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Editorial

Treat the numbers or treat the patient?

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Key words: diabetes, patient compliance.

(Aust Prescr 2011;34:94–5)

Current practice guidelines, regardless of healthcare system and country of origin, increasingly carry a similar message: treat to target. These targets are often expressed in terms of laboratory parameters which are presumed to reflect the control of a patient's condition, and by extension their health and prognosis. The assumption is that 'normalising' parameters, such as lipids, blood pressure and blood glucose in patients with type 2 diabetes, will lead to better outcomes. However, these parameters are surrogate outcomes and do not guarantee long-term clinical benefits.

Is the assumption of benefit from intense control of these parameters based on high quality evidence? Some evidence suggests that there is no benefit, but there may be marginal harm associated with intensive control of risk factors in patients with diabetes.[1-3] Benefits may still accrue for younger less sick patients, but this remains speculative. Even if true, those benefits would have to offset the downside of treatment, a task made difficult by the relative good health of the patients and the necessarily prolonged course of treatment. In these younger and healthier patients, intense lifestyle modification – smoking cessation, diet, exercise, stress reduction – may be more compelling than intensive drug treatment.

Treat-to-target often requires clinicians to prescribe more drugs at higher doses. This in turn calls for more laboratory testing to determine the efficacy of these interventions on the parameters of interest and to monitor the safety of the drugs on the patient's body. Treat-to-target requires patient self-monitoring and self-management in response to the monitoring results plus more visits to nurses and physicians. Higher doses and combination therapy may also increase the likelihood of adverse effects, which in turn may require increased medical attention and reduce the patient's capacity to do patient work.

The increasing demand for treatments, investigations and visits will test the capacity of the patient and their caregivers to implement these complex programs. By some estimates, the work of being a patient with diabetes requires more than two hours every day.[4] Patients are expected to prioritise this 'part-time job' – to understand, plan and enrol others to help with the plan, to implement and adhere to the plan, and to reflect and value the treatment enough to keep going day after day. They have to fit this around the work of being a parent, sibling, child, spouse or relative, the work of being an employee or boss, and the work of being a citizen, a hobbyist, or a sports player.

The extent to which the patient's other 'jobs' are flexible enough to accommodate the ever-increasing work of being a patient and the ability of patients to enrol others to assist with the tasks of 'patienthood' may vary over time. Eventually, the expansion of patient workload may exceed the capacity of the patient or their caregivers to accommodate its demands. This forces the patient to prioritise, compromise and do only part of the expected patient work. They may then appear to be non-adherent to treatment.

In this issue…

Patients, particularly those with chronic illnesses, need patience. The work of being a patient, discussed by Victor Montori, will be increased by having to manage adverse effects, such as those mentioned by Tim Lambert in his review of antipsychotic drugs. Some frustrated patients can become agitated and Gordian Fulde advises how to help them.

Atrial fibrillation is a common chronic condition. With alternatives to warfarin therapy now emerging, Himabindu Samardhi and colleagues review the treatment of the arrhythmia.

Drug treatment is delivered in different formulations. These formulations often contain several substances apart from the active ingredient. Alison Haywood and Beverley Glass briefly review the common excipients and the adverse reactions they can cause.

Some excipients can cause anaphylaxis so it is appropriate that this issue is accompanied by the latest version of the *Australian Prescriber* wallchart. This has been produced with the assistance of several specialist colleges and should enable health professionals to deal with most cases of anaphylaxis.

The clinician may notice this non-adherence as missed appointments, incomplete self-monitoring data and in test results that reflect poor control. The clinician at this point, under a treat-to-target approach, may feel obliged to intensify the therapy. This carries the unintended consequence of increasing the treatment workload, further overflowing the patient's capacity to execute the plan, with ongoing deterioration not only of disease control but also of the patient–clinician relationship.

Our research group is exploring how best to respond to this form of non-adherence, which reflects the constraints of many competing demands that patients face. What can clinicians do in the meantime?

While these are early days in our journey, I would think clinicians should consider rejecting treat-to-target as not being consistent with evidence-based medicine. Why? Because the targets are not always based on high quality evidence and may be promoted and enforced without consideration of patient context and goals. We should redefine targets, prioritising goals that patients value, and involve patients with this prioritisation. Treatment burden should be favourably balanced by treatment value expressed in the answer to questions, such as, will this treatment or procedure (for example checking your glucose daily) increase the odds that you will live longer, feel better, or live unhindered by complications of disease or treatment? These are the new targets and not many treatments achieve these goals. Let us focus on treating to these patient goals and make healthcare fit the lives of our patients. That is the basis for minimally disruptive medicine.[5]

References

1. Montori VM, Fernandez-Balsells M. Glycemic control in type 2 diabetes: time for an evidence-based about-face? Ann Intern Med 2009;150:803-8.
2. Hayward RA, Krumholz HM, Zulman DM, Timbie JW, Vijan S. Optimizing statin treatment for primary prevention of coronary artery disease. Ann Intern Med 2010;152:69-77.
3. Nilsson PM. ACCORD and risk-factor control in type 2 diabetes. N Engl J Med 2010;362:1628-30.
4. Russell LB, Suh DC, Safford MA. Time requirements for diabetes self-management: too much for many? J Fam Pract 2005;54:52-6.
5. May C, Montori VM, Mair FS. We need minimally disruptive medicine. BMJ 2009;339:b2803.

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Letters

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. Letters are usually published together with their responses or comments in the same issue. The Editorial Executive Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

Drug-induced hyponatraemia

Editor, – I have read Dr Shannon's article (Aust Prescr 2011;34:42-5) and the article in Medicines Safety Update (April 2011), both of which are excellent, simply written summaries on hyponatraemia. However, I have two objections to the traditional advice of stopping the medication that causes hyponatraemia and then giving other treatments as necessary.

