can sometimes be useful.

Patients with motor fluctuations

Patients' mobility may fluctuate throughout the day. It is important to determine whether these motor fluctuations are occurring because of inadequate dopaminergic stimulation ('off-periods') or excessive dopaminergic stimulation. Common off-period fluctuations include 'end of dose failure', in which the benefit of levodopa wears off before the next dose, and painful twisting and cramping of the feet or legs at the end of a dose cycle ('end of dose dystonia') or early in the morning. Dyskinesia (involuntary movements of the limbs or trunk) usually occurs when the plasma levels of levodopa are maximal ('peak dose dyskinesia'). Dyskinesias may also occur before and after an 'on-period' ('diphasic dyskinesias').

Off-periods and diphasic dyskinesias are managed by attempting to maintain the level of dopaminergic stimulation above the critical threshold for motor benefit. This can be achieved by giving levodopa more frequently or adding a COMT inhibitor or a dopamine agonist. The latter is preferable in younger patients. Selegiline has been disappointing in this situation.

Failure of a dose to induce an 'on' period is often due to delayed gastric emptying and can be reduced by taking tablets on an empty stomach 30 minutes before meals, or by using a dispersible formulation of levodopa. Slow-release preparations are useful for nocturnal off-periods or early morning akinesia. They are less effective in treating daytime motor fluctuations.

Peak dose dyskinesia may be managed by reducing individual levodopa doses, but this may increase 'off' time. An alternative is to gradually introduce, or increase, a dopamine agonist while reducing the dose of levodopa by about 25%. In many patients amantadine 100 mg two or three times daily is effective in reducing dyskinesia. Amantadine can cause nightmares, anticholinergic adverse effects and livedo reticularis. It should be avoided in patients with hallucinations or dementia and the last dose should not be given after mid-afternoon.

Role of physical therapy and surgery

Medical treatment with dopaminergic drugs is the mainstay of therapy, however, physical therapies have an important adjunctive role. Early in the course of the disease, patients should be advised to exercise regularly in order to maintain good muscle tone and to shed excess weight. This reduces impediments to movement, other than those caused by the disease. Later in the course of the disease, specific treatments by allied health professionals can be extremely helpful. Involvement of the carer in these therapies is crucial.

Physiotherapists and occupational therapists can provide gait and balance retraining and instruction about compensatory strategies which emphasise the use of external cues to help initiate movement, or how to break down complex movements into simpler sequences. Speech therapy can improve speech clarity and volume, and swallowing difficulties also necessitate careful assessment and treatment. Dietary advice, especially regarding the effects of meals and protein intake on drug pharmacokinetics, should be offered.

In younger patients without obvious cognitive impairment, who have severe motor fluctuations that are poorly controlled with medical therapy, stereotactic functional neurosurgery or deep brain stimulation can be extremely effective. Assessment by a movement disorder specialist, with or without neuropsychological assessment, is recommended prior to referral to the neurosurgeon.

Treatment of late stage complications of Parkinson's disease

Postural hypotension

Levodopa and dopamine agonists worsen postural hypotension and it may be necessary to lower the dose of levodopa or withdraw the agonist. Treatment is difficult, but patients should be advised to sleep with the head of the bed raised by one or two bricks and to add salt to their diet. Fludrocortisone

can then be added at a dose of 0.1 mg in the morning, increasing if necessary up to 0.5 mg in the morning. If these measures are ineffective, the alpha agonist midodrine 10–20 mg four hourly can be useful but it is experimental and only available via the Special Access Scheme. Patients treated for postural hypotension need to have electrolytes, renal function and supine blood pressures closely monitored.

Parkinsonian psychosis, depression and dementia

Psychotic symptoms such as visual hallucinations and persecutory delusions occur most commonly in the setting of dementia, which may be mild and therefore easily missed. Most drugs for Parkinson's disease make these symptoms worse. Depression is also common and requires treatment in its own right.

Occasional visual hallucinations with retained insight do not require treatment. Acute psychosis is a medical emergency. It can be triggered by a change of environment, treatment or intercurrent illness. Apart from levodopa all the drugs for Parkinson's disease should be ceased. If possible stop the drugs over a few days rather than abruptly to avoid provoking neuroleptic malignant syndrome from dopaminergic withdrawal, or a cholinergic crisis from withdrawal of anticholinergics.

