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EDITORIAL

Electronic prescribing in hospitals: the road ahead

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Index words: drug information, drug utilisation.

(Aust Prescr 2001;24:2–3)

The use of computers in general practice has grown dramatically in response to initiatives such as the Commonwealth Government's Practice Incentives Program (PIP). In contrast, the use of computers in hospitals has changed little over the past few years. Whereas 65% of general practices qualified for the electronic prescribing component of the PIP[1], a survey in three Melbourne teaching hospitals revealed that only two out of 30 residents used computers for purposes other than reviewing patient results.[2]

The progress of computing in Australian general practice has recently deviated markedly from that of our public hospitals. Whereas electronic prescribing has become commonplace in general practice, our hospitals still rely on paper-based drug charts and outdated reference texts to support the management of inpatients' medication. While general practitioners are rapidly embracing the internet as a real-time source of clinical knowledge, many hospitals do not offer doctors and healthcare professionals internet access on the wards. This deviation represents a reversal of fortune for our hospitals which have provided doctors with electronic access to patients' laboratory results for many years.

In this issue...

There has been rapid growth in the use of information technology in medicine. Many general practitioners are now prescribing electronically, but Hugo Stephenson informs us that hospitals are being left behind.

The management of opioid dependence is controversial, but new treatments are becoming available. Alex Wodak briefly reviews the available options.

Successful treatment depends on an understanding of physiology. Brian Nankivell tells us how to assess renal function, while Jenny Martin and Michael Fay explain the principles of drug interactions involving the cytochrome P450 system.

Interactions are a risk of drug treatment, but Andrew Herxheimer proposes that we should talk more about harms than risks. Neil Buchanan gives examples of drugs that can provoke seizures, while Geraldine Moses reminds us that even 'natural' substances can cause harm.

The Quality in Australian Health Care Study suggested that 50% of adverse events occurring in our hospitals are highly preventable.[3] A recent study in the USA has also highlighted problems with hospital prescribing.[4] These include:

- unawareness of best-practice recommendations
- failure to alter drug therapy in the face of altered physiology
- disregarding a patient history of allergy to the same medication class
- prescribing the wrong drug name, dose form or abbreviation
- incorrect dosage or frequency calculations
- illegible writing and failure to communicate important information.

How many of these adverse events could have been prevented by electronic prescribing and decision-support programs?

Most medical schools incorporate information technology into the undergraduate curriculum. When working for prolonged periods in our public hospitals, new graduates will not have the opportunity to use their knowledge of computers. There is now a real risk that these doctors will become deskilled.

Why has general practice taken the lead in leveraging information technology to improve clinical practice? While financial incentives have certainly contributed significantly to the dramatic growth seen over the past year, factors such as increasing consumerism and the evolution of communication technology have contributed to this growth.[5] Furthermore, the commitment to 'legacy' systems has prevented large hospitals from embracing evolving technologies.

These legacy systems, which have been purchased over the past decade at enormous cost, provide access to patient management information and clinical results. Due to the proprietary nature of these systems, adding new applications can be both costly and time-consuming. Many hospitals are essentially locked into a cycle of dependence upon a single software provider that can only be broken by significant investment in system design and integration. Unfortunately, given the range of proprietary systems used within our hospitals, there cannot be a 'one size fits all' solution.

Hospitals have also suffered from the lack of practical solutions for the clinical interface. While the nature of most general practice consultations remains compatible with the use of a desktop computer, it is impractical (and prohibitively expensive) to expect medical officers to carry laptops on ward rounds, or to continually log on to computers located at every bedside.

Although bulky pen-based systems have been hailed as potential solutions for several years, the release of affordable hand-held computers should bring the possibility of electronic prescribing and decision support at the bedside closer to reality.

In further contrast to general practice, the hospital prescribing environment involves multiple prescribers, a wide range of drugs and methods of delivery and, importantly, is intimately related to drug dispensing. As a result, even the functionality of existing general practice prescribing packages must be significantly re-engineered to be useful in the hospital environment.

Despite the problems, considerable efforts are now being made to implement electronic strategies in our public hospitals. Several major hospitals are evaluating existing general practice prescribing packages to assess their suitability for hospital practice. Others have been developing software in-house to integrate with their existing information technology infrastructure. The Royal Melbourne Hospital is developing an antibiotic decision-support system which will suggest appropriate antibiotics based on patients' microbiology records. Many hospitals are now piloting programs that promote electronic communication with local general practitioners to encourage greater continuity of care. Importantly, as interest in clinical information technology is rapidly spreading throughout the hospital system, clinicians are now participating more actively in this new era of hospital-based clinical practice.

Hospitals in the USA are providing hand-held computers to doctors and nurses to use at the bedside. Many integrated healthcare packages now offer electronic prescribing through these hand-held systems. The popularity of these hand-held computers across a wide range of industries will result in even greater functionality emerging without significantly increasing deployment costs.

With the introduction of State-based legislation, such as the Electronic Transactions (Victoria) Act 2000, pre-existing legal obstacles to electronic prescribing are rapidly disappearing. While a handful of hospitals have called for tenders to pilot electronic prescribing systems as isolated projects, a co-ordinated approach is required to ensure that the benefits of electronic prescribing can be delivered consistently across our hospital system.

Financial incentives have clearly been effective in promoting the use of computers in general practice. These incentives have coincided with increased consumer awareness, exponentially increasing volumes of clinical knowledge and decreasing costs of upgrading technology. With the same forces for change now appearing in our hospitals, the opportunity is emerging for incentive programs to encourage hospitals to follow the lead of general practice by adopting electronic prescribing and decision-support systems.

REFERENCES

1. Quinlan F. Electronic prescribing in general practice: one small step. Aust Prescr 2000;23:50-1.
2. Stephenson H. Decision support in Australian public hospitals. Presentation to pharmaceutical decision support workshop; 2000 Feb 7; Melbourne, Australia. http://www.clininfo.health.nsw.gov.au/pdsp/pdsp_presentat.html
3. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. Med J Aust 1995;163:458-71.
4. Kohn LT, Corrigan JM, Donaldson MS, editors. Committee on Quality of health care in America. To err is human: building a safer health system. Washington DC: National Academy Press; 2000.
5. Yellowlees P. E-therapy – your guide to mental health in cyberspace. 2000 Oct. Available from: http://www.mightywords.com (EB00019384)

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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.

Treating head lice

Editor, – I would like to correct an error in the article by Dr Wargon (Aust Prescr 2000;23:62-3).

The comment that an organophosphate insecticide 'acts by non-reversibly blocking acetylcholine' is not correct. These compounds act by non-reversibly blocking the enzyme acetylcholinesterase which is responsible for degrading acetylcholine at nerve terminals. The effect of this enzyme inhibition is an excess acetylcholine activity rather than any blocking of the effects of this neurotransmitter.

Maldison (malathion) initially undergoes bioactivation in the insect to the active compound which, by my understanding, acts predominantly in the insect's central nervous system.

Pyrethroids (also mentioned in the article) act on voltage-dependent sodium channels in the nerve cell membranes. With some of these drugs, this results in repetitive nerve firing and release of excess acetylcholine at the nerve terminal. The end result with some pyrethroids is therefore similar to that with the organophosphates.

Excess muscarinic activity resulting from the clinical use of reversible anticholinesterases (e.g. neostigmine) is a common problem which is overcome in anaesthetic practice by the concurrent administration of an antimuscarinic drug (e.g. atropine) that does block the action of acetylcholine at muscarinic receptors. This is important to prevent the severe bradycardia that would otherwise occur.

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Drug treatment for opioid dependence

Alex Wodak, Director, Alcohol and Drug Service, St Vincent's Hospital, Sydney

SYNOPSIS

The number of Australians dependent on heroin is increasing. This is resulting in more deaths and disease. Treatment of heroin dependency usually begins with detoxification, followed by maintenance treatment. Some patients become abstinent. While non-drug therapy has a role there is more evidence to support the use of pharmacotherapy for drug dependence. Methadone is a cost-effective maintenance treatment. Other options include buprenorphine and naltrexone, but further evaluation of these treatments is needed in Australian practice.

Index words: buprenorphine, heroin, methadone, naltrexone.

(Aust Prescr 2001;24:4–6)

Introduction

Heroin is the most commonly injected illicit drug in Australia. Heroin injecting began in Australia in the late 1960s. Using several different methods, it was estimated that there were about 70 000 heroin-dependent persons in Australia in 1997.[1] In the last few years, the number of heroin injectors in Australia has increased more rapidly than in the previous quarter century.

Reported deaths from heroin overdose have increased in Australia fifty-five fold from six in 1964 (1.3/million people aged 15–44 years) to 600 in 1997 (71.5/million).[2] In 1998, there were 737 such deaths. HIV remains under good control among injecting drug users in Australia, but an estimated 11000 hepatitis C infections in 1997 were attributed to the sharing of injection equipment.[3]

Heroin dependency is a poorly understood, chronic, relapsing, remitting condition. Mortality, estimated to be 1–2% per annum, is about 15 times that expected in a population of similar age and sex who do not inject drugs.

Heroin-dependent persons benefit from treatment.[4] Evidence for the persistence of benefit after treatment is less impressive. Pharmacological treatments attract and retain many more drug users than non-pharmacological interventions and are also far better supported by evidence of benefit. Psychosocial interventions play an important role in pharmacological treatments, but the optimal nature and extent of these psychosocial components remains controversial. Some heroin-dependent persons are not suitable for pharmacological treatments or are unwilling to consider them. We therefore need a diverse range of treatment options, including non-pharmacological interventions.

Benefits of treatment

Treatment can improve social and economic outcomes as well as the patient's health (see box). As a generalisation, heroin use falls dramatically. The longer patients stay in treatment, the lower it falls. Reducing the use of heroin will result in decreased deaths, fewer infections and less crime. Although not all patients will completely stop using drugs, the reduction in deaths from overdose makes treatment worthwhile.

Detoxification

The aim of detoxification is to provide a safe and comfortable withdrawal from mood-altering substances. Detoxification should not be regarded as the sole treatment, but it is often a useful prelude to other forms of treatment. Furthermore, some patients undergoing detoxification manage to achieve enduring abstinence without proceeding through subsequent formal treatment. In Australia, most detoxification provided to heroin-dependent persons is still provided in residential care. Outpatient detoxification is increasing, although not all patients are suitable for or will accept this approach.