Firstly, it is sometimes impossible to stop an antidepressant or antipsychotic which is necessary. Also, it is unlikely that any other psychotropic drug will be better as they can all cause hyponatraemia due to the syndrome of inappropriate antidiuretic hormone secretion.[1] Secondly, the situation can be remedied by fluid restriction, either on an inpatient or outpatient basis, provided adequate explanation is given to the patient.[2]

The mechanism of hyponatraemia with psychotropics is probably a combination of increased fluid intake[3,4] and stimulation of central serotonergic and alpha$_1$ adrenergic receptors to release antidiuretic hormone.[5]

Antidepressant-induced hyponatraemia can spontaneously remit in spite of continuing treatment,[6] although it is safer if there is fluid restriction of 800 ml/day with gradual liberalising of the restriction as the serum sodium rises. This approach successfully raised the serum sodium in all patients in our study, and maintained levels over a six-month follow-up period.[2] It seems to re-set the hypothalamic osmostat and there is rarely need for sodium replacement.

To detect hyponatraemia, I assess urea and electrolyte concentrations three days after starting an antidepressant in all patients over 65 years old. If present, I treat with modest fluid restriction and monitor the patient.

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References

1. Spigset O, Hedenmalm K. Hyponatremia in relation to treatment with antidepressants: a survey of reports in the

World Health Organization data base for spontaneous reporting of adverse drug reactions. Pharmacotherapy 1997;17:348-52.
2. Roxanas M, Hibbert E, Field M. Venlafaxine hyponatraemia: incidence, mechanism and management. Aust N Z J Psychiatry 2007;41:411-8.
3. Fabian TJ, Amico JA, Kroboth PD, Mulsant BH, Corey SE, Begley AE, et al. Paroxetine-induced hyponatremia in older adults: a 12-week prospective study. Arch Intern Med 2004;164:327-32.
4. Marar IE, Amico JA. Vasopressin, oxytocin, corticotrophin-releasing factor, and sodium reponses during fluoxetine administration in the rat. Endocrine 1998;8:13-8.
5. Anderson IK, Martin GR, Ramage AG. Central administration of 5-HT activates 5-HT1A receptors to cause sympathoexcitation and 5-HT2/5-HT1C receptors to release vasopressin in anaesthetized rats. Br J Pharmacol 1992;107:1020-8.
6. Strachan J, Shepherd J. Hyponatraemia associated with the use of selective serotonin re-uptake inhibitors. Aust N Z J Psychiatry 1998;32:295-8.

Dr G Shannon, author of the article, comments:

I thank Dr Roxanas for his comments. My article specifically looked at the recognition and management of severe hyponatraemia, rather than the milder forms. In severe hyponatraemia, particularly if the patient is symptomatic, I think stopping of any medications known to be associated with hyponatraemia (e.g. selective serotonin reuptake inhibitors) is an essential part of the emergency management of this life-threatening condition. Consultation with the patient's psychiatric team about ongoing management of their psychiatric condition is important in the management plan.

In an asymptomatic patient with non-severe hyponatraemia, the possibility of continuing their selective serotonin reuptake inhibitor would depend on the availability of close monitoring and perceived compliance with fluid restriction, and should only be considered in consultation with the treating psychiatrist.

Book review

Therapeutic Guidelines: Rheumatology Version 2 (2010)

***Casey Maddren**, Academic general practice registrar, Department of General Practice, The University of Sydney, Westmead Hospital, Sydney*

When looking at a resource my first question is, do I need this? The title Therapeutic Guidelines: Rheumatology is music to my ears, a guidebook for often difficult to manage, chronic complaints.

The guidelines have undergone rigorous assessment and reassessment with feedback from practitioners to editors. The results of this 'closing the loop' are obvious in the text.

This edition has multiple new features. These are summarised in the electronic Therapeutic Guidelines (eTG) and as an insert in the book format. All these additions are clinically relevant.

I foresee this guide will be immensely useful within my own practice with potential application as a reference guide for diagnostic dilemmas, patient information handouts, red flags and drugs in pregnancy (including for men planning to conceive with their partner). Of particular note are clinical boxes throughout the text which provide an easily accessible guide to interpretation of results, comparison of presentation of arthropathies, doses of injectable steroid, joint aspiration and other common situations when a quick answer is needed. The electronic contents page improves accessibility.

A strength of the text is its holistic approach, reflecting the needs of general practice and including nonpharmacological methods, exercises (with pdf files for printing from eTG) and recommendations for ongoing monitoring of disease. Not only does the guide provide the means but also the evidence that this approach benefits patients.

Sound rheumatological management hinges on the doctor–patient relationship, with an emphasis on clear understandable information being provided by the practitioner. This text is succinct and comprehensible, enabling its use as a resource for such discussions.

Overall, Therapeutic Guidelines: Rheumatology is a useful resource for practitioners, students and allied health professionals.

Managing the metabolic adverse effects of antipsychotic drugs in patients with psychosis

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Summary

Antipsychotic medications are widely prescribed and carry a variable propensity to cause weight gain and its attendant sequelae – hyperglycaemia, hypertension and hyperlipidaemia. These metabolic risks, along with smoking and poor lifestyle habits, occur between two and five times more often in patients with psychosis than in the general population. Early detection and intervention for cardiometabolic risks, and a judicious tailoring of the use of antipsychotic medications can help to improve long-term outcomes in these patients.

Key words: adverse effects, obesity, psychotic disorders.

(Aust Prescr 2011;34:97–9)

Introduction

Antipsychotic drugs remain the cornerstone of treatment for a number of psychiatric illnesses, including schizophrenia and bipolar disorder, however they have a wide range of adverse effects. A major problem of the older antipsychotics is the neurological effects such as parkinsonism, dystonia, dyskinesia and akathisia. With some of the newer 'atypical' antipsychotics, obesity and other risk factors for cardiovascular and metabolic disease are a problem. Although these metabolic effects can also be caused by the older antipsychotics, they have assumed greater importance as the incidence of premature mortality from preventable cardiovascular disease and diabetes has become increasingly evident.