If psychotic symptoms persist it may be necessary to introduce a neuroleptic drug. This is always a difficult decision because neuroleptics are dopamine antagonists which can cause profound worsening of parkinsonism. The role of the new atypical neuroleptic drugs, including clozapine, olanzapine, quetiapine and risperidone, is still being assessed.[2] At present they have only been approved in Australia for the treatment of schizophrenia. If the patient is aggressive and potentially violent, the most suitable way to achieve immediate control is to withhold one to two doses of levodopa until control is achieved. Sometimes benzodiazepines, orally or parenterally, may be required. This will sedate the patient and allow oral neuroleptic medication to be given if needed.

Summary

For patients moderately affected by Parkinson's disease the first-line treatment is levodopa with a peripheral dopa decarboxylase inhibitor. A dopamine agonist may be added to minimise the dose of levodopa. Anticholinergic drugs may help patients with tremor. Physical therapy is an important adjunct to drugs. Patients with more severe disease may require injections of apomorphine. All the drugs have unpleasant adverse effects, so therapy should aim to minimise the complications of treatment.

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Self-test questions

The following statements are either true or false (answers)

7. Metoclopramide is the drug of choice for treating the nausea caused by levodopa.
8. If levodopa has failed to benefit the patient they are unlikely to respond to a dopamine agonist.

Parkinson's disease: a personal experience

Editor's note:

Kay Messiter is a 47-year-old single mother who has had Parkinson's disease for 13 years.

AP: *When did you develop Parkinson's disease?*

KM: It was around Christmas 1987 that I noticed a tremor in the top part of my right arm. There was nothing to see at that stage, but I could feel it when I did things like picking up the telephone. The tremor gradually increased.

The neurologists were uncertain of the diagnosis at that stage. There was nothing that could be done anyway because I was three months pregnant. I did not do anything until after my second child was born four years later.

AP: *How was the diagnosis made?*

KM: I diagnosed myself. My general practitioner had mentioned Parkinson's disease as a possible cause of my tremor so I got some information from the Parkinson's Association. As soon as I read that information I knew I had Parkinson's disease.

AP: *How did you react when you realised the diagnosis?*

KM: I remember my flesh beginning to crawl when I read that Parkinson's disease was incurable, but it was a relief to know what I had. I decided I was not going to take tablets so I waited about two years before seeing a neurologist to confirm the diagnosis.

AP: *What treatment were you given?*

KM: I avoided treatment for a few years, but I was having problems with bumping into things, and everyday tasks

like fastening buttons. My first treatment was selegiline. It had just come out and there was talk about it protecting the neurons, so I told my doctor I wanted to be on it.

AP: *Did the treatment work?*

KM: Selegiline held the tremor back enough for me not to need other treatment for about a year. I then started levodopa/carbidopa. I continued the selegiline, but eventually I had to stop it because of side effects. At times I could barely walk and had difficulty eating. These symptoms improved after I stopped selegiline, but it seemed to take months to get it out of my system. I also had to increase my dose of levodopa/carbidopa.

AP: *What other treatments have you had?*

KM: The dose of levodopa quickly increased to 950 mg a day. I was still having periods when I would have to stop what I was doing and lie down. I would have to take a rapid acting tablet levodopa/benserazide and wait for it to switch me on again.

As time progressed walking became a chore and it was difficult to get moving. If I had something important to do I would take amantadine and diazepam. They would keep me pretty normal; they were my 'special occasion' drugs.

During 2000 things became more difficult. I had no energy and I was having to spend more time lying down despite having cabergoline added to my treatment. My nerves were on edge so I was also taking amitriptyline.

AP: *When the medication became less effective what did you do?*

KM: I decided to have surgery. If it worked I would get a number of better years, if it did not, I would just be in a nursing home a few years earlier than expected. It was an option I had to take.

AP: *What was the surgery like?*

KM: It did not worry me. My main concern was having to lie in the MRI scanner with a frame attached to my skull. My anxiety was relieved by the time I eventually had the scan because hospital delays made me wait all day in the ward with this frame stuck on my head.

The surgery was done with a local anaesthetic. Although the surgeon was prodding around in my brain, I did not feel anything. After what seemed like a couple of hours the surgeon was going to give up. As I had kept quiet about having surgery and had got somebody to look after my children, I did not want to have a second operation three months later. I asked the surgeon to have another go and luckily he found the spot.