Benefits of treatment

Health

- Reduction in deaths (all-cause mortality but especially drug overdose)
- Reduction in morbidity (mainly infections – HIV, hepatitis B, hepatitis C, also bacterial infections both proximal, e.g. abscesses around injection sites, and distal, e.g. sub-acute bacterial endocarditis – but also reduction in non-fatal overdoses)
- Improvement in mental health

Social

- Improved relationships and parenting
- Reduction in crime
- Increased employment
- Improved residential status (i.e. less homelessness)
- Increased education and training
- Reduction in drug use (all sorts)
- Reduced heroin use (including abstinence)

Economic

- Earning income legally, or social security
- Less debt
- Benefits outweigh costs to individuals and society

Clonidine, an alpha$_2$-adrenergic agonist, helps to ameliorate some of the more distressing symptoms of heroin withdrawal. It is usually used in combination with several other oral drugs to provide symptomatic relief. These drugs include paracetamol for bone pain, diphenoxylate or loperamide for control of diarrhoea and hyoscine to control abdominal cramps. Benzodiazepines such as nitrazepam can be used for the short-term treatment of insomnia. A small proportion of patients prescribed clonidine may develop hypotension. Some patients who cease clonidine abruptly develop rebound hypertension. Lofexidine, which has many of the useful features of clonidine but possibly fewer adverse cardiovascular effects, may become available in Australia.

Relapse following detoxification is very common. Doctors, their patients and the patients' families should be prepared for the possibility of relapse and not despair if this occurs. Relapse should either prompt a repeat attempt at detoxification, or alternatively, a review of all available options.

Methadone maintenance

Methadone, an opioid agonist which is well-absorbed orally, was introduced for the treatment of heroin dependence in 1964. The rationale involves replacing an illegal, short-acting, expensive drug injected intravenously with an oral drug which is legal, inexpensive and has a longer half-life (requiring only once-daily administration). Patients attend a clinic or pharmacy every day (or several days a week) to be dispensed methadone under supervision. Detoxification is not required for patients starting methadone. Psychosocial interventions are an important part of treatment.

Methadone maintenance is one of the most thoroughly investigated interventions in medicine. A vast scientific literature provides compelling evidence that methadone maintenance reduces heroin consumption, death from drug overdose, HIV infection and criminal activity.[4] Methadone maintenance is generally very safe, but injudicious use can prove fatal. Methadone also appears to be cost-effective[3] and in most countries, demand for treatment exceeds the availability of methadone programs.

Methadone treatment is often subjected to relentless ill-informed criticism in the lay press despite strong scientific support. This criticism undermines community support and makes authorities ambivalent towards funding programs. Local opposition to programs is also not uncommon. Much of the opposition to methadone arises from the fact that it involves giving a patient with drug dependence another drug of dependence. This concern does not arise with nicotine replacement therapy for cigarette smokers even though 20% of patients experience great difficulty stopping nicotine chewing gum.

As many as 85% of patients will stay on methadone for 12 months. Patients retained in treatment on a larger dose and for a longer duration generally achieve better results. For most patients, optimal results are achieved with a dose of 60–100 mg per day. Many patients require treatment for at least two years. Some heroin-dependent persons will not consider methadone maintenance treatment, while others who agreed to enrol achieve unsatisfactory outcomes. Better results are often achieved in older patients. Not uncommonly, patients who have had poor results from earlier episodes of treatment achieve better results from a subsequent treatment episode. There is good evidence to suggest that as much as 80% of the variance in treatment outcome results from treatment rather than pre- or post-treatment factors.[5] Important treatment factors include the dose of methadone and the morale of the clinic staff.

Methadone maintenance therapy is provided in a diverse range of programs. New patients or those with more difficult medical or psychosocial problems are often better managed in large public or private clinics. Patients who have achieved some stability are often better managed in general practice with methadone dispensed from a community pharmacy. (Methadone programs are not available in the Northern Territory.)

Naltrexone

Naltrexone is a long-acting opioid antagonist which is well-absorbed orally. A severe withdrawal reaction may be precipitated if the patient has recently taken heroin or another opioid. The manufacturer recommends that naltrexone is not commenced until seven to 10 days after the last use of heroin. If heroin or another opioid is taken by a patient who has already been taking naltrexone, all opioid effects are blocked. The results of naltrexone maintenance treatments are consistently modest for street drug using populations.[6] Better results may possibly be achieved if naltrexone administration is supervised as part of a comprehensive treatment program, or if more 'motivated' patients are selected (white-collar professionals, persons on parole, probation or in jail).

Some concern has recently been raised about the possibility of an increased risk of death from overdose during naltrexone maintenance. The proposed explanation is that opioid tolerance declines during naltrexone administration. If naltrexone is taken intermittently and then heroin consumed in intervening periods, the risk of death from overdose may be increased.

Accelerated detoxification with general anaesthesia or heavy sedation has been added recently to naltrexone maintenance. This is sometimes referred to as Ultra Rapid Opiate Detoxification (UROD) or Rapid Opiate Detoxification (ROD). Published evaluations have substantial methodological shortcomings and accelerated detoxification can only be considered to be experimental.[7] Nevertheless, astonishing success is often claimed for this intervention in the lay press.

Buprenorphine

This partial agonist is taken sublingually as it has a high first-pass metabolism when taken orally. It has been used extensively in France and evaluated in a number of countries. Results overall are generally comparable with methadone maintenance, but each drug has particular advantages

(and some special disadvantages). Buprenorphine can be taken on alternate days.

The risk of overdose is minimal but people on large doses of heroin may experience some withdrawal symptoms. Although buprenorphine is more expensive than methadone it may become the treatment of choice for detoxification.

Leva-alpha-acetylmethadol (LAAM)

LAAM (also known as levomethodyl acetate) is a methadone derivative. It has a longer half-life than methadone, but has similar effects. Administration on alternate days reduces the cost of providing the drug and also reduces the burden on patients who are doing well. The metabolites are active and other drugs can interfere with the production of the metabolites. LAAM may be available in Australia within the next few years.

Sustained release oral morphine (SROM)

Few studies have been conducted. A trial has commenced in Australia.

Prescription heroin

Heroin prescription has been available for the management of heroin dependence in the UK since 1926. It has never been studied or utilised commonly in that country. A handful of papers of variable quality suggest that results might be comparable to methadone. A heroin trial conducted in Switzerland in the 1990s obtained some impressive results but lacked a control group. Nevertheless, results were sufficiently impressive to stimulate research in other European countries. The major argument in favour of heroin prescription is for the management of heroin injectors refractory to other treatments.

Intravenous methadone

Intravenous methadone has been prescribed in the UK for decades although evaluation studies are scant.

Non-pharmacological treatments

These include drug-free outpatient counselling, residential rehabilitation (therapeutic communities) and self-help groups (Narcotics Anonymous). Retention is often poor and good evidence of benefit is difficult to find. Residential rehabilitation is more expensive than outpatient pharmacological treatment and is difficult to combine with continued employment.

Summary

Pharmacotherapeutic treatments attract and retain large numbers of heroin-dependent patients. Evaluation studies show that agonist treatments are safe, effective and cost-effective. The range of pharmacotherapeutic options for management of heroin dependency in Australia is now being expanded. Demand for all forms of treatment (especially pharmacological treatments) for heroin dependence far outstrips supply.

REFERENCES

1. Hall WD, Ross JE, Lynskey MT, Law MG, Degenhardt LJ. How many dependent heroin users are there in Australia? Med J Aust 2000;173: 528-31.
2. Hall WD, Degenhardt LJ, Lynskey MT. Opioid overdose mortality in Australia, 1964-1997: birth-cohort trends. Med J Aust 1999;171:34-7.
3. Law MG. Modelling the hepatitis C virus epidemic in Australia. J Gastroenterol Hepatol 1999;14:1100-7.
4. Ward J, Mattick RP, Hall W. Methadone maintenance treatment and other opioid replacement therapies. Sydney: Harwood Academic Publishers; 1999.
5. Ball JC, Ross A. The effectiveness of methadone maintenance treatment: patients, programs, services, and outcome. New York: Springer-Verlag; 1991.
6. Greenstein RA, O'Brien CP, McLellan AT, Woody GE, Grabowski J, Long M, et al. Naltrexone: a short-term treatment for opiate dependence. Am J Drug Alcohol Abuse 1981;8:291-300.
7. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. JAMA 1998;279:229-34.

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Self-test questions

The following statements are either true or false (answers on page 23)

1. Buprenorphine is taken sublingually because of its low oral bioavailability.
2. The long half-life of methadone allows it to be given once a day.

Thyroxine interacts with celery seed tablets?

Geraldine Moses, Senior Pharmacist and Manager, Queensland Medication Helpline, Mater Misericordiae Public Hospitals, South Brisbane

Introduction

Interactions between so-called 'natural therapies' and clinical medicines are an unquantified problem in the Australian community, due to a lack of awareness and reporting from consumers and health professionals alike.

The Queensland Medication Helpline is a direct link to consumers and their medication concerns. Over the past five years we have reported, to the Adverse Drug Reactions Advisory Committee, a variety of suspected adverse effects and interactions between clinical and herbal/nutritional

medicines. An interesting example is the potential interaction between thyroxine and celery seed tablets.

Case reports

Our first case involved a 55-year-old woman who, after considerable monitoring, had finally been stabilised on a daily dose of thyroxine 100 microgram. A month later, her doctor found that her T_4 levels were low again and her dose was doubled. The patient then remembered that in the past month she had also started taking celery seed tablets for osteoarthritis. Suspecting a potential interaction, she ceased the celery seed tablets without increasing the thyroxine dose as the doctor had advised. Next time her thyroxine levels were checked they had increased to within the normal range. She tried recommencing celery seed a month later but after a week she felt lethargic, bloated and had dry skin. When she stopped the celery seed tablets, she reported that her 'general energy levels improved'.

A second report was received from a 49-year-old woman who had taken thyroxine for many years. When her T_4 became extremely low her doctor suspected that she had not been taking her tablets. The patient argued that she had taken her thyroxine, but she had recently commenced taking celery seed tablets to treat arthritis. She ceased the celery seed tablets and one month later her thyroxine levels had returned to within the normal range.

Evidence

Celery seed extracts (*Apium graveolens*) are a popular herbal remedy for the treatment of arthritis, gout, fluid retention and cystitis. Celery seed/fruit should not be confused with the edible celery stem.[1] Studies have shown that celery plant extracts have anti-inflammatory activity against carrageenan-induced rat paw oedema.[2] Hypotensive and hypoglycemic activities have also been reported.[1] In preliminary research, five of 23 celery-based preparations showed antiarthritic effects, but no anti-inflammatory or antipyretic effects. The celery seed activity was thought to be dependent on processing at low temperatures.[3]

An extensive literature search did not find other reports of an interaction between celery seed extracts and thyroxine. However, when reference was made to these case studies in an article in a Queensland newspaper, the Queensland Medication Helpline received a flood of calls about similar experiences. A total of 10 cases are now on file. Although the validity of these anecdotal reports needs to be tested, as their number accumulates so too does the suspicion that the interaction is real. A pharmacokinetic study of the T_4-celery interaction is under consideration by the Mater Hospital Pharmacy Services' Therapeutic Advisory Service.