It is estimated that the life expectancy of patients with schizophrenia will be shortened by up to 25 years compared to the general population, even after controlling for the risk of suicide.[1] At the same time, age-adjusted rates of cardiovascular death in the general population have been falling. For patients with schizophrenia or bipolar disorder as well as diabetes, the chances of premature death are significantly higher compared to matched persons with diabetes alone.[2] Clearly the illness and its treatment may be contributing to the development of metabolic risk.

Psychosis and cardiometabolic risk factors

Risk factors for cardiovascular disease are over-represented in people with psychosis. In a West Australian study of an adult community psychiatric service, over half of people with severe mental illness had metabolic syndrome.[3] This was broadly in agreement with a database of chronic psychiatric patients from Victorian and NSW community and inpatient services (www.ccchip.com.au). Up to 89% of patients had an excess waist circumference. Females had higher rates of obesity.

It is estimated that the risk of diabetes in the people with psychosis is 2–6 times higher than the rest of the population, depending on age (the young have accelerated risk rates). Depending on the sample, impaired fasting glucose was found in up to 41% of those with severe psychiatric illness. People from certain ethnic backgrounds are more likely to develop diabetes than Caucasians. This includes people from Asia, the Middle East and the Indian subcontinent, African Americans and Latinos.*

Hyperlipidaemia is often an early metabolic response to some antipsychotics and is thought to be up to five times higher in those who have received antipsychotics than in the general population. The most common abnormality is a low level of high density lipoprotein cholesterol in up to 58% of patients. Raised triglycerides have been found in up to 53% of people with psychosis.[3]

High blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic in those with diabetes or at risk, as defined by the International Diabetes Federation, www.idf.org) was found in up to two-thirds of patients who are screened.[3] This represents a rate at least twice that of the healthy population. Gender differences are common with males being more likely to have elevated blood pressure.

In the West Australian study, 64% of patients with psychosis smoked cigarettes.[3] This is compared to 25–30% of the general population. This incidence appears to be similar across western countries over time.

Physical inactivity and unhealthy eating are extremely common in people with psychosis. There are many drivers of inactivity

* www.ahrq.gov/research/diabdisp.htm#HighDiabetes

including sedation and neuroleptic-induced cognitive deficits, negative symptoms, social withdrawal, inadequate social stimuli, lack of opportunity, poverty and severity of persecutory and other positive symptoms. These same clinical drivers as well as the appetite stimulating effects of the patient's psychotropic medication and the inability to plan and carry out meal preparation lead many patients to consume fast foods and sugared fizzy drinks as principal dietary components. Such drinks contribute enormously to obesity and the metabolic syndrome.[4]

Antipsychotics and cardiometabolic risk factors

There remains considerable debate as to the degree that antipsychotics contribute to cardiometabolic risks. In the short term there appears a clear hierarchy of drugs that promote weight gain, but in the longer term (and generally, patients with persistent psychosis are on lifelong maintenance therapy) it is less clear (Table 1).[5] Clozapine has the highest potential to cause weight gain, followed by olanzapine and then quetiapine. The choice of antipsychotic will depend on many factors relating primarily to the patient's psychopathology. However if there is a family history of diabetes or cardiovascular disease, if the person is from a high-risk ethnic background or is young, the choice of antipsychotic should consider potential metabolic consequences of the prescription. Additionally, many commonly prescribed psychotropics (including valproate, lithium, mirtazepine, tricyclic antidepressants and some selective serotonin reuptake inhibitors) that are used in combination with antipsychotics may themselves lead to considerable weight gain. The weight gain potential of all of the patient's drugs should be considered as a whole.

Assessing cardiometabolic risk factors – how often?

It is important to start monitoring patients immediately after they have started antipsychotics, then every three months during the first year and every six months after that.

Lifestyle interventions

Recommended lifestyle changes are the same for patients taking antipsychotics as they are for the general population. A package of care comprising aerobic exercise, weight loss, smoking cessation, consuming a high soluble fibre diet, reducing alcohol intake and potentially adding omega-3 fish oils may lead to significant improvements in cardiovascular risks.

Modifying lifestyle, including diet and exercise, is difficult in any population. However, the response of patients with psychosis may be more vigorous than anticipated and participation rates in structured programs may be high.[6] Behavioural interventions for weight loss have been shown to reduce weight gain in patients starting antipsychotics. They also lead to weight loss and improved lipid and glucose profiles in those who are already receiving treatment.[7]

Table 1

Potential of atypical antipsychotics to cause weight gain

Drug	Metabolic potential
clozapine olanzapine quetiapine	high
risperidone amisulpride paliperidone	mild–moderate
aripiprazole ziprasidone	low

Prescribers should also be aware of the other common drivers of cardiometabolic risk in this population

Using general practice care plans and forming partnerships with patient support organisations will help to offer lifestyle interventions as a routine practice. It is also important to work with families and carers when devising educational and lifestyle changes. Many families play an extensive role in the community care and support of patients with psychosis and may have well-intentioned but medically unhelpful approaches to diet and exercise.

Pharmacotherapeutic interventions

Should lifestyle management fail to provide adequate control of the developing risks, a number of additional strategies should be considered.

Switching antipsychotics

The potential of antipsychotics to cause metabolic effects varies (Table 1). In many cases it is very difficult to find an optimal antipsychotic drug for the individual.[8] If you are considering switching the patient's antipsychotic, consult a psychiatrist first. A switching protocol can then be worked out. If the patient is becoming increasingly metabolically compromised, but their psychiatric history supports continuing their current medication, it may be wise to enhance the lifestyle modification as much as possible. Patients taking clozapine have probably not responded to other antipsychotics and switching is not advisable. Also, consider the weight gain potential of co-prescribed medications. If these are not absolutely required, they should be either discontinued or substituted for drugs with a lower potential to cause weight gain.