AP: *How has the pallidotomy helped you?*

KM: So far I have had a good response. I can now go to a restaurant and eat with a knife and fork, walking is a joy and I look normal. I still get off-periods. They are not pleasant, but they are not as bad as they were. I now take entacapone and cabergoline, but I only need a smaller dose of levodopa/carbidopa.

AP: *Do you have any suggestions for how doctors could better help people in your situation?*

KM: Doctors need to listen more to their patients with Parkinson's disease, because we can find it difficult to express ourselves. While it is easy to focus on the physical problems, there is often an internal mental battle going on. I was prone to panic attacks, other people get depressed. Encouraging people to have a positive attitude is important. I am now working for Parkinson's New South Wales and can say to doctors that it will offer good support to people who want to talk about their experiences with other people who have Parkinson's disease.

Patient support organisations

Parkinson's disease

Parkinson's Australia is a not-for-profit community organisation with a branch in every State and Territory. It provides information and support to people living with Parkinson's disease, their carers, families and friends. You can obtain an information kit by calling the toll free number 1800 644 189, or reach the State and Territory branches through the Parkinson's Australia web site www.parkinsons.org.au

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Web site: www.parkinsons.org.au

Australian Capital Territory

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Fax: (02) 6286 4475

New South Wales

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Book review

Clinical pharmacology essentials
Evan Begg. Auckland: Adis Books; 2000.
84 pages.
Price $22.95

R.F.W. Moulds, Associate Professor in Clinical Pharmacology, University of Melbourne, Clinical Dean, Royal Melbourne and Western Hospital Clinical School, and Director of Clinical Pharmacology and Therapeutics, Royal Melbourne Hospital, Melbourne

This is a very useful short book which lives up to its name. It is divided into 32 topics, each topic being covered in two opposing pages. The list of topics fully covers clinical pharmacology, although the formula of two pages per topic results in some topics being covered in a little more or less detail than others. The selection of the topics is also a little arbitrary, and has clearly been determined to a significant extent by the requirement of two pages per topic.

It should be noted that this is not a textbook of therapeutics, nor is it a textbook of pharmacology. It bridges the gap between those two disciplines by covering such topics as drug clearance, the half-life, dosing in renal impairment, drug interactions, and compliance with medications.

This book should be very useful for undergraduate medical and pharmacy students, and also for postgraduate trainees in disciplines such as internal medicine and anaesthetics. I highly recommend it.

Needle-stick injuries in primary care

Francis J. Bowden, Associate Professor, Director, Canberra Sexual Health Centre, and Infectious Diseases Physician, Canberra Hospital, Canberra

SYNOPSIS

Needle-stick injuries in health-care workers are almost completely preventable by improving workplace practices, but when they do occur the consequences for the individual can be serious, regardless of the outcome in terms of infection. Post-exposure management includes first aid, serological testing and counselling in all cases. Immunoprophylaxis and antiviral medications are used in some cases. Advice and guidance should always be sought from local specialist services. With needle-stick injuries in members of the public the risk of transmission is extremely low. While there is usually no place for pharmacotherapy, counselling is essential.

Index words: hepatitis B, hepatitis C, HIV.

(Aust Prescr 2001;24:98–100)

Introduction

A needle-stick injury can be a devastating event. Although the risk of contracting a blood-borne pathogen is low, the psychological trauma that follows the injury can be disabling. However, where the risk is significant, the immediate administration of post-exposure prophylaxis may reduce the chance of seroconversion to some pathogens. The provision of counselling can mitigate the psychosocial consequences of the accident. While hospital workers often have immediate access to specialist support, these services may not be available to healthcare workers in the community.

Risks of transmission

The major blood-borne pathogens of concern are the human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV). In some settings, other infections may be relevant, for example *Treponema pallidum* and human T-cell lymphoma virus (HTLV-1) are endemic in some populations in remote Australia.

Estimating the probability of transmission following a needle-stick injury is difficult as there are many factors which contribute to the risk. These include the type of injury and the viral load of the source patient at the time of the injury. Hollow-bore needles with visible traces of fresh blood carry the highest risk, while splashes to mucosal surfaces and intact skin carry the lowest risk. The risk of acquiring infection is greatest for HBV and least for HIV, with HCV being of intermediate risk (Table 1).