Conclusion

Anecdotal evidence indicates a potential interaction between thyroxine and celery seed tablets. Since consumers often fail to volunteer details of self-medication with complementary medicines, prescribers and pharmacists should ask directly what herbal/nutritional medicines consumers are taking. If celery seed tablets are being co-administered with thyroxine, it is strongly recommended that thyroid function tests are closely monitored and any suspected interaction reported.

REFERENCES

1. Newall CA, Anderson LA, Phillipson JD. Herbal medicines – a guide for health-care professionals. London: Pharmaceutical Press; 1996.
2. Lewis DA, Tharib SM, Veitch GBA. The anti-inflammatory activity of celery *Apium graveolens* L. (Fam. Umbelliferae). Int J Crude Drug Res 1985;23:27-32.
3. Turmeric has anti-inflammatory effects. Reuters Health eLine [serial online] 2000 June 8. http://www.reutershealth.com/frame/eline.html

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Your questions to the PBAC

Celecoxib

The listing of celecoxib as a general benefit on the Pharmaceutical Benefits Scheme (PBS) from 1 August 2000 was welcomed by arthritis sufferers Australia-wide. However, the decision to list the 200 mg capsules with an issue quantity of 60 rather than 30 has surprised many pharmacists. This exceeds the 30 day supply rule, taking into account the manufacturer's recommended one capsule a day dosage.

A more serious problem is the number of potential adverse sulfonamide-type reactions that may occur around Australia, and the subsequent waste of Commonwealth funds when celecoxib is discontinued by the patients. In our town of 5000 there has been a high demand for celecoxib and within one week of listing we had six adverse sulfonamide-type reactions, with swelling of the throat, body rash and fever. One patient ended up in Moruya Hospital and the rest were referred to their general practitioner.

As a medication review pharmacist, I am concerned about the incidence and severity of these reactions. They usually occur within a few days of commencing celecoxib and the patient has to cease the medication. As celecoxib 200 mg is the most commonly prescribed dose, I believe that the decision by the Pharmaceutical Benefits Advisory Committee to list the 200 mg capsules in a quantity of 60 was a poor one, and will result in a significant waste of PBS funds.

Richard Lord
Pharmacist
Narooma, NSW

PBAC response:

The Pharmaceutical Benefits Advisory Committee (PBAC) recommends the maximum quantity and the number of repeats that should apply to the prescribing of a particular medication. The maximum quantity recommended for listing by the PBAC

usually corresponds to the pack size produced by the manufacturer.

For drugs which are intended for use in chronic conditions, the PBAC recommends a maximum quantity and number of repeats which will provide sufficient supply of the drug for six months' therapy at normal dosage levels.

The current dosage of celecoxib for the treatment of osteoarthritis is 200 mg once daily or 100 mg twice daily, with some patients requiring 200 mg twice daily. The dosage for rheumatoid arthritis is 100 mg or 200 mg twice daily. The PBAC therefore recommended a maximum quantity of 60 capsules for both the 100 mg and 200 mg strengths of celecoxib in an attempt to encompass the complete dosage range required by patients. The maximum quantity listed in the Pharmaceutical Benefits Scheme (PBS) Schedule for celecoxib 200 mg provides for one month's therapy at maximum dosage levels and for two months' therapy at minimum dosage levels. The maximum number of repeats (three, for consistency with the listings of the non-steroidal anti-inflammatory drugs) provides for a supply of four months or eight months of medication depending on the patient's dose.

Doctors are under no obligation to prescribe the full maximum quantity specified in the Schedule for a particular drug. They may, at their discretion, prescribe smaller quantities than those listed in the Schedule.

The mechanism via which adverse drug reactions are monitored in Australia is administered by the Adverse Drug Reactions Advisory Committee (ADRAC) of the Therapeutic Goods Administration. Pharmacists who see unexpected reactions can notify the ADRAC Secretariat by filling out the blue report card which is enclosed in every copy of the PBS Schedule.

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Medications which may lower seizure threshold

Neil Buchanan, Emeritus Professor, University of Sydney, Sydney

Most people who have epilepsy are warned that certain substances, especially other medications and alcohol, 'do not mix with their pills'. This is partly correct and is more valid with the older, enzyme-inducing drugs (phenytoin, phenobarbitone and carbamazepine) than with the newer antiepileptic drugs.

What people with epilepsy are not sufficiently informed about are the factors which lower the seizure threshold and make them more liable to have seizures. Such factors include stress, sleep deprivation, alcohol, menstruation and, especially in children, intercurrent infection and fever. Antiepileptic drugs may occasionally make seizures worse, either idiosyncratically when being introduced, or if the dose is excessive. Table 1 shows some medications which may provoke seizures by lowering the seizure threshold, rather than by interacting with antiepileptic drugs.

We do not know how often seizures occur because a drug has altered the seizure threshold. Many reports are anecdotal. In the past two years of specialist practice I have seen 25 patients where clinical judgement would suggest a particular medication has provoked a seizure. The commonest seizure-provoking drug was pethidine. With hindsight, 19 of the 25 patients might have avoided this problem if they had known that it could have occurred. The severity of the seizures varied, but three patients were admitted to intensive care units.

The list of potential seizure-provoking medications shown in Table 1 is probably incomplete. The list has been compiled from personal observations, discussions with colleagues, data from the Adverse Drug Reactions Advisory Committee (ADRAC) and published product information. The purpose of compiling such a list does not imply the use of these drugs is prohibited. Rather it aims to alert doctors and people with epilepsy to medications that could provoke seizures. Attention to the mention of epilepsy in the precautions section of published product information would identify most potential problems.

With regard to anaesthetic agents, there are reports of seizures post-anaesthesia. Whether this relates to the anaesthetic agent itself or withdrawal seizures after an anaesthetic is not clear. While propofol is effectively used in the management of status epilepticus, there are definite reports of seizures after its use as an anaesthetic. From the patient's point of view, the reason why is not of great concern.

The implications are:

- medical practitioners should be aware of the possibility of a change in seizure threshold
- people with epilepsy should be aware of the possibility that medicines may lower their seizure threshold
- medications which may alter the seizure threshold should only be used if really necessary and no safer alternative exists.

Table 1

Medications which may lower seizure threshold

Medications	*Relative frequency of seizure provocation*	*Comments*
Anaesthetic drugs		
enflurane	rare	
isoflurane	rare	
propofol	well described	
Antiarrhythmics		
lignocaine	uncommon	
mexiletine	rare	
Antibiotics		
penicillins, cephalosporins, amphotericin, imipenem	relatively common in high dosage	• with big intravenous doses • probably cannot be avoided
Antidepressants		
tricyclics	uncommon	• patients should be informed of risk • increased seizures usually occur within 2–6 weeks of starting antidepressant
selective serotonin reuptake inhibitors	uncommon	
monoamine oxidase inhibitors	uncommon	
doxepin	rare	
nefazodone	uncommon	
Antihistamines		
azatadine, cyproheptadine, dexchlorpheniramine, methdilazine, pheniramine maleate, promethazine	probably quite rare	• widely used and found in many over-the-counter medicines • suggest avoiding unless essential • use non-sedating antihistamines in preference
Antimigraine		
sumatriptan	rare	
Antipsychotics		
chlorpromazine	uncommon	avoid – if possible
clozapine	common	avoid – if possible
flupenthixol	rare	
fluphenazine	rare	
haloperidol	uncommon	
olanzapine	uncommon	See ADRAC Bulletin 1999;18:3
pimozide	uncommon	
risperidone	uncommon	
thioridazine	uncommon	
thiothixene	uncommon	
trifluoperazine	uncommon	
Bronchodilators		
aminophylline, theophylline	well described	avoid – if possible
Cough and cold remedies		
triprolidine and pseudoephedrine, pseudoephedrine	probably quite rare	• widely used and found in many over-the-counter medicines • suggest avoiding unless essential
Hormonal preparations		
oral contraceptives	uncommon	• patients should be warned of risk • increased seizures occur within 1–4 weeks of starting oral contraceptives or hormone replacement therapy
hormone replacement therapy	uncommon	
Immunomodifiers		
cyclosporin	common	
Narcotic analgesics		
pethidine	common	avoid – use morphine See ADRAC Bulletin 1997;16:3
fentanyl	uncommon	avoid – if possible
Stimulant medications		
dexamphetamine	uncommon	parents/patients should probably be made aware of a quite low risk
methylphenidate	anecdotal reports	

Cytochrome P450 drug interactions: are they clinically relevant?

Jennifer Martin, Clinical Pharmacology Registrar, and Michael Fay, Medical Oncology Registrar, Alfred Hospital, Melbourne

SYNOPSIS

The cytochrome P450 system is an evolutionary system to deal with the breakdown of endogenous and exogenous chemicals in the body. There is an increasing amount of interest in this area as new information is enabling us to understand why people metabolise drugs differently and why there is a spectrum of adverse effects in different people. Understanding the cytochrome P450 system also explains the mechanisms of some drug interactions, and enables us to predict which of these are likely to be relevant in clinical practice.

Index words: pharmacokinetics, drug metabolism, warfarin.

(Aust Prescr 2001;24:10–2)

Introduction

The cytochrome P450 enzyme system is one of several metabolic systems which evolved to enable organisms to deal with lipid-soluble environmental chemicals. Latterly, the importance of the system in metabolising drugs has been recognised. The cytochrome P450 system performs this function by oxidising, hydrolysing or reducing the chemicals. This enables another group of enzymes, conjugation enzymes, to attach polar groups to make the metabolites water soluble so that they can be excreted in the urine. Although there are other enzyme systems that perform similar functions, the cytochrome P450 system is important because it is involved in most clinically relevant metabolic drug interactions.

The cytochrome P450 family

To date, about 55 human isoforms of cytochrome P450 have been discovered. These isoforms are given numbers and letters to signify their common evolutionary families. CYP1, CYP2 and CYP3 are important in drug metabolism. Each member of a family contains similar amino acids. Subfamilies are classified by the protein sequence. The known clinically relevant cytochromes are CYP3A4, CYP2D6, CYP1A2, CYP2C9, CYP2C19 and CYP2E1. CYP3A4 is the most abundant enzyme. Most of the enzymes are involved in metabolising endogenous substrates to carry out housekeeping functions. For example, they are involved in the intermediary metabolism of steroids such as testosterone, and of lipids. Other isoforms are responsible mainly for metabolising exogenous chemicals including drugs.

Each of the isoforms has a wide substrate specificity, but each has its own specific substrate profile. This enables the whole range of chemical structures to be metabolised. These isoforms have differing regulatory mechanisms to control their activity. The regulatory mechanisms involve chemicals which induce or inhibit the enzyme. For example, CYP1A2 metabolises some carcinogenic tars in cigarette smoke and is induced by these chemicals. Members of other CYP gene families are induced by drugs such as barbiturates, anticonvulsants and rifampicin.