Drugs for metabolic illness

The use of standard pharmaceutical approaches for psychiatric

patients is similar to those for patients without mental illness. Sadly for those with mental illness, the likelihood of receiving adequate and appropriate pharmaceutical therapies, such as statins, is significantly less than for those without mental illness.[9]

Adherence

Up to two-thirds of patients with schizophrenia are non-adherent or partially adherent to their antipsychotic treatments. Adherence is reduced in those who take other medications and adherence rates are lower for hypoglycaemics and antihypertensives than for antipsychotics.[10]

Patient counselling to promote adherence should be a mainstay of all interventions offered to patients with metabolic comorbidity, just as it is an essential component of antipsychotic management. The key to success is regular follow-up with the general practitioner, itself an issue of partial adherence. If diabetes has been diagnosed, engaging the patient with appropriate specialist services such as a diabetes nurse educator may help with adherence.

Bariatric surgery

In a small case series, outcomes after bariatric surgery for morbidly obese patients with schizophrenia were similar to controls.[11] There are few studies that have carefully considered longer-term outcomes, or formulated consent guidelines for this population. However, it remains an option for those with severe complicated obesity where postoperative medical review is available and patient adherence is adequate.[12]

Conclusion

The rates of metabolic disorder and general cardiovascular risks are high in those receiving antipsychotics. Patients receiving these drugs should be regularly monitored for cardiometabolic risk factors. Prescribing appropriate lifestyle and drug interventions, establishing links with programs that deal with psychosocial aspects of medical and psychiatric illness, being mindful of poor adherence and taking a family-based proactive approach are all important when managing these patients. In some circumstances patients may be switched to an antipsychotic with a lower potential to cause weight gain, after consultation with a psychiatrist.

References

1. Hennekens CH. Increasing global burden of cardiovascular disease in general populations and patients with schizophrenia. J Clin Psychiatry 2007;68 Suppl:4-7.
2. De Hert M, Kalnicka D, van Winkel R, Wampers M, Hanssens L, Van Eyck D, et al. Treatment with rosuvastatin for severe dyslipidemia in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2006;67:1889-96.
3. John AP, Koloth R, Dragovic M, Lim SC. Prevalence of metabolic syndrome among Australians with severe mental illness. Med J Aust 2009;190:176-9.
4. Dekker MJ, Su Q, Baker C, Rutledge AC, Adeli K. Fructose: a highly lipogenic nutrient implicated in insulin resistance, hepatic steatosis, and the metabolic syndrome. Am J Physiol Endocrinol Metab 2010;299:E685-94.
5. Gentile S. Long-term treatment with atypical antipsychotics and the risk of weight gain: a literature analysis. Drug Saf 2006;29:303-19.
6. Poulin MJ, Chaput JP, Simard V, Vincent P, Beriner J, Gauthier Y, et al. Management of antipsychotic-induced weight gain: prospective naturalistic study of the effectiveness of a supervised exercise programme. Aust N Z J Psychiatry 2007;41:980-9.
7. Gabriele JM, Dubbert PM, Reeves RR. Efficacy of behavioural interventions in managing atypical antipsychotic weight gain. Obes Rev 2009;10:442-55.
8. Lambert TJ, Chapman LH; Consensus Working Group. Diabetes, psychotic disorders and antipsychotic therapy: a consensus statement. Med J Aust 2004;181:544-8.
9. Kreyenbuhl J, Dickerson FB, Medoff DR, Brown CH, Goldberg RW, Fang L, et al. Extent and management of cardiovascular risk factors in patients with type 2 diabetes and serious mental illness. J Nerv Ment Dis 2006;194:404-10.
10. Piette JD, Heisler M, Ganoczy D, McCarthy JF, Valenstein M. Differential medication adherence among patients with schizophrenia and comorbid diabetes and hypertension. Psychiatr Serv 2007;58:207-12.
11. Hamoui N, Kingsbury S, Anthone GJ, Crookes PF. Surgical treatment of morbid obesity in schizophrenic patients. Obes Surg 2004;14:349-52.
12. Strohmayer E, Via MA, Yanagisawa R. Metabolic management following bariatric surgery. Mt Sinai J Med 2010;77:431-45.

Further reading

Lambert TJ, Newcomer JW. Are the cardiometabolic complications of schizophrenia still neglected? Barriers to care. Med J Aust 2009;190:S39-42.

Coghlan R; Centre for Health Services Research. Duty to care: Physical illness in people with mental illness. Perth: Dept. of Public Health, The University of Western Australia; 2001.

Professor Lambert has worked with Janssen Cilag, Pfizer, Hospira, Bristol-Myers Squibb, AstraZeneca and Eli Lilly as a speaker and on advisory boards, and has received education or research support from Janssen Cilag, Hospira, Bristol-Myers Squibb and Eli Lilly.

Self-test questions

The following statements are either true or false (answers on page 123)

1. Patients with psychosis are twice as likely to have high blood pressure than the general population.
2. Ziprasidone has a high potential to cause weight gain.

Current management of atrial fibrillation

***Himabindu Samardhi**, Advanced trainee in cardiology, **Maria Santos**, Fellow in electrophysiology, **Russell Denman**, Clinical director, Electrophysiology service, **Darren L Walters**, Director of cardiology, and **Nicholas Bett**, Cardiologist, Department of Cardiology, Prince Charles Hospital, Brisbane*

Summary

Atrial fibrillation is a common condition and carries the risk of cerebral thromboembolism. The $CHADS_2$ score is often used to stratify this risk. Anticoagulant therapy with warfarin significantly reduces this risk, but there are limitations to its use. This has prompted the use of antiplatelet drugs. Patients with mitral valve disease should always be considered for anticoagulant therapy. However for other patients with atrial fibrillation, the decision about which drug to use is based on the patient's risk of thromboembolism. In addition to stroke prevention, management is directed towards restoring and maintaining sinus rhythm or controlling the ventricular rate in those for whom permanent atrial fibrillation is accepted. For some patients percutaneous (catheter-directed) creation of lesions within the left atrium may be effective in maintaining sinus rhythm.