Reducing the risk of transmission

Although they carry the lowest risk of transmission, exposures to skin and mucosal surfaces can be virtually eliminated by using eye protection and gloves in any circumstance where contact with bodily fluids is possible. Safe disposal of sharps is the most important means of reducing needle-stick injuries. Sharps containers should comply with the Australian standards, should have a wide neck to avoid the need to push objects into the container and must never be overfilled. Sharps containers should not be easily accessible, as they can pose a threat to visitors to clinics, especially young children. Winged infusion needles ('butterflies') and intravenous catheters are associated with high rates of needle-stick injury and special care should be taken during insertion and disposal. Some institutions have stopped using butterfly needles or adopted newer items with safety devices fitted.[1,2]

Post-exposure management

Following exposure to a potentially infected fluid, simple first aid measures are needed. The wound or mucous membrane should be flushed with water. There is no evidence that expressing fluid from the wound reduces the risk of transmission. The use of bleach or the injection of antiseptics or disinfectants is not recommended.

A quick risk assessment should be made. Common sense has a role here and often the risk of the patient having a transmissible infection can be easily estimated. However, the most important determinant of subsequent action is the type of exposure, rather than the source patient's risk factors. If the infectivity of the source patient is unknown, serological testing should be immediately undertaken after obtaining informed consent.

Issues relating to the so-called window-period, where viral replication is present but antibodies have not appeared, may cause concern. This concern can be dismissed in most cases where the history excludes behaviour which may have put the patient at risk of infection in the preceding three months. For medicolegal reasons, the injured worker should also have baseline serological testing.

Post-exposure prophylaxis

Hepatitis B

The source patient should be tested for hepatitis B surface antigen (HBsAg) as soon as possible. No further action is required if the test is negative. If the injured person has not

Table 1
Estimated risk of transmission per exposure*

Exposure	*Hepatitis B*	*Hepatitis C*	*HIV*
Puncture by contaminated needle	1:16–1:3.3	1:55	1:313

* Source: Centers for Disease Control, Atlanta, USA

been immunised and the result is likely to be delayed, a dose of HBV vaccine is given immediately, with subsequent doses at one and six months. A single dose (400 IU) of hepatitis B immunoglobulin should also be given as soon as possible (preferably within 72 hours).

If the injured person has been vaccinated against HBV and seroconversion has been documented, then no further action is required. When seroconversion has not been documented, a booster dose of hepatitis B vaccine should be given immediately and, if surface antibodies cannot be measured within 72 hours, a dose of HBIG given.

Hepatitis C and HTLV-1

There is no evidence to support the use of any drugs for post-exposure prophylaxis for HCV and HTLV-1.

HIV

The rationale for antiretroviral drugs is based on observational studies which showed decreased seroconversion rates in those who received prophylaxis. No randomised clinical trials have been (or will be) performed to determine the efficacy of this approach. Prophylaxis is not a trivial undertaking as antiretroviral drugs are associated with serious, and rarely life-threatening, adverse effects; an assessment of the risks of benefit and harm should be made in all cases. Access to HIV antiretroviral medication is restricted and usually confined to major hospitals. Liaison with the local Sexual Health service or Infectious Diseases/HIV unit will facilitate the prescription of appropriate drugs.

The American Centers for Disease Control and Prevention recommend two regimens – a two drug regimen where the risk of transmission is low, or a three drug regimen where a higher risk exists or where there is a possibility of viral resistance to one or more of the drugs. Examples of three drug regimens would be zidovudine/lamivudine plus either indinavir or nelfinavir. This is a complex area and expert advice should always be sought. 'Empiric' HIV post-exposure prophylaxis should only be used if the risk of HIV in the source patient is high and the results of the source patient's HIV test will not be available promptly. Testing for HIV can be done in a few hours if the laboratory is prepared to do emergency testing.

If a decision is made to commence antiretroviral prophylaxis, therapy must begin as soon as possible after the injury (preferably within two hours) but may still be indicated if a longer interval has elapsed and the risk of transmission is thought to be high. Therapy continues for four weeks. The drugs can be stopped if the HIV test of the source is negative and the patient is not thought to be in the window-period. If the status of the source patient is unknown, a decision to continue prophylaxis should be made on a case by case basis.