As well as showing some degree of substrate selectivity, the individual isoforms also show selectivity for inhibitors. For example, sulfaphenazole is a specific inhibitor of CYP2C9 whereas quinidine is a potent and selective inhibitor of the isoform CYP2D6.

Some of the isoforms exhibit genetic polymorphisms. The frequency of these polymorphisms differs markedly between ethnic groups. These genetic differences mean some people have an enzyme with reduced or no activity. Patients who are 'slow metabolisers' may have an increased risk of adverse reactions to a drug metabolised by the affected enzyme. One isoform, CYP2D6, also has alleles that result in 'superfast' metabolisers.

The liver is the main site of drug metabolism. However, isoforms occur in many tissues and CYP3A4, in particular, is found at quite high concentrations in the mucosa of the small intestine. This means that drug substrates for this isoform are subject to metabolism during absorption, while they are passing through the small intestinal mucosa, and during their first pass through the liver. Serious drug interactions resulted in the withdrawal of mibefradil (a T-type calcium channel blocker that inhibits CYP3A4) because of deaths occurring from the concurrent administration of drugs that are CYP3A4 substrates.

Principles

With new knowledge regarding substrate specificity, drug interactions involving the cytochrome P450 system are often predictable. However, they may not necessarily be clinically significant. There are several principles that help predict whether or not a drug interaction will be clinically significant. These include pharmacokinetic (what the body does to the drug) and pharmacodynamic (what the drug does to the body) factors. Other factors such as the wide variability of patient response to the same drug, concomitant medical illness and factors relating to the route and timing of administration may also be important.

Concentration-effect relationship

Clinically significant interactions occur when one drug affects the metabolism of another causing a change in concentration.

This change in concentration can have clinical implications depending on the concentration-effect relationship. A number of factors influence this, including:

- the position of the drug concentration on the dose-response curve at the time of the interaction
- the slope of the concentration-effect curve
- the size of the change in concentration of the drug
- the therapeutic index of the drug.

If the drug concentration is near the top of the response curve, adding a drug that increases its concentration will not increase its efficacy, regardless of the size of the interaction. However, the increase in concentration still may be relevant with respect to toxicity. An example of this is with drugs that increase the concentration of amlodipine. Increasing the concentration beyond a certain point does not increase the hypotensive effect.

As a general rule, if an enzyme inhibitor doubles the concentration, an enhanced drug response can occur. However, even a small increase may be important for medications with a narrow therapeutic index. Likewise a small decrease may be important for medications (such as cyclosporin) that rely on a certain concentration for their efficacy.

Patient factors

Gender, hormonal status, age and pre-existing conditions can all affect whether a drug interaction is likely to be clinically significant. For example, giving high doses of cisapride to someone with a normal heart, or normal doses to someone with a long ECG QT interval, will increase the likelihood of an arrhythmia. Drugs which reduce cisapride metabolism by inhibiting CYP3A4 (e.g. macrolides) can increase its concentration and further increase the chance of a potentially fatal arrhythmia occurring.

Administration

The route of administration and the timing of a dose can be important. Oral administration is more likely to have cytochrome P450 interactions because the drug is then subject to cytochrome P450 interactions in the gut wall as well as in the liver. An example of this is grapefruit juice. When taken at the same time as felodipine, it inhibits gut wall CYP3A4, increasing felodipine absorption across the gut wall and therefore bioavailability.

First-pass metabolism

In general, if a drug has a high first-pass metabolism through the liver one can expect a marked increase in its concentration if it is taken with another drug which inhibits metabolism. Whether or not this change in concentration is clinically significant is related to the factors affecting the concentration-effect relationship. Examples of drugs which undergo first-pass metabolism by CYP3A4 include[1]:

- **very high** first-pass metabolism: buspirone, ergotamine, lovastatin, nimodipine, saquinavir, simvastatin
- **high** first-pass metabolism: oestradiol, atorvastatin, felodipine, indinavir, isradipine, nicardipine, propafenone and tacrolimus
- **intermediate** first-pass metabolism: amiodarone, carbamazepine, carvedilol, cisapride, cyclosporin, diltiazem, ethinyloestradiol, etoposide, losartan, midazolam, nifedipine, nelfinavir, ondansetron, pimozide, sildenafil, triazolam and verapamil.

Significant interactions by drug class

Anticonvulsants

Carbamazepine, oxcarbazepine, and phenytoin reduce the concentration of oral contraceptives by inducing CYP3A4. This has resulted in some women having unplanned pregnancies.[2] Carbamazepine toxicity has occurred with 3A4 inhibitors. Phenytoin reduces the concentrations of many drugs metabolised by the cytochrome P450 system. This results in clinically significant effects for some drugs with a low therapeutic index such as warfarin and cyclosporin**.**

Immunosuppressants

Ketoconazole widely inhibits the cytochrome P450 system and doubles the oral availability of concurrently administered cyclosporin. This interaction has been used to enable patients to be given lower doses of cyclosporin. Other inhibitors of CYP3A4 have been used with similar, but less predictable results.

Tacrolimus is a substrate for CYP3A4. Clinically significant toxicity has been reported when co-administered with CYP3A4 inhibitors, such as diltiazem. CYP3A4 inducers such as carbamazepine reduce tacrolimus concentrations.

St John's wort has caused organ rejection when added to cyclosporin therapy, by inducing CYP3A4.[3]

Protease inhibitors

Ritonavir, a CYP3A4 inhibitor, is often added to saquinavir, a CYP3A4 substrate, as their interaction results in a 33% increase in the maximum concentration of saquinavir. Grapefruit juice can double the bioavailability of saquinavir, although this is not reliable enough to be used clinically. St John's wort, a CYP3A4 inducer, reduces the concentration of indinavir, a CYP3A4 substrate, by 57%. This is clinically significant as the reduction can lead to failure of therapy.[4]

Non-drug

Grapefruit juice, by inhibiting CYP3A4, increases the concentrations of several drugs. This could be clinically relevant especially in older patients, or those with liver failure.[5] Although there is an interaction with felodipine[5], there is no clinically significant effect from the interaction with amlodipine.[6]

Anti-infectives

Ketoconazole and to a lesser extent itraconazole inhibit all cytochrome P450 enzymes. These antifungal drugs can cause many clinically significant interactions by increasing the concentrations of other drugs. Fluconazole has clinically significant interactions only if the other drug has a low therapeutic index, e.g. cyclosporin. Miconazole oral gel increases the INR in patients taking warfarin.[7] Erythromycin has similar interactions to ketoconazole. Rifampicin is an

enzyme inducer and has been reported to reduce the concentration of drugs metabolised by cytochrome P450.

Cardiovascular

Felodipine concentrations are increased by grapefruit juice, erythromycin, and itraconazole, but the change in blood pressure is not usually significant.[8] It is more likely to be a problem in people who cannot tolerate even a small reduction in blood pressure. Diltiazem and verapamil increase the concentration of cyclosporin and, because of cyclosporin's low therapeutic index, this is likely to be clinically significant.

Cisapride and pimozide can cause QT prolongation by themselves if their concentrations are high enough. However, this effect will occur more frequently if the drugs are taken with CYP3A4 inhibitors such as diltiazem, macrolides, ketoconazole or grapefruit juice.

Rhabdomyolysis occurs more frequently with increasing concentration of 'statins'. The risk may be increased when statins such as the predominantly CYP3A4 metabolised lovastatin, simvastatin and atorvastatin are given with CYP3A4 inhibitors like macrolides, diltiazem and grapefruit juice.

Warfarin has a complex metabolic pathway acting as a substrate for a number of cytochrome P450 enzymes. Any change in medication in patients on warfarin requires close monitoring of the INR for a period long enough to ensure the plasma concentrations are at steady state. For example, when amiodarone, which has a half-life of 26–107 days, is added to or subtracted from warfarin it may not have its full impact on the INR for 100–400 days.

Antidepressants

Some selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine, paroxetine and fluvoxamine) inhibit CYP2D6. If a patient taking one of these drugs is given codeine, it cannot be converted to morphine. This results in lack of analgesic activity. The same drugs have been reported to prolong the INR when used with warfarin. Paroxetine has also caused a serious interaction by inhibiting the metabolism of perhexilene.[3]

Nefazodone is a substrate and an inhibitor of CYP3A4. It increases the concentration of several CYP3A4 substrates including cisapride, terfenadine, astemizole and pimozide. This may cause arrhythmias. Similarly nefazodone reduces the required doses of triazolam and alprazolam by 75% and 50% respectively.[10] ADRAC has reported a death from rhabdomyolysis due to the addition of nefazodone to simvastatin, a CYP3A4 substrate.[3]

Tricyclic antidepressants and SSRIs should not routinely be used together as the combination can result in a serotonergic syndrome. Most tricyclics are extensively metabolised by CYP2D6 and concentrations will increase if an inhibitory drug, e.g. an SSRI, is co-administered. The addition of fluoxetine, paroxetine or fluvoxamine (CYP2D6 inhibitors) to patients on desipramine, imipramine or nortriptyline results in a clinically significant (but often unpredictable) increase in tricyclic concentration.

Others

The concentration of oral contraceptives may be reduced by enzyme inducers. This interaction is clinically relevant with griseofulvin, rifampicin and carbamazepine. Sildenafil is a substrate of CYP3A4. It should not be prescribed with CYP3A4 inhibitors as they increase its concentration and therefore the likelihood of systemic hypotensive effects.

Conclusion

The safest way of knowing which drugs are likely to have metabolic interactions is to understand the principles behind the interactions. Drugs which induce or inhibit the enzymes of cytochrome P450 should ring alarm bells. Interacting drugs with a low therapeutic index are likely to be affected by even small changes in concentration. The importance of the change in clinical effect (such as organ rejection) also needs to be considered.

ACKNOWLEDGEMENT

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NOTE

For a table of drugs metabolised by cytochrome P450 see http://www.drug-interactions.com

REFERENCES

1. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 2000;38:41-57.
2. Wilbur K, Ensom MH. Pharmacokinetic drug interactions between oral contraceptives and second-generation anticonvulsants. Clin Pharmacokinet 2000;38:355-65.
3. Drug interactions and adverse drug reactions. Aust Adv Drug React Bull 2000;19:10-2.
4. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort [letter]. Lancet 2000;355:547-8.
5. Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. Br J Clin Pharmacol 1998;46:101-10.
6. Josefsson M, Zackrisson AL, Ahlner J. Effect of grapefruit juice on the pharmacokinetics of amlodipine in healthy volunteers. Eur J Clin Pharmacol 1996;51:189-93.
7. Shenfield GM, Page M. Potentiation of warfarin action by miconazole oral gel [letter]. Aust N Z J Med 1991;21:928.
8. Edgar B, Bailey D, Bergstrand R, Johnsson G, Regardh CG. Acute effects of drinking grapefruit juice on the pharmacokinetics and dynamics of felodipine – and its potential clinical relevance. Eur J Clin Pharmacol 1992;42:313-7.
9. Kivisto KT, Kroemer HK, Eichelbaum M. The role of human cytochrome P450 enzymes in the metabolism of anticancer agents: implications for drug interactions. Br J Clin Pharmacol 1995;40:523-30.
10. Kent JM. SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression [published erratum appears in Lancet 2000;355:2000]. Lancet 2000;355:911-8.