Key words: anticoagulants, aspirin, clopidogrel, dabigatran, Pradaxa, rivaroxaban, thromboembolism, warfarin.

(Aust Prescr 2011;34:100–4)

Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, occurring in 1–2% of the population of the developed world.[1] Its prevalence increases with age so that around 8% of people over 80 years of age have atrial fibrillation.[2] It may occur in isolation or secondary to structural heart disease, hypertension, myocardial ischaemia and infarction, hyperthyroidism, obesity and sleep apnoea. It can also develop following cardiac surgery or excess consumption of alcohol.[3-5] Symptoms include palpitations, dizziness, dyspnoea, angina and worsening heart failure.[1,3,5]

Atrial fibrillation may be categorised according to its presentation (initial, paroxysmal or recurrent, persistent) and duration.[1] Its management depends on the assessment of thromboembolic risk and control of symptoms. In general, a decision is made to pursue either a rhythm or rate control strategy.[1,2,6-8] With rhythm control the aim is to maintain the patient in sinus rhythm, while with rate control the aim is to control the ventricular rate with medication and accept permanent atrial fibrillation.

Assessing stroke risk

Atrial fibrillation carries the risk of cerebral thromboembolism[2] and may be responsible for one in five of all strokes.[1] Systemic thromboembolism, leading to stroke, transient ischaemic attacks or embolisation to other sites, is the most dreaded complication of atrial fibrillation. Anticoagulant therapy reduces this risk. The decision to use anticoagulant or antiplatelet therapy is dictated by the patient's risk of these events. Those with mitral valve disease should always be considered for anticoagulant therapy.[1,2] The $CHADS_2$ score has been commonly used to stratify risk (see Box 1).[1-3] A score of 2 or more is generally taken to indicate a risk of thromboembolism which may warrant warfarin therapy, depending on the patient's haemorrhagic risk, although even those with only one risk factor ($CHADS_2$ score of 1) may benefit from oral anticoagulants (Fig. 1).[1]

The CHA_2DS_2-VASc score, introduced by the European Society of Cardiology, provides a more comprehensive stroke risk assessment. It extends the $CHADS_2$ score with points also being allotted for female sex, vascular disease and age 65–74 years.[1] The European guidelines also introduced the concept of assessing the bleeding risk (see Box 2). Any patient with a bleeding score of 3 or above is at high risk and regular review during antithrombotic therapy is recommended.

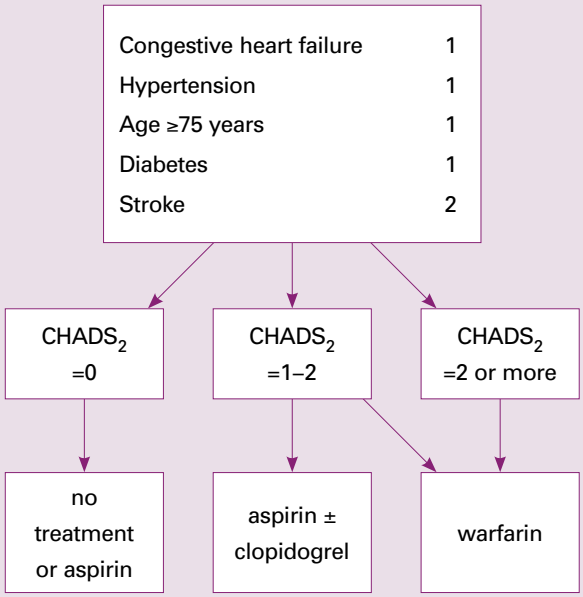
Box 1

$CHADS_2$ score: stratifying risk of stroke in patients with atrial fibrillation

Congestive heart failure	1 point
Hypertension	1 point
Age ≥ 75 years	1 point
Diabetes	1 point
Systemic embolism, including **S**troke (previous episode)	2 points

Fig. 1

Treating patients with non-valvular atrial fibrillation depending on their $CHADS_2$ score



There are other models for assessing stroke risk. These incorporate echocardiographic findings such as left atrial size, left ventricular systolic dysfunction and spontaneous echo contrast or thrombus in the left atrium.

Drug therapies for preventing stroke

For low-risk patients with atrial fibrillation, aspirin, or no treatment, may be sufficient. For higher-risk patients, treatment options include warfarin, aspirin and clopidogrel. Several studies have compared the efficacy of antiplatelet regimens to warfarin.[9-11] The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study showed that warfarin (target INR 2–3) was superior to aspirin 75 mg daily.[10] The ACTIVE-W trial showed that clopidogrel plus aspirin was associated with a 45% increase in the risk of stroke, non-central nervous system embolism, myocardial infarction or vascular death compared to oral anticoagulation (annual rates for events 5.60% vs 3.93% respectively, p=0.0002). However, the cumulative risk of major bleeding complications was nearly identical (2.4% vs 2.2% per year, p=0.67).[11] In summary, warfarin is more effective in preventing cerebrovascular events than dual antiplatelet therapy, although the danger of major bleeding is similar.[11]

The INR is usually maintained between 2 and 3,[12] but a higher range may be appropriate in patients with prosthetic heart valves or rheumatic mitral valve disease. In patients unable to take warfarin, adding clopidogrel to aspirin reduces the risk of major vascular events by 11%, particularly stroke, but increases the risk of major haemorrhage by 57%.[13]

Box 2

HASBLED score

Hypertension	1 point
Abnormal liver or kidney function	1 point each
Stroke	1 point
Bleeding	1 point
Labile INRs	1 point
Elderly (e.g. >65 years)	1 point
Drugs or alcohol	1 point each

Hypertension = systolic blood pressure >160 mmHg

Abnormal renal function = dialysis/renal transplantation/ serum creatinine ≥200 mmol/L

Abnormal liver function = chronic hepatic dysfunction (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin 2 x upper limit of normal in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase 3 x upper limit normal etc.)