Syphilis

In settings where the prevalence of syphilis is high, testing of the source patient is indicated. If there is evidence of active syphilis, a single dose of benzathine penicillin (2.4 million units intramuscularly) should be administered. Interpretation of syphilis serology can be difficult and expert advice should be sought.

Needle-stick injuries in members of the public

A major source of distress is the needle-stick injury sustained by members of the community – usually from syringe/needle combinations that have been discarded in a public place. The anxiety is even higher when a child is involved. The general principles of management apply but a few points are worth noting:

- there is no role for testing dried blood in syringes as this is unreliable
- the risk of transmission is extremely low – there have been no confirmed reports of transmission of HIV from a needle-stick injury from a needle/syringe discarded in a public place
- post-exposure prophylaxis for HIV is not indicated.

The major issue to deal with is the potential for psychological trauma, and counselling is therefore essential.

Prophylaxis in pregnancy

Pregnancy or lactation do not preclude the use of prophylaxis, but the risks for the fetus or child must be discussed. Expert advice should be sought.

Post-exposure testing

HIV testing should be repeated at six and 12 weeks post-exposure (and again at six months if post-exposure prophylaxis has been given). Tests for HCV are performed at six, 12 and 24 weeks (HBV testing should be added if the injured person is not immune). Repeat testing is not routinely performed if the source case is negative for the relevant pathogens.

When the source is unknown

If the source of the needle-stick injury is unknown, for example exposure from a needle discarded in a linen bag, the protocol for hepatitis B prophylaxis and serological follow-up should be followed. Establishing the need for HIV post-exposure prophylaxis is problematic in this situation. In general, unless it is likely that the needle was associated with a patient known to be infected with HIV, post-exposure prophylaxis is not indicated. For example, in a general practice not specialising in HIV the risk that the needle is contaminated is extremely low.

In the community the source is usually unknown, but the risks of transmission are extremely low (see box).

Counselling

The knowledge that the risk of transmission of HIV from a significant needle-stick injury is 0.3% only partially comforts the injured person. Many people have varying degrees of anxiety until the serological follow-up is completed. While the majority of individuals will cope with this natural anxiety, a small number will require more intensive support. This may involve informal discussions, formal counselling or psychiatric intervention. It is important to make the arrangements for

follow-up flexible and to allow ready access to help. While most attention is usually focused on the injured person, the source patient also requires counselling and support during this process.

ACKNOWLEDGEMENTS

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Public health service guidelines for the management of health-care worker exposures to HIV and recommendations for postexposure prophylaxis. MMWR 1998;47(RR-7):1-28.

Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR 1998;47(RR-19):1-39.

(These documents are available through the CDC website http://www.cdc.gov/mmwr/)

The Australian Immunisation Handbook. 7th ed. Canberra: Commonwealth of Australia; 2000.

Self-test questions

The following statements are either true or false (answers)

9. Hepatitis C is more likely to be transmitted by a needle-stick injury than hepatitis B.
10. Health workers who have seroconverted after hepatitis B vaccination still require hepatitis B immunoglobulin if they have a needle-stick injury with a high risk of hepatitis B infection.

New drugs

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

Desonide

Desowen (Galderma)

0.05% cream, lotion and ointment

Approved indication: dermatoses

Australian Medicines Handbook Section 8.1.2

Desonide is a topical non-fluorinated steroid which has been available overseas for many years. It has a similar structure to triamcinolone (see 'The role of corticosteroids in dermatology' Aust Prescr 1998;21:9–11).

Patients apply desonide two or three times a day. Systemic absorption occurs, so continuous treatment is limited to a maximum of eight weeks.

Desonide has been compared with hydrocortisone 1% in the treatment of children with atopic eczema. Although it is more potent than hydrocortisone and had greater efficacy, desonide had a similar safety profile.[1] Topical treatment for four weeks does not significantly affect the hypothalamic-pituitary-adrenal axis.[2] Desonide should not be used on children younger than two years.

The adverse effects of desonide resemble those of other topical steroids. These are more likely to occur if occlusive dressings are used. Patients may complain of burning, itching, irritation or dryness of the skin.