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Self-test questions

The following statements are either true or false (answers on page 23)

3. The inhibition of CYP3A4 by grapefruit juice can cause clinically significant drug interactions.
4. Fluoxetine, paroxetine and fluvoxamine can reduce the analgesic effect of codeine.

Stopping antidepressants

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SYNOPSIS

Depressive illness is now recognised as a major health problem. As many patients do not need indefinite treatment, clinicians need to be aware of the symptoms associated with the discontinuation of antidepressants. Gradually reducing the dose is the best approach. Abrupt cessation of antidepressants should be avoided unless medical urgency necessitates it. Particular care is required when changing from one antidepressant to another.

Index words: depression, withdrawal symptoms.

(Aust Prescr 2001;24:13–5)

Introduction

By 2020, major depression is projected to become second only to heart disease as the leading cause of morbidity.[1] The lifetime risk of depressive illness is 12–26% for women and 4–12% for men.[2] It is usually a chronic and recurrent illness (75–80% of treated patients have recurrences) that frequently requires long-term maintenance treatment. Depression is often both unrecognised and undertreated. The aim of treatment is a full remission and long-term recovery rather than short-term response.

When is the right time to stop treatment?

The decision to stop treatment should be made after an assessment of the patient's current mood state and other factors that may indicate the likelihood of a relapse or recurrence of depression. These factors include the number and severity of previous episodes, success of treatment of earlier episodes, the risk of suicide if another episode were to ensue and the disruption caused by depression to the lives of the patient and their family. Discussion of these factors with the patient (and a key family member, if possible) would be essential in coming to a decision about discontinuing therapy.[3]

How to stop treatment

If antidepressants are withdrawn, higher doses should be gradually tapered off, unless there are medical indications for an abrupt cessation. These indications could include pregnancy, severe adverse reactions or inability to take oral medications. Precise guidelines concerning the time needed to taper off the dose are lacking. A gradual reduction is recommended to prevent discontinuation effects and to allow adaptation at the receptor level. A rule of thumb is 6–8 weeks after 6–8 months treatment[3] or 3–6 months after maintenance therapy. Many patients, particularly those on lower doses, may be able to stop more quickly without adverse effects.

If the response to treatment has been unsatisfactory, a switch to a different antidepressant may be necessary. The prescriber should check the product information to see if the two drugs interact, but reducing the dose over a 1–2 week period may be adequate. Patients taking high doses of an antidepressant or who are on an antidepressant with a shorter half-life (e.g. paroxetine and venlafaxine) are more likely to develop discontinuation symptoms during short taper periods. Patients must be educated about the importance of supervised dose reduction when discontinuing antidepressants and about what symptoms they may experience. They can be reassured that these symptoms will remit with time.

Monitoring

Education is a critical aspect of treatment and enhances compliance with medication. The patient and their family should be informed that adverse effects are common, but are usually mild and resolve on continued treatment, and that the depression is likely to recur if treatment is stopped too soon.[4] Other educational messages that are associated with better compliance include advice to take the medication every day and to continue even when feeling better.

Patients must be warned that as depression is typically a recurring disorder, stopping medication is always a trial and may lead to symptoms reappearing. They also need to be instructed to contact their doctor as soon as any symptoms start to recur. The assistance of a key family member can play a crucial role in this respect. The doctor may need to continue to monitor patients periodically after medication has been stopped.

Problems associated with discontinuation

Discontinuation reactions may have physical or psychological symptoms, which appear after stopping or reducing the dose of medication. The symptoms may start within 1–10 days, but usually within three days of stopping treatment. These are distinct from the symptoms of depression, which can also recur within hours to days after cessation of treatment. However, recurrences are less likely than discontinuation reactions to occur in the first week after stopping treatment. Discontinuation reactions are more common in patients who have been treated for more than eight weeks and with higher dosages of antidepressants. Discontinuation symptoms must also be distinguished from an intercurrent illness. They are often overlooked in the acute hospital setting.

Table 1

Symptoms associated with withdrawal of tricyclic antidepressants[4,6]

Gastrointestinal	nausea, vomiting, abdominal cramps, diarrhoea
General somatic distress	lethargy, flu-like symptoms, headache
Sleep disturbance	insomnia, abnormal dreams including nightmares
Affective symptoms	anxiety, agitation, low mood
Less commonly	movement disorders, mania, hypomania, arrhythmias, tachycardia, ventricular ectopic beats

Discontinuation symptoms from abrupt cessation of tricyclic antidepressants (TCAs) (see Table 1) and monoamine oxidase inhibitors (MAOIs) have long been recognised, but features of addiction such as tolerance and addictive use are rare.[5] Gastrointestinal effects, flu-like symptoms, affective symptoms and sleep disturbance are the most common problems after stopping a TCA. Discontinuation effects are also common after withdrawal of MAOIs and include disorientation, confusion, myoclonus, ataxia, agitation, cognitive impairment, catatonia, paranoid delusions, aggressiveness, hallucinations, depression, suicidality, slowed speech and sleep disturbance.

The commonest cessation effects of SSRIs are dizziness, light-headedness, nausea, lethargy and headache (see Table 2). Distinguishing a discontinuation syndrome from a recurring depression can be difficult (see 'Medicinal mishaps: serotonin states' Aust Prescr 1998;21:63). The cessation effects of SSRIs are generally less frequent than those of the TCAs. Reports vary from 33% for clomipramine to 80% for amitriptyline, while the rate is 35% for paroxetine and much less (2–14%) for other SSRIs.[6] The commonest withdrawal symptoms are also different for each class of antidepressant. Two symptoms which are prominent after stopping an SSRI are balance and sensory abnormalities. These do not occur after a TCA is stopped.

There are few reports in the literature about the cessation of newer antidepressants. Stopping venlafaxine has resulted in symptoms of dizziness, light-headedness, irritability, dysphoria, insomnia and sweating.[6]

Effects when changing treatment

If a patient is not responding to an antidepressant, or relapses, a different drug may be necessary. The effects of discontinuing the first drug may not appear until after starting the new drug. It is important not to confuse the symptoms of discontinuation with the adverse effects of the new drug. If time permits, it is helpful if the patient has 3–4 days off medication before starting the new drug. This allows discontinuation symptoms to be identified and distinguished from new adverse events. Advice for changing from one antidepressant to another is published in Therapeutic Guidelines: Psychotropic.[7]

Table 2

Symptoms associated with withdrawal of selective serotonin reuptake inhibitors[6]

Gastrointestinal	nausea, vomiting, diarrhoea, loss of appetite, abdominal pain, abdominal distress
General somatic distress	lethargy, flu-like symptoms
Sleep disturbance	insomnia, abnormal dreams including nightmares and decreased need for sleep
Affective symptoms	irritability, anxiety symptoms, agitation
Problems with balance	dizziness, vertigo, light-headedness, ataxia
Sensory abnormalities	paraesthesia, numbness, blurred vision/diplopia, 'electric shock', visual lag

Management of discontinuation reactions

Problems occurring on cessation of an antidepressant may be minimised by preventative measures, supportive treatment and, if necessary, specific treatment. Preventative measures include emphasising the need for a supervised reduction of the dosage, advising the patient of the risk of discontinuation reactions and warning of possible symptoms that may occur. If possible, avoid high doses and abrupt cessation of medication.

Usually supportive treatment is sufficient. The patient should be reassured that symptoms are not life-threatening and that they will resolve spontaneously within 1–2 weeks. If symptoms are severe, resuming therapy may be necessary. The discontinuation syndrome will then typically resolve within 24 hours or so. A slower reduction of the dose may minimise cessation reactions the next time withdrawal is attempted.

Conclusion

Depressive illness is now recognised as a major health problem. Recent guidelines recommend long-term maintenance treatment for patients with recurrent depression. Higher doses and longer treatment periods may lead to the more frequent occurrence of discontinuation reactions in future. Approximately one in three patients do not respond to the first antidepressant they are prescribed and are switched to another. This changeover period is a risk time for discontinuation reactions as well as drug interactions.

Clinicians need to be aware of the symptoms associated with discontinuation of antidepressants and inform their patients what to expect. Abrupt cessation of antidepressants should be avoided unless medically necessary and gradually tapering off the dosage should be the norm.

REFERENCES

1. Murray CJL, Lopez AD, editors. The global burden of disease. Vol 1. Boston: Harvard School of Public Health; 1996.
2. Keller MB. The long-term treatment of depression. J Clin Psychiatry 1999;60 Suppl 17:41-5.

3. Withdrawing patients from antidepressants. Drug Ther Bull 1999;37: 49-52.
4. Delgado PL. Approaches to the enhancement of patient adherence to antidepressant medication treatment. J Clin Psychiatry 2000;61 Suppl 2:6-9.
5. Haddad P. Do antidepressants have any potential to cause addiction? J Psychopharmacol 1999;13:300-7.
6. Thompson C. Discontinuation of antidepressant therapy: Emerging complications and their relevance. J Clin Psychiatry 1998;59:541-8.
7. Writing Group for Therapeutic Guidelines: Psychotropic. Therapeutic Guidelines: Psychotropic. Version 4. Melbourne: Therapeutic Guidelines Limited; 2000.

Self-test questions

The following statements are either true or false (answers on page 23)

5. When changing from one antidepressant to another it can be difficult to differentiate discontinuation symptoms from adverse effects of the new medication.
6. After a patient has recovered from depression, the antidepressant dose is usually tapered off.

ABNORMAL LABORATORY RESULTS

Creatinine clearance and the assessment of renal function

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SYNOPSIS

The selection of the most appropriate measurement of renal function depends on the clinical question being asked, the accuracy required and the inconvenience to the patient. Serum creatinine and calculated creatinine clearance yield a reasonable estimation of renal function with minimal cost and inconvenience. A urinary creatinine clearance is more accurate if the urine collection is complete. Isotopic measurement of glomerular filtration rate can be used when greater accuracy is required, when renal function is poor or muscle mass is significantly outside the normal range. Glomerular filtration rate should be corrected for body surface area and interpreted in the context of physiological effects such as pregnancy and blood pressure.

Index words: glomerular filtration, kidney.

(Aust Prescr 2001;24:15–7)

Introduction

Estimation of renal function is important in a number of clinical situations (Table 1), including assessing renal damage and monitoring the progression of renal disease. Renal function should also be calculated if a potentially toxic drug is mainly cleared by renal excretion. The dose of the drug may need to be adjusted if renal function is abnormal.