Bleeding = history of bleeding or a bleeding diathesis

Drugs = concomitant use of antiplatelet or non-steroidal anti-inflammatory drugs

Alternative oral anticoagulants

Several effective substitutes for warfarin are used for stroke prevention in North America and Europe. These include the direct thrombin antagonist dabigatran and factor Xa inhibitors such as rivaroxaban, apixaban, betrixaban and edoxaban.[14]

Dabigatran is the first drug to show non-inferiority to warfarin for stroke prevention in atrial fibrillation.[4,14-16] The 150 mg twice-daily dose was superior to warfarin in efficacy with a similar risk of major bleeding whereas 110 mg twice daily was non-inferior for efficacy with a reduced risk of major bleeding. The risk of intracranial haemorrhage was less with both doses of dabigatran than with warfarin.[15-18] Rivaroxaban is also an effective anticoagulant.[19,20] The main advantage of rivaroxaban and dabigatran over warfarin is they have more predictable pharmacokinetics, and routine anticoagulation monitoring is not needed. No interaction between cytochrome P450 enzymes and dabigatran has been observed, although P-glycoprotein inhibitors such as amiodarone and verapamil may increase plasma concentrations of dabigatran and lead to an increased bleeding risk. There is also a risk of dabigatran accumulation in renal impairment.[14] There is no antidote if bleeding occurs with dabigatran and rivaroxaban.

These drugs may replace warfarin for thromboembolic prophylaxis in atrial fibrillation if their cost-effectiveness can

be shown.[21] However, for a condition that requires long-term prophylaxis there are no long-term data to suggest that they will be safe and effective alternatives.

Device-based strategies for preventing stroke

Medical prophylaxis of stroke in patients with atrial fibrillation has been plagued by a high risk of bleeding complications, frequent drug interactions and a narrow therapeutic range of the drugs and hence poor compliance. Alternative approaches have been sought and a number of device-based treatments are becoming available or being evaluated.

Thrombi have been demonstrated in the left atrial appendage in up to 90% of patients with non-valvular atrial fibrillation.[22] For many years surgeons have combined mitral valve surgery with ligation of the left atrial appendage to try and reduce the risk of subsequent embolism.

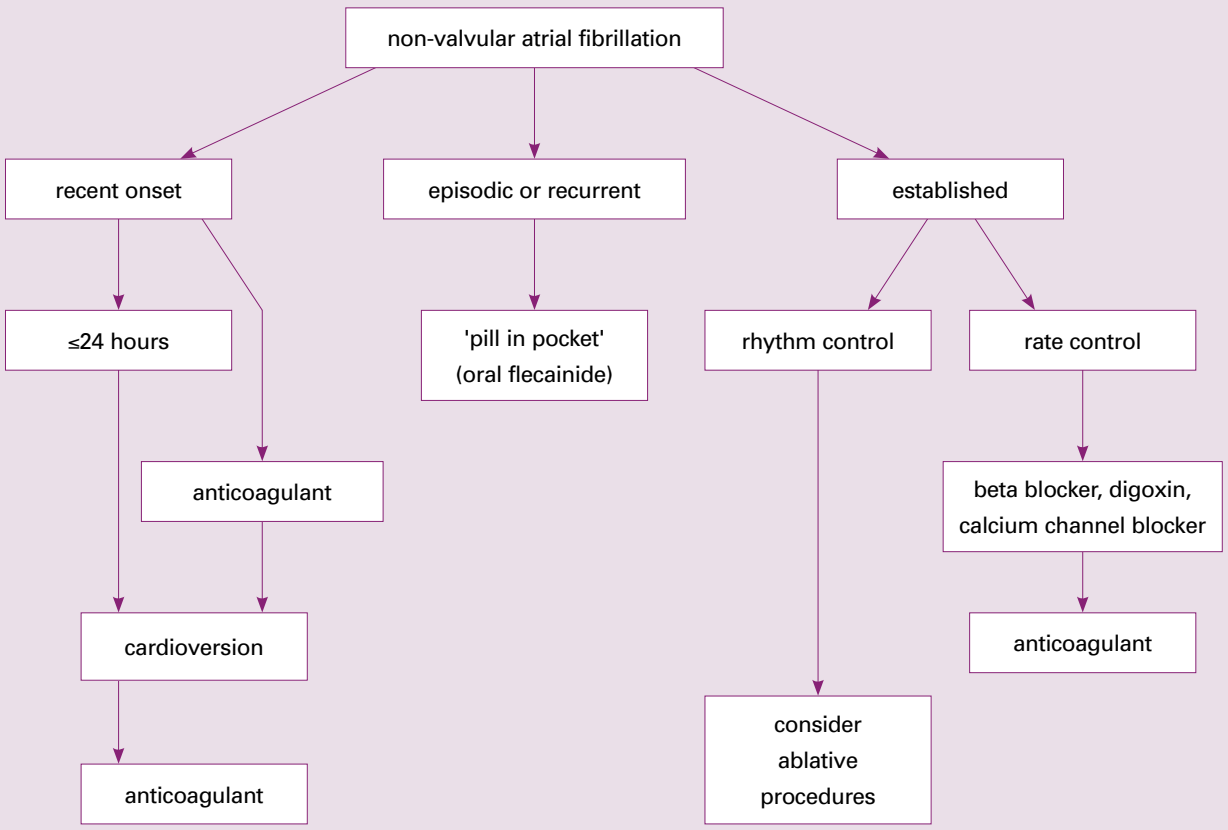
The Watchman device is delivered by catheter to the left atrial appendage. It has been shown to be non-inferior to chronic warfarin therapy in patients with a $CHADS_2$ score of more than 1. This was despite a peri-procedural complication rate of 10.6% which included major bleeding, stroke and sequelae such as device or air embolism and pericardial effusion that may have reflected operator inexperience. Most ischaemic strokes occurred at the time of the procedure – their subsequent incidence was less than in control patients treated with warfarin. These results support the hypothesis that thrombus in the left atrial appendage is the likely source of embolic stroke in patients with non-valvular atrial fibrillation, and appear to endorse a role for left atrial appendage closure.[22,23] Longer-term follow-up is necessary before the use of these devices can be generally recommended.