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Galantamine hydrobromide

Reminyl (Janssen-Cilag)

4 mg, 8 mg and 12 mg tablets

Approved indication: Alzheimer's disease

Australian Medicines Handbook Section 16.5

There is now a choice of acetylcholinesterase inhibitors (donepezil, rivastigmine and tacrine) for the treatment of mild to moderate Alzheimer's disease. Galantamine is a new inhibitor of acetylcholinesterase which has been extracted from flower bulbs such as daffodils and snowdrops. In addition to increasing acetylcholine concentrations by inhibition galantamine is also thought to modulate nicotinic receptors. Activation of presynaptic nicotinic receptors can increase the release of acetylcholine.

Patients begin treatment with a twice daily dose of 4 mg. This can be increased to a total daily dose of 16 mg and then 24 mg at monthly intervals according to the patient's response and their ability to tolerate galantamine. The drug is rapidly absorbed. Although food slows the rate of absorption, it is recommended that galantamine is taken with meals. Approximately 20% of the drug is excreted unchanged in the urine. The metabolism of galantamine involves cytochrome P450 2D6 and 3A4, so there is a potential for drugs which inhibit these enzymes, for example paroxetine and

erythromycin, to increase the bioavailability of galantamine. Severe hepatic or renal impairment is a contraindication.

There have been several double-blind randomised placebo-controlled trials of galantamine. These trials used daily maintenance doses of 8 mg, 16 mg, 24 mg or 32 mg and measured the effects on rating scales such as the cognitive subscale of the Alzheimer's disease assessment scale. In a study lasting five months there was a difference of 3.3–3.6 points on this 70 point scale.[1] The difference between galantamine (24 mg daily) and placebo was 3.1 points in a study lasting six months[2], and 3.9 points halfway through a year-long study.[3] Clinicians and carers both considered that galantamine was significantly more effective than placebo in all three trials.

Discontinuations because of adverse reactions were more frequent at higher doses. Common adverse effects include nausea, gastrointestinal upsets, weight loss and headache. Galantamine should be used cautiously in patients with a cardiac conduction disorder and those who are taking drugs which reduce the heart rate. The cholinergic effects of the drug also preclude its use in patients with urinary outflow obstruction, severe asthma or obstructive pulmonary disease.

Approximately one patient in five will be unable to tolerate galantamine. Those that do may achieve a statistically significant benefit on rating scales, but the long-term clinical benefits are unclear. The clinical relevance of a three point change may vary considerably from one patient to another. In the study which continued for 12 months the patients' disability did not significantly change.[3] Galantamine is not approved for more severe cases of dementia.

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Levetiracetam

Keppra (UCB Pharma)

250 mg, 500 mg and 1000 mg film-coated tablets

Approved indication: epilepsy

Australian Medicines Handbook Section 16.1

Over the past few years several drugs have been developed as 'add-on therapy' for patients whose epilepsy is not well controlled by conventional treatment (see 'New antiepileptic drugs' Aust Prescr 1999;22:61–3). Levetiracetam is a new drug which has been approved as add-on therapy for patients with partial onset seizures with or without secondary generalisation.

The mechanism of action is unknown. Levetiracetam does not act in the same way as other antiepileptic drugs.

Patients take levetiracetam twice a day. Absorption is rapid and unaffected by food. Most of the drug is excreted unchanged in the urine. The dose should be adjusted if renal function is reduced. Although 24% of each dose is metabolised no dose adjustment is needed in hepatic impairment unless liver function is severely reduced.

A double-blind trial compared levetiracetam with placebo as add-on therapy for 294 patients with refractory partial seizures. The frequency of seizures was halved in 33% of patients taking levetiracetam 1000 mg daily and in 40% of patients taking 3000 mg daily. Only 11% of the placebo group had similar reductions in seizure frequency. Patients taking the higher dose of levetiracetam had a 30% reduction in the weekly frequency of seizures relative to placebo.[1]

The common adverse effects of levetiracetam are somnolence, asthenia and headache. If treatment has to stop it should be gradually withdrawn. In the clinical trials 13% of patients given levetiracetam developed an infection compared with 7% of patients given a placebo. A few patients will have a decreased white blood cell count. Some patients taking levetiracetam will develop behavioural problems such as hostility, particularly in the first few weeks of treatment. There have been a few reports of psychotic symptoms.

As levetiracetam is mainly excreted in urine it is unlikely to have significant interactions with drugs metabolised by the liver. It does not inhibit the cytochrome P450 system. The pharmacokinetics of levetiracetam are unchanged by phenytoin, carbamazepine, phenobarbitone, lamotrigine and gabapentin.