Renal function and glomerular filtration rate

The glomerulus is a high-pressure filtration system, composed of a specialised capillary network. It generates an ultrafiltrate that is free of blood and significant amounts of blood proteins. Renal damage or alterations in glomerular function affect the kidneys' ability to remove metabolic substances from the blood into the urine.

Glomerular filtration rate (GFR) is the rate (volume per unit of time) at which ultrafiltrate is formed by the glomerulus. Approximately 120 mL are formed per minute. The GFR is a direct measure of renal function. It is reduced before the onset of symptoms of renal failure and is related to the severity of the structural abnormalities in chronic renal disease. The GFR can

Table 1

Indications for renal function testing

Test	*Setting*	*Clinical indication*
Serum creatinine	Screening for renal disease	Hypertension Urine abnormalities Potential renal diseases (e.g. diabetes) Non-specific symptoms (e.g. tiredness)
	Monitoring renal function	Chronic renal disease Transplantation Drug toxicity
Calculated GFR/ creatinine clearance	Initial evaluation of renal disease	Glomerulonephritis Proteinuria Chronic renal failure Chemotherapy dosing
	Monitoring of renal disease	Glomerulonephritis Chronic renal failure
Isotopic GFR	Accurate GFR	Monitoring therapy in glomerulonephritis
	Low levels of GFR	Deciding when to start dialysis Chronic renal failure
	Altered muscle mass	Body builder Chemotherapy dose in wasted patient

GFR = Glomerular filtration rate

predict the signs and symptoms of uraemia, especially when it falls to below 10–15 mL/min. Unfortunately it is not an ideal index, being difficult to measure directly, and is sometimes insensitive for detecting renal disease.

Tubular function

Although glomeruli control the GFR, damage to the tubulointerstitium is also an important predictor of GFR and progression towards renal failure. Renal tubules make up 95% of the renal mass, do the bulk of the metabolic work and modify the ultrafiltrate into urine. They control a number of kidney functions including acid-base balance, sodium excretion, urine concentration or dilution, water balance, potassium excretion and small molecule metabolism (such as insulin clearance). Measurement of tubular function is impractical for daily clinical use, so we usually use the GFR to assess renal function.

Normal range for GFR

The GFR varies according to renal mass and correspondingly to body mass. GFR is conventionally corrected for body surface area (which equates with renal mass), which in normal humans is approximately 1.73m^2 and represents an average value for normal young men and women. When the GFR is corrected for body surface area, a normal range can be derived to assess renal impairment.

The normal corrected GFR is 80–120 mL/min/1.73m^2, impaired renal function is 30–80 mL/min/1.73m^2 and renal failure is less than 30 mL/min/1.73m^2. The corrected GFR is approximately 8% lower in women than in men, and declines with age at an annual rate of 1 mL/min/1.73m^2 from the age of 40.

In addition to ageing there are a number of physiological and pathological conditions that can affect GFR, including pregnancy, hypertension, medications and renal disease. These conditions should be considered when interpreting a patient's GFR.

Measurement of GFR by renal clearance

The GFR cannot be directly measured in humans, but can be estimated from urinary clearance of a substance (x), given by the equation:

$$\text{Urinary clearance (x)} = \frac{U_x V}{P_x}$$

where U is the urinary concentration of an ideal filtration marker of x, V is the urine flow rate and P_x is the average plasma concentration of x.

An 'ideal filtration marker' is a substance that is freely excreted by glomerular filtration, without tubular reabsorption or secretion. The clearance of ideal filtration markers can be shown mathematically to be an accurate estimate of GFR.

The balance concept

The plasma concentration of a substance in a steady state depends on the balance of the input (from either endogenous production or exogenous intake) and the clearance from the blood (by either excretion or metabolism). When an ideal filtration marker is used (and there is no hepatic metabolism or non-renal clearance) and the input is constant (for example, by endogenous creatinine generation), then the plasma concentration is inversely proportional to the GFR.

Methods to estimate GFR

The GFR can be estimated from the serum concentration of filtration markers (such as creatinine or urea) or the renal clearance of these markers. Each method has its advantages and disadvantages in terms of accuracy, cost and convenience (Table 2).

Serum creatinine or calculated creatinine clearance are the most convenient estimates of GFR, requiring only a single blood sample. Measured creatinine clearance requires a 24-hour urinary collection while isotopic methods involve intravenous injection of a nuclear tracer, and two subsequent blood samples to estimate clearance. Both these methods are more expensive and less convenient to the patient. Selection of the most appropriate test depends on the clinical question, the required accuracy and cost (Table 2).

Serum creatinine

Serum creatinine is commonly used to screen for renal disease or to investigate urinary sediment abnormalities, hypertension or non-specific symptoms such as tiredness. It is also used to monitor renal function after transplantation, in chronic renal disease, and in patients with glomerulonephritis taking disease-modifying therapy. Serum creatinine can also be used to monitor the effects of nephrotoxic drugs such as gentamicin or anticancer drugs. Serum urea can be used to estimate renal function but is highly variable, less accurate and prone to errors.

Serum creatinine is mainly produced by the metabolism of creatine in muscle, but also originates from dietary sources of creatinine such as cooked meat. Creatinine generation from the muscles is proportional to the total muscle mass and muscle catabolism. In people with a relatively low muscle mass, including children, women, the elderly, malnourished patients and cancer patients, the serum creatinine is lower for a given GFR. There is a danger of underestimating the amount of renal impairment in these patients, as their serum creatinine is also relatively lower. For example, the GFR may be reduced as low as 20–30 mL/min in a small elderly woman, while her serum creatinine remains in the upper range of normal.

Table 2

Assessment of renal function

Method	*Accuracy*	*Cost*	*Convenience*
Serum creatinine	**	$	***
Serum urea	*	$	***
Calculated creatinine clearance	***	$	***
Measured creatinine clearance	** to ***	$$	*
Isotopic glomerular filtration rate	****	$$$	*

Creatinine is an imperfect filtration marker, because it is secreted by the tubular cells into the tubular lumen, especially if renal function is impaired. When the GFR is low, the serum creatinine and creatinine clearance overestimate the true GFR. Some drugs (such as cimetidine or trimethoprim) have the effect of reducing tubular secretion of creatinine. This increases the serum creatinine and decreases the measured creatinine clearance (Table 3). Paradoxically, when these drugs are used, a more accurate measurement of GFR is obtained as it is largely free from the error contributed by the physiological tubular secretion of creatinine.

Calculated creatinine clearance

As serum creatinine is so highly dependent on age, sex and body size, a number of corrections and formulae have been developed to estimate the muscle mass and assumed creatinine production. The most well-known formula is the Cockcroft-Gault formula, which is relatively simple to use and reasonably accurate. It is given as:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age [yrs]}) \times \text{weight [kg]}}{\text{serum creatinine (micromol/L)}}$$

Multiply result x 1.22 for male patients

This is a good estimate of GFR, but it becomes inaccurate when a patient's body mass is significantly outside the normal range (for example, morbid obesity or severe malnutrition) or when renal function is very impaired (i.e. GFR <20 mL/min). In these circumstances an isotopic method can be used if the GFR needs to be accurately measured.

Creatinine clearance

Creatinine clearance has been used for many decades to estimate GFR. It involves a 24-hour urine collection to measure creatinine excretion. As the same sample can be used to measure the protein excretion rate, creatinine clearance is often used for the initial evaluation of renal diseases, such as glomerulonephritis. It can also be used to monitor the progression of chronic renal failure, the response to therapy or to help decide when to start dialysis in patients with declining renal function.

The major problem with measuring creatinine clearance is that the collection may be incomplete; often urine is passed into the toilet rather than into the collection bottles. This results in an underestimation of renal function, and has led some commentators to recommend alternative measures such as calculated creatinine clearance or an isotopic GFR. In hospital, especially when the patient is catheterised, creatinine clearance provides an accurate estimate of GFR. Overestimation of the GFR occurs at low levels of renal function, due to tubular secretion of creatinine. This can be corrected by collecting the urine while the patient is taking cimetidine or by averaging a urea and creatinine clearance in a single 24-hour collection. To accurately define the GFR at low levels of renal function, an isotopic GFR is recommended.

Table 3

Errors in measurement of renal function using creatinine

	Effects on creatinine clearance	*Effects on serum creatinine*
Assay interference		
ketosis	Nil	↑
hyperbilirubinaemia	Nil	↑
cephalosporin	Nil	↑
Inhibition of tubular secretion of creatinine		
cimetidine or trimethoprim	↓*	↑
Alteration of creatine/creatinine load		
eating cooked meat	↑	↑
low protein diet	↓	↓
body building	Nil	↑
muscle wasting	Nil	↓
Renal disease	↓	↑

* becomes **more** accurate at low levels of GFR when increased tubular secretion of creatinine is blocked

Isotopic GFR

Isotopic GFR is the most accurate measurement of GFR, especially at low levels of renal function or with alterations of muscle mass. The most common isotopic marker is technetium 99m DTPA, given as a single injection. Two plasma samples are taken at 1–3 hours after injection. The GFR is calculated from the plasma clearance of the isotope. Isotopic GFR can be used for monitoring renal function over time, or in chronic renal failure patients approaching dialysis. Patients are usually tested every two to five years, because of the cost and inconvenience of the procedure.

Summary

Renal function can be evaluated by measuring the GFR. As it is not easy to measure the GFR directly, the serum creatinine concentration is often used to assess renal function. Creatinine clearance provides a more accurate assessment and can be calculated from the serum creatinine or more exactly from the results of a 24-hour urine collection. Isotopic methods can be used if a very accurate measurement of the GFR is required.

Self-test questions

The following statements are either true or false (answers on page 23)

7. In renal disease the creatinine clearance is increased.
8. Cimetidine can increase the serum concentration of creatinine.

Benefit, risk and harm

Andrew Herxheimer, Emeritus Fellow, UK Cochrane Centre, Oxford, UK

Whenever we choose a treatment, we do so because we believe that on balance it will help the patient – that is, the advantages outweigh the disadvantages. Common decisions have been made many times before, and are embedded in traditions, guidelines and formularies, but there are still many situations that require an individual 'benefit/risk evaluation' or determination of the 'benefit:risk ratio'. Unfortunately these widely accepted terms muddle thought.

The confusion arises because benefits and risks in the ordinary uses of the words have completely different dimensions. A benefit is a material or experiential good 'thing', while a risk is a 'probability', the chance that something bad will happen. The asymmetry is clear. We should therefore be weighing **benefit** against **harm**, and the probability of benefit against the probability of harm. In doing that we should consider the kinds of benefit and harm, their chance of occurring, their magnitude and importance (primarily to the patient), as well as their timing and duration.

The idea of a benefit:risk ratio is especially wrong, because very often, the benefit and the risk are not of the same nature, and no one can really 'weight' them. One can ask populations about how many days, weeks or years of their life they would exchange to get rid of this or that handicap, but such comparisons are very fragile, and such enquiries are rare.