Rate control

Most patients with atrial fibrillation are managed by controlling the ventricular rate. In patients with minimal symptoms, aggressive attempts to maintain sinus rhythm have not been shown to reduce mortality, improve quality of life, or prevent heart failure or thromboembolic complications.[6-8] The ventricular rate may be controlled using beta blockers, non-dihydropyridine calcium channel blockers (for example verapamil) or digoxin.[1,3,5] However, beta blockers should be avoided in patients with asthma, and digoxin and calcium channel blockers should be avoided in those with pre-excitation. Lenient control (resting heart rate less than 110 beats/minute) is as effective as strict rate control and is easier to achieve.[6] Anticoagulation should be continued in these patients (Fig. 2).

Fig. 2

Proposed management of non-valvular atrial fibrillation



Rhythm control

The severity of symptoms usually drives the decision to pursue a rhythm control strategy. In symptomatic patients it may be reasonable to attempt to restore sinus rhythm. For those without structural heart disease who present within 48 hours of the onset of atrial fibrillation, immediate cardioversion (electrical or drug) may be attempted under cover of unfractionated or low molecular weight heparin.[1] Those who present later should be presumed to have left atrial thrombus (unless this has been excluded with a trans-oesophageal echocardiogram) and cardioversion should be deferred until they have been effectively anticoagulated for at least three weeks.[1,3,5] Anticoagulants should be continued for at least four weeks after successful cardioversion even if transoesophageal echo has excluded left atrial thrombus.[2,3]

Although amiodarone is the most effective antiarrhythmic drug for maintenance of sinus rhythm its long-term value is limited by adverse effects.[2,3] Sotalol combines beta blocking and antiarrhythmic properties but prolongs the QT interval and may provoke torsades de pointes and cardiac arrest,[3,5] particularly in patients with renal dysfunction and impaired drug clearance or hypokalaemia, which may occur with concomitant diuretic therapy.[23] Intravenous or oral flecainide ('pill in pocket')[1,3,5] may be effective but should be avoided in those with left ventricular dysfunction or ischaemia.[24]

Dronedarone cannot be recommended as a first-line drug.[25] Although it may not have the pulmonary and thyroid toxicity of amiodarone[25-27] and is more effective than placebo in maintaining sinus rhythm and reducing the ventricular rate during recurrent atrial fibrillation,[26,28] its use has been associated with worsening heart failure and increased mortality in patients with severe left ventricular systolic dysfunction.[29]

Catheter-directed creation of lesions within the left atrium has become an acceptable treatment for selected patients who have not responded to at least one antiarrhythmic drug. Most strategies depend on electrical isolation of the pulmonary veins, with successful maintenance of sinus rhythm for 12 months in excess of 80% for paroxysmal atrial fibrillation and 70% for persistent atrial fibrillation.[28,30] However, atrial fibrillation may recur and patients may need to remain on medications, including anticoagulants. In recent surveys the complication rate was 5.9% and included cardiac tamponade, pulmonary vein stenosis, stroke, phrenic nerve palsy, atrio-oesophageal fistula and death.[31,32] For those who are highly symptomatic with uncontrolled ventricular rates despite optimal medical therapy, atrio-ventricular node ablation and insertion of a permanent pacemaker may improve quality of life.

Conclusion

The burden of atrial fibrillation will grow further as populations age. The major adverse outcome is embolic stroke. Newer antithrombotic regimens offer an alternative to warfarin as do techniques for left atrial appendage occlusion.

If the management of atrial fibrillation is directed towards restoring and maintaining sinus rhythm, percutaneous (catheter-directed) creation of lesions within the left atrium may be warranted, but for most patients with permanent atrial fibrillation controlling the ventricular rate is the most practical strategy.

References

1. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369-429.
2. Medi C, Hankey GJ, Freedman SB. Atrial fibrillation. Med J Aust 2007;186:197-202.
3. Ninio D. Contemporary management of atrial fibrillation. Aust Prescr 2000;23:100-2.
4. Savelieva I, Camm J. Update on atrial fibrillation: part I. Clin Cardiol 2008;31:55-62.
5. Crandall MA, Bradley DJ, Packer DL, Asirvatham SJ. Contemporary management of atrial fibrillation: update on anticoagulation and invasive management strategies. Mayo Clin Proc 2009;84:643-62.
6. van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010;362:1363-73.
7. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33.
8. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667-77.
9. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.
10. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007;370:493-503.
11. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006;367:1903-12.
12. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med 1994;120:897-902.
13. ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360:2066-78.