The studies show that levetiracetam is a better adjunctive therapy than placebo, but its long-term safety is unknown. There is also no information about its use in children or how it compares with the other add-on therapies.

REFERENCE

1. Cereghino JJ, Biton V, Abou-Khalil B, Dreifuss F, Gauer LJ, Leppik I, et al. Levetiracetam for partial seizures. Results of a double-blind, randomized clinical trial. Neurology 2000;55:236-42.

NEW FORMULATIONS

Didanosine

Videx EC (Bristol-Myers Squibb)

125 mg, 200 mg, 250 mg and 400 mg modified-release capsules

Hepatitis B vaccine (recombinant)

HB-VAX-II (CSL)

5 microgram/0.5 mL vials

Naproxen sodium

Nurolasts (Boots)

275 mg tablets

Salmeterol/fluticasone propionate

Seretide MDI (GlaxoSmithKline)

50 microgram fluticasone/25 microgram salmeterol

125 microgram fluticasone/25 microgram salmeterol

250 microgram fluticasone/25 microgram salmeterol

Testosterone
Androderm (Faulding)
12.2 mg transdermal patch

NEW STRENGTHS

Alendronate
Fosamax (Merck Sharp & Dohme)
70 mg tablets

Frusemide
Lasix (Aventis Pharma)
40 mg/4 mL ampoules

Isotretinoin
Oratane (Douglas)
10 mg capsules

Mitozantrone
Onkotrone (ASTA Medica)
10 mg/5 mL, 20 mg/10 mL and 25 mg/12.5 mL

Montelukast sodium
Singulair (Merck Sharp & Dohme)
4 mg tablets

Ramipril
Tritace (Aventis Pharma)
10 mg capsules

Rh D immunoglobulin (human)
Rh D immunoglobulin (CSL)
250 IU vials

Lamotrigine
Lamictal (GlaxoSmithKline)
2 mg tablets

NEW PROPRIETARY BRANDS

Bleomycin sulfate
Blenemax (ASTA Medica)
15 000 IU powder for injection

Ceftriaxone sodium
Ceftriaxone-BC (Biochemie Australia)
1 g/15 mL and 2 g/50 mL vials

Diphtheria, tetanus and pertussis vaccine
Boostrix (GlaxoSmithKline Australia)
0.5 mL pre-filled syringes

Enalapril maleate
Enalapril-BC (Biochemie Australia)
5 mg, 10 mg and 20 mg tablets

Fluticasone propionate
Flixotide Junior CFC-Free Inhaler (GlaxoSmithKline)
50 microgram/actuation

Ipratropium bromide
Apoven 250 (Douglas)
250 microgram/mL nebuliser solution in 1 mL containers

Metformin hydrochloride
Metformin-BC (Biochemie Australia)
50 mg and 800 mg tablets

Moclobemide
Moclobemide-BC (Biochemie Australia)
150 mg and 300 mg tablets

Propofol
Propofol Injection (Abbott)
10 mg/mL emulsion for infusion

Tamoxifen
Tamoxifen-BC (Biochemie Australia)
10 mg and 20 mg tablets

Implementing JETACAR

With reference to Professor Turnidge's editorial 'Antibiotics in animals – much ado about something' which was recently published in *Australian Prescriber* (2001;24:26–7), the 'Implementing JETACAR' web site was recently launched.

The web site is a gateway to information on what the Commonwealth Government is doing to address the growing problem of antibiotic resistant bacteria.

The address is http://www.health.gov.au/pubhlth/strateg/jetacar/index.htm

Therapeutic Guidelines: Endocrinology
Version 2, 2001

A new revised, updated version of Therapeutic Guidelines: Endocrinology has been published, giving recommendations for the management of endocrine-related illness. New chapters have been added on menstrual disorders, hormonal contraception, paediatric implications of endocrine disorders, overweight and obesity, and androgenisation in women.

For information about Endocrinology or any other Guidelines title, contact Therapeutic Guidelines Limited, freecall 1800 061 260, e-mail sales@tg.com.au or visit the web site at www.tg.com.au All Therapeutic Guidelines titles are available in electronic format.

The painting on the cover

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

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

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

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

Answers to self-test questions

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

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