With the oral contraceptive pill we are left comparing a benefit such as making love with no fear of getting pregnant (tomorrow) with a risk of venous thrombosis or myocardial infarction (15 to 25 years in the future). Doctors should not take such decisions unless the case is very clear: it is the population or individual patients who should decide for themselves.

Controlled trials are designed to assess expected benefits, while harmful effects are mostly unexpected and noted only incidentally and unsystematically. This asymmetry is inherent in reports of trials, and leads to a bias that is insufficiently recognised.

A thorough evaluation of benefits and harms can be complicated and difficult, not least because they vary greatly with different drug dosages and regimens. In the absence of reliable estimates of the probabilities and the relative magnitudes of benefits and harms a meaningful evaluation is impossible.

What are the implications for practice? I think that in our roles as clinicians, members of formulary or guideline committees, or regulators, we must try to be much more specific when we consider the benefits of treatments and the kinds of harm they may do. We also need to consider the probabilities of those benefits and harms. If we can explain to each other how we weigh up the pluses and minuses for a particular intervention, then we will also be able to explain and discuss them more clearly and easily with patients. In that process we will come to understand better what our patients want and what they fear. When they too can weigh the pros and cons of treatments, they can better contribute to the therapeutic choice and are more likely to be content with it.

ACKNOWLEDGEMENT

I thank Charles Medawar for valuable discussion.

REFERENCE

1. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998;351: 1451-67.

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Two brief illustrations

Adjuvant tamoxifen after mastectomy for breast cancer

Benefits: Five years' treatment reduced the recurrence rate in women with oestrogen receptor positive tumours from 38% to 23%, with a corresponding improvement in survival.[1]

Harms: Five years' treatment increased the risk of endometrial cancer, over 10 years causing about two extra deaths per 1000 women treated. Premenopausal women have bone loss (1.4% per year). There is an increased risk of thrombosis.[1] Anti-oestrogen adverse effects include hot flushes, nausea and vomiting in up to 25% of patients, less commonly vaginal dryness or itching, dry skin, deepening of the voice.

Comment: Whether treatment beyond five years adds to the benefit is not yet clear.

Tolterodine 2 mg twice daily for symptoms of unstable bladder

Benefits: During four weeks' treatment, only 9% of patients had no or minimal bladder problems. On average patients voided 25 mL urine per micturition instead of 12 mL on placebo, and had one fewer incontinence episode every three days.

Harms: Headache. Anticholinergic effects – dry mouth, dry eyes, somnolence, nervousness, impaired accommodation, constipation, urinary retention; incidence stated as '>1–0.1%'. All wear off when the drug is stopped.

Comment: A minimally effective, but rather troublesome drug – hardly worth using.

The management of acute dystonic reactions

Diane Campbell, Emergency Physician, Emergency Department, Bendigo Hospital, Bendigo, Victoria

Index words: dystonia, benztropine, metoclopramide, adverse effects.

(Aust Prescr 2001;24:19–20)

Introduction

Drug-induced acute dystonic reactions are a common presentation to the emergency department. They occur in 0.5% to 1% of patients given metoclopramide or prochlorperazine.[1] Up to 33% of acutely psychotic patients will have some sort of drug-induced movement disorder within the first few days of treatment with a typical antipsychotic drug. Younger men are at higher risk of acute extrapyramidal symptoms.

Although there are case reports of oculogyric crises from other classes of drugs, including H_2 antagonists, erythromycin and antihistamines, the majority of patients will have received an antiemetic or an antipsychotic drug.

Differential diagnosis

The manifestations of acute dystonia can appear alone, or in any combination (Table 1).

Patients and carers find these reactions alarming. The diagnosis is not always obvious, and in one particularly challenging fortnight last year I saw four patients who were initially misdiagnosed as:

- a 'dislocated jaw' from prochlorperazine given for labyrinthitis
- an 'allergy with swollen tongue' which was a dystonic reaction to metoclopramide
- a 'hyperventilation' who was exhibiting a classic oculogyric reaction
- increasingly 'strange behaviour' caused by the overdose of trifluoperazine for which a young man had been admitted two days previously.

These were all acute dystonic reactions. Upper airway obstruction from pharyngeal muscle spasm or laryngospasm is a rare but potentially life-threatening complication.

The differential diagnosis includes:

- tetanus and strychnine poisoning
- hyperventilation (carpopedal spasm is usually more prominent than it is in acute dystonic reactions)
- hypocalcaemia and hypomagnesaemia
- primary neurological causes such as Wilson's disease.

If there is any doubt, it is reasonable to treat as an acute dystonic reaction in the first instance, and investigate further if there is no response.

Treatment

Dystonia responds promptly to the anticholinergic benztropine 1–2 mg by slow intravenous injection. Most patients respond within 5 minutes and are symptom-free by 15 minutes. If there is no response the dose can be repeated after 10 minutes, but if that does not work then the diagnosis is probably wrong.

The alternatives are antihistamines. Popular American texts[2,3] recommend diphenhydramine 1–2 mg/kg up to 100 mg by slow intravenous injection, and the current Oxford Handbook of Clinical Medicine[4] suggests procyclidine, but neither of these drugs is available in Australia as a parenteral preparation.

Promethazine, 25–50 mg intravenously or intramuscularly, has been used less frequently but it works and it is readily available in most emergency departments and doctors' bags. It may be a useful alternative for the uncommon patient who has both dystonia and significant anticholinergic symptoms from antipsychotic drugs.

Diazepam, 5–10 mg intravenously, has been used for the rare patient who does not completely respond to the more specific antidotes. Unlike the other antidotes, it cannot be given intramuscularly.

There are rare case reports of dystonia **caused** by all of these treatments, including diazepam.

Children should be given parenteral benztropine, 0.02 mg/kg

Table 1

Manifestations of acute dystonia

Oculogyric crisis	Spasm of the extraorbital muscles, causing upwards and outwards deviation of the eyes
	Blephorospasm
Torticollis	Head held turned to one side
Opisthotonus	Painful forced extension of the neck. When severe the back is involved and the patient arches off the bed.
Macroglossia	The tongue does not swell, but it protrudes and feels swollen
Buccolingual crisis	May be accompanied by trismus, risus sardonicus, dysarthria and grimacing
Laryngospasm	Uncommon but frightening
Spasticity	Trunk muscles and less commonly limbs can be affected

to a maximum of 1 mg, either intramuscularly or intravenously. This can be repeated once, but if the intramuscular route is chosen, allow 30 minutes to elapse before repeating. The same dose should be given orally, twice daily for the next 24–48 hours to prevent recurrence. Benztropine comes in a 2 mg tablet, so the dose needs to be approximated to the nearest 0.5 mg, or quarter tablet.

Avoiding recurrences

After initial treatment, patients should be given oral medication for two or three days, usually benztropine 1–2 mg twice daily. In general practice, most reactions will have been caused by antiemetics. Fortunately benztropine, diphenhydramine and promethazine all have antiemetic effects so the causative agent can be safely discontinued.

The best predictor of an acute dystonic reaction is a previous history of having had one. Patients should avoid exposure to the precipitating drug, but they are also at higher than average risk if exposed to another drug which causes dystonic reactions. It may be possible to find a substitute which does not cause dystonia.

Antiemetics are usually avoided in children and need not be given for short-term problems such as gastroenteritis. If an antiemetic is necessary, then antihistamines such as promethazine have a long established place.

Conclusion

Acute dystonic reactions are a common and distressing complication of antiemetic and antipsychotic drugs. Treatment with intravenous benztropine is safe and produces rapid relief. Patients who have a possible acute dystonic reaction should initially be treated with benztropine. If they do not respond less common disorders may be considered.

REFERENCES

1. Bateman DN, Darling WM, Boys R, Rawlins MD. Extrapyramidal reactions to metoclopramide and prochlorperazine. QJM 1989;71:307-11.
2. Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, et al. Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw-Hill; 1998. p. 2361.
3. Shy K, Rund DA. Psychotropic Medications. In Tintinalli JE, Ruiz E, Krome RL, editors. Emergency Medicine: A comprehensive study guide. 4th ed. New York: McGraw-Hill; 1996.
4. Hope RA, Longmore JM, McManus SK, Wood-Allum CA. Oxford Handbook of Clinical Medicine. 4th ed. Oxford: Oxford University Press; 1998. p. 428.

FURTHER READING

Rosen P, Barkin RM, Hayden SR, Schaider JJ, Wolfe R. The 5 minute emergency medicine consult. Philadelphia: Lippincott Williams & Wilkins; 1999.

Rosen P, Barkin RM, Braen CR, Dailey RH, Hedges JR, Hockberger RS, et al, editors. Emergency medicine: concepts and clinical practice. 3rd ed. St Louis (MO): Mosby-Year Book, Inc.; 1992.

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New drugs

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

Bupropion

Zyban (Glaxo Wellcome)

150 mg sustained-release tablets

Approved indication: nicotine dependence

Australian Medicines Handbook Section 18.6.2

Bupropion is not a new drug. It was approved in the USA for the treatment of depression more than 10 years ago. The antidepressant effect probably involves the drug's action on neurotransmitters. These actions may also help smokers to quit; depressed smokers gave up smoking during the clinical trials of bupropion.

To study the usefulness of bupropion in assisting smoking cessation, 615 smokers were enrolled in a randomised placebo-controlled trial. All the participants were given counselling in addition to drug treatment. After seven weeks of treatment, 19% of the placebo group had given up smoking. In the bupropion group the success rate increased with the dose. Approximately 29% of those taking 100 mg daily gave up, compared with 39% of those taking 150 mg and 44% of those taking 300 mg. All the participants put on weight, but the least weight gain (1.5 kg) was in the patients taking the highest (300 mg) dose of bupropion.[1]

Bupropion has also been compared with nicotine patches. In this trial 244 people were randomised to take bupropion, 244 used a nicotine patch, 245 used both medications and 160 were given placebos. During the nine weeks of treatment the participants were also counselled. When the participants were reviewed after six months, 35% of the bupropion group had stopped smoking compared with 21% of those using the nicotine patch and 19% of the placebo group. In the combined treatment group, 39% had stopped smoking. Treatment with bupropion alone, or in combination with a nicotine patch, was significantly better than treatment with the patch alone.[2]

Patients begin bupropion when they are still smoking. They start with 150 mg once a day, and after three days they take 150 mg twice a day. Smoking should stop in the second week of treatment. If the patient is still smoking after seven weeks they are unlikely to benefit by continuing bupropion.

There is extensive first-pass metabolism and metabolism is the main method of clearance. Less than 1% of the drug is

excreted unchanged in the urine. Bupropion is metabolised by cytochrome P450 2B6. Although clinical interactions have not been studied, caution is needed when prescribing other drugs metabolised by this system. The metabolism of bupropion may be altered by drugs such as phenytoin and carbamazepine. There is a risk of seizures, so bupropion is contraindicated in patients with epilepsy or other conditions which alter the seizure threshold.

The drug's effect on neurotransmitters may cause insomnia as an adverse effect. In clinical trials 40% of patients complained of insomnia. Other complaints included altered concentration, anxiety and dizziness. Some patients will experience nausea and a dry mouth. Severe allergic reactions have also been reported. In the comparative study[2] approximately 12% of the people taking bupropion stopped treatment because of its adverse effects.

As with other interventions for smoking, the effectiveness of bupropion declines with time. A year after the start of the placebo-controlled trial 23% of those given bupropion had not resumed smoking.[1] In the comparative trial 30% of the bupropion group were still abstinent after one year.[2]

Bupropion has only been approved for short-term use by patients who are committed to stopping smoking. It should always be used in conjunction with counselling.

REFERENCES

1. Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med 1997;337:1195-202.
2. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 1999;340:685-91.

Insulin aspart

NovoRapid (Novo Nordisk)

100 IU/mL in 10 mL vials, 1.5 mL and 3 mL cartridges, and 1.5 mL and 3 mL prefilled syringes

Approved indication: diabetes mellitus

Australian Medicines Handbook Section 10.1.1

Genetic engineering allows scientists to develop analogues of natural substances. Insulin aspart is an analogue of human insulin. The properties of the insulin molecule have been altered by the substitution of one amino acid.

Substituting aspartic acid for proline increases the rate of absorption of insulin after subcutaneous injection. This gives insulin aspart a rapid onset of action mimicking the physiological secretion of insulin. The effect begins within 20 minutes of an injection and reaches a peak within one to three hours, with a total duration of action of three to five hours. This effect gives better control of postprandial glucose concentrations than human insulin injected 30 minutes before a meal.[1]

In patients with type 1 diabetes, the reduction in glycated haemoglobin (HbA_{1c}) was greater with insulin aspart than with soluble human insulin. Although the difference was significant it was small; the HbA_{1c} was reduced by 0.12–0.16. In type 2 diabetes, insulin aspart also caused a greater reduction in HbA_{1c}, but this was not statistically significant.

The adverse effects of insulin aspart are similar to those of soluble human insulin, but there are no long-term safety data. To reduce the risk of hypoglycaemia, insulin aspart should be injected immediately before a meal.

REFERENCE

1. Lindholm A, McEwen J, Riis AP. Improved postprandial glycemic control with insulin aspart. A randomized double-blind cross-over trial in type 1 diabetes. Diabetes Care 1999;22:801-5.

Risedronate sodium

Actonel (Aventis Pharma)

5 mg film-coated tablets

Approved indication: osteoporosis, Paget's disease

Australian Medicines Handbook Section 10.4.2

Bisphosphonates inhibit the resorption of bone by osteoclasts. By reducing the turnover of bone and increasing bone density the bisphosphonates can help patients with Paget's disease or osteoporosis.

Like the other bisphosphonates, risedronate is poorly absorbed. The bioavailability of the tablet is only 0.63% and this is reduced by food. Patients should only take the tablets with water. After absorption risedronate is distributed to bone. Although half the absorbed dose is excreted within 24 hours the elimination of the drug from bone is slow. The half-life is approximately 20 days.

Patients must take the tablets while they are standing. They should remain upright for at least 30 minutes. This helps to ensure the tablet reaches the stomach and does not irritate the oesophagus. Approximately 12% of patients will complain of abdominal pain. Other adverse events reported in clinical trials include arthralgia, itching, flu-like symptoms, diarrhoea and dizziness.

Risedronate is approved for several indications. There is evidence from clinical trials to support each indication.

Postmenopausal osteoporosis

More than 3500 women were randomised to take risedronate or a placebo for three years. The women enrolled in the trials had a history of vertebral fractures. Their fracture risk was reduced significantly by risedronate. In one study the cumulative frequency of new vertebral fractures after three years was 11% in patients taking risedronate and 16% in those taking a placebo. Compared to placebo, risedronate also increased bone density in the lumbar spine by 5%.[1]

Glucocorticoid-induced osteoporosis

When patients who are taking long-term corticosteroids are given risedronate, calcium and vitamin D, their bone density increases. Although they are statistically significant, these increases are small. After a year of treatment the mean increase, compared to placebo, was 2.4% in the femoral trochanter and 2.7% in the lumbar spine.

Risedronate has also been given to patients who had recently started corticosteroids. This prevented the bone loss seen in patients who were only given calcium supplements.

Paget's disease

In Paget's disease bone resorption and formation are increased. Compared with osteoporosis, a higher dose is needed to control the activity of the disease. This activity can be assessed by measuring the serum alkaline phosphatose.

One study compared the effect of taking risedronate for two months with taking etidronate for six months. After 12 months, the concentrations of alkaline phosphatase were normal in 73% of the patients taking risedronate, but in only 15% of those taking etidronate. Relapses were less common in the risedronate group. After 18 months, 53% of the group were still in remission compared with only 14% of the etidronate group. Risedronate also produced significant reductions in bone pain.[2]

Although risedronate has an advantage over etidronate so do other oral bisphosphonates such as alendronate and tiludronate. Further studies are needed to find the best bisphosphonate and to assess the safety of long-term treatment.

REFERENCES

1. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. JAMA 1999;282:1344-52.
2. Miller PD, Brown JP, Siris ES, Hoseyni MS, Axelrod DW, Bekker PJ. A randomised, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. Am J Med 1999;106:513-20.

Rosiglitazone maleate

Avandia (SmithKline Beecham)

4 mg and 8 mg film-coated tablets

Approved indication: type 2 diabetes

Australian Medicines Handbook Section 10.1

Rosiglitazone is the second drug of its class to be approved for use in Australia. It has wider indications than troglitazone, the first drug to be approved (see 'New drugs' Aust Prescr 1999;22:150). Rosiglitazone can be prescribed when a patient's blood glucose is not controlled by diet. It can also be used in combination with metformin and sulfonylureas.

Like troglitazone, rosiglitazone reduces insulin resistance. Although reductions in fasting blood glucose occur soon after starting treatment, the full effect on insulin sensitivity is not seen for six to eight weeks. The starting dose of 4 mg daily may be increased to 8 mg daily after this interval.

The tablets can be taken once or twice daily. They are completely absorbed and have a bioavailability of 99%. Rosiglitazone is completely metabolised by the liver. Cytochrome P450 2C8 is the main enzyme involved. The drug is not recommended for people with liver disease. Most of the metabolites are excreted in the urine, but a dose reduction is not required if there is renal impairment.

There are not many published clinical trials of rosiglitazone. A 26-week study of 493 patients with type 2 diabetes found that a twice-daily dose of 2 mg or 4 mg reduced glycated haemoglobin ($HbA1_c$) by 0.9–1.5% more than placebo. Twice-daily doses appeared to have greater efficacy than once daily.

Rosiglitazone was as effective as glibenclamide in reducing $HbA1_c$ in a comparative study. After a year, $HbA1_c$ was reduced 0.7% by glibenclamide and 0.5% by rosiglitazone 4 mg twice daily. The $HbA1_c$ of patients given 2 mg rosiglitazone twice daily fell by only 0.3%, but both doses of rosiglitazone had a greater effect on fasting plasma glucose than glibenclamide did.

Other trials have studied the use of rosiglitazone in combination with metformin or sulfonylureas. The combinations usually improve glycaemic control more than monotherapy. For example, adding rosiglitazone 4 mg twice daily to metformin will reduce $HbA1_c$ by 0.8% more than metformin alone.

In the clinical trials rosiglitazone was generally well tolerated. Some patients will develop fluid retention so there is a risk of precipitating heart failure. Rosiglitazone increases LDL and HDL cholesterol and can cause anaemia.

The first drug of this class, troglitazone, was withdrawn following reports of hepatic toxicity. Although only 0.2% of patients taking rosiglitazone have had hepatic adverse events, there is a concern that the toxicity may be a class effect. Patients should therefore have their liver function checked before treatment and every two months during the first year of therapy, then periodically thereafter. Rosiglitazone has not been approved for use in Europe and an American consumer drug bulletin has advised its readers not to use rosiglitazone for five years.[1]

REFERENCE

1. Health Research Group. The new diabetes drug rosiglitazone (Avandia) rejected by European regulators. Worst Pills Best Pills 1999;12:93-4.

Zolpidem tartrate

Stilnox (Sanofi Synthelabo)

10 mg tablets

Approved indication: insomnia

Australian Medicines Handbook Section 18.4.2

Zolpidem acts on benzodiazepine receptors. Although it has a different structure and is said to be more selective in its action, zolpidem has similar effects to the benzodiazepines.

The drug is rapidly absorbed and peak plasma levels are reached within 3 hours. First-pass metabolism reduces bioavailability to 70%. The liver also eliminates most of the drug with only 1% appearing unchanged in the urine. A lower dose is recommended for the elderly and patients with hepatic impairment. Zolpidem has a half-life of two hours, but its hypnotic effect can last up to 6 hours.

In clinical trials, zolpidem has been more effective than placebo in treating chronic insomnia, but does not appear to have any advantage over temazepam.

Adverse effects caused 4% of patients in clinical trials to discontinue zolpidem. These effects included dizziness, headache, nausea and daytime drowsiness. Dizziness was the most common adverse effect reported in patients taking zolpidem for 28–35 nights. All patients should be warned of the possible risk of feeling drowsy the morning after taking zolpidem. The drug interacts with others, such as alcohol, which depress the central nervous system.

Patients complaining of insomnia need to be assessed to exclude underlying causes such as depression. Often insomnia does not require drug treatment. If a patient is prescribed zolpidem, they should take it for less than 4 weeks. The potential for withdrawal, tolerance or rebound insomnia is uncertain. Higher doses should not be used because, like other benzodiazepines, they have been associated with amnesia.

NEW FORMULATIONS

Morphine sulfate

MS Mono (Mundipharma)

30 mg, 60 mg, 90 mg and 120 mg capsules

Nevirapine

Viramune (Boehringer Ingelheim)

10 mg/mL suspension

Reteplase

Rapilysin (Roche)

10 U powder for injection

NEW STRENGTHS

Diltiazem hydrochloride

Cardizem CD (Aventis Pharma)

360 mg modified-release capsules

Oestradiol

Femtran 25 and Femtran 75 (3M Pharmaceuticals)

2 mg and 5.7 mg transdermal patches

NEW COMBINATION

Enalapril maleate/hydrochlorothiazide

Renitec Plus 20/6 (Merck Sharp & Dohme)

20 mg enalapril maleate/6 mg hydrochlorothiazide tablets

NEW PROPRIETARY BRANDS

Cefaclor

GenRx Cefaclor CD (Faulding)

375 mg sustained-release tablets

Ipratropium bromide

GenRx Ipratropium (Faulding)

250 microgram/mL solution for inhalation

Answers to self-test questions

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

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