14. Schirmer SH, Baumhakel M, Neuberger HR, Hohnloser SH, van Gelder IC, Lip GY, et al. Novel anticoagulants for stroke prevention in atrial fibrillation: current clinical evidence and future developments. J Am Coll Cardiol 2010;56:2067-76.
15. Ezekowitz MD, Aikens TH, Brown A, Ellis Z. The evolving field of stroke prevention in patients with atrial fibrillation. Stroke 2010;41:S17-20.
16. Ezekowitz MD, Wallentin L, Connolly SJ, Parekh A, Chernick MR, Pogue J, et al. Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation. Circulation 2010;122:2246-53.
17. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
18. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010;376:975-83.
19. Brighton T. New oral anticoagulant drugs – mechanisms of action. Aust Prescr 2010;33:38-41.
20. Gallus A. New oral anticoagulants – clinical applications. Aust Prescr 2010;33:42-7.
21. Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Ann Intern Med 2010;154:1-11.
22. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755-9.
23. Onalan O, Crystal E. Left atrial appendage exclusion for stroke prevention in patients with nonrheumatic atrial fibrillation. Stroke 2007;38(2 Suppl):624-30.
24. Ruskin JN. The cardiac arrhythmia suppression trial (CAST). N Engl J Med 1989;321:386-8.
25. Singh D, Cingolani E, Diamond GA, Kaul S. Dronedarone for atrial fibrillation: have we expanded the antiarrhythmic armamentarium? J Am Coll Cardiol 2010;55:1569-76.
26. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007;357:987-99.
27. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360:668-78.
28. Wann LS, Curtis AB, Ellenbogen KA, Estes NA 3rd, Ezekowitz MD, Jackman WM, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2011;57:1330-7.
29. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358:2678-87.
30. Nault I, Miyazaki S, Forclaz A, Wright M, Jadidi A, Jais P, et al. Drugs vs. ablation for the treatment of atrial fibrillation: the evidence supporting catheter ablation. Eur Heart J 2010;31:1046-54.
31. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation 2010;122:2368-77.
32. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 2005;111:1100-5.

Further reading

Eikelboom JW, Weitz JI. New anticoagulants. Circulation 2010;121:1523-32.

Turpie AG. New oral anticoagulants in atrial fibrillation. Eur Heart J 2008;29:155-65.

Mueller PS. CHA_2DS_2-VASc performs better than $CHADS_2$ in predicting stroke risk. J Watch 2011;31:50.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 123)

3. A 76-year-old woman with atrial fibrillation, type 2 diabetes and hypertension should be considered for anticoagulation therapy.
4. Dual antiplatelet therapy is more effective than warfarin for stroke prevention.

Securing the supply chain

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Summary

Medicines are distributed through a complex supply chain which may be disrupted anywhere from manufacturing to dispensing. Factors that contribute to unanticipated shortages of medicines include manufacturing causes, logistical failures and unexpected or unpredictable disease outbreaks. Additionally, in the postmarketing environment unexpected safety signals may require recall of batches, with a consequential scarcity of remaining supplies at short notice. Early identification of potential stock shortages and early engagement with the Therapeutic Goods Administration will facilitate a coordinated response in managing interruptions or changes to patient care. Pharmaceutical companies and the Therapeutic Goods Administration will endeavour to provide the right product or appropriate alternative therapies to ensure that patient care is not appreciably diminished.

Key words: drug industry, drug regulation.

(Aust Prescr 2011;34:105–7)

Introduction

The National Medicines Policy has four central objectives focused on delivering medication and related health services that meet best possible health and economic objectives.[1] These objectives are:

- timely access to the medicines that Australians need, at a cost individuals and the community can afford
- medicines meeting appropriate standards of quality, safety and efficacy
- quality use of medicines
- maintaining a responsible and viable medicines industry.

Ensuring timely access to medicines encompasses the entire journey from molecule to patient. It includes research and development programs, a rigorous regulatory system for assessing quality, safety and efficacy,[2] and a government subsidy scheme.[3]

There have been a few notable unexpected shortages in the supply of prescription medicines in Australia. While these events are generally few and far between, when they occur they generate concern and incredulity at the vulnerability of the medicines supply chain.

The supply chain

Medicines are distributed through a complex supply chain starting with formulation and manufacturing. After packaging and labelling, the medicines go to wholesalers and then to pharmacies for dispensing. Within this supply chain there may be international customs and importation hurdles, complex transport needs and a number of rigorous regulatory requirements.

Sponsors of prescription medicines in Australia are typically global companies supplying their drugs to worldwide markets. Determining the quantities which each country requires is largely calculated from historical usage information, recurrent ordering practices and forecasting methods. Intermittent variations in demand and supply may be envisaged and ameliorated, but occasionally this is not the case. Forecasting methodologies are susceptible to numerous variations. These may result in shortages of medicines that are difficult to predict and, at times, impossible to counteract.

Interruptions to supply

Supply may be restricted or delayed anywhere in the supply chain from manufacturing to the dispensary. While sponsors are reliant on accurate forecasting to establish supply requirements, they also depend on successful production. Factors that contribute to unanticipated shortages in medicines supply include manufacturing problems, logistical failures, and unexpected or unpredictable outbreaks of disease. After marketing, unexpected safety concerns may require batches or products to be recalled at short notice. This results in shortages of remaining supplies or of alternative treatment options.

Manufacturing

The causes of production failures can be diverse. Changes in manufacturing processes can cause challenges in meeting regulatory requirements. This is a particular problem with biological products where apparently minor manufacturing changes may create unexpected variations in the quality of the final product.

Many manufacturers rely on third parties for raw materials. If supplies are not received or raw materials fail to meet the required specifications this will disrupt production schedules.

Other examples of production failure include equipment malfunction at factories, finished products not meeting specifications and packaging component failures. Such nonconformities detected during manufacturing processes may lead to losses of whole batches from production with consequent delays in making adequate quantities of the final product available.

Logistics

Non-manufacturing causes may include logistical support failures. For example, inadequate refrigeration during transportation may render a cold chain product unusable. The eruption of an Icelandic volcano in 2010 caused widespread interruption to the transport of air freight. Fortunately, available reserves in Australia meant there were no shortages reported although some safety stocks were drawn upon. Other unanticipated incidents, such as the terrorist attacks on 11 September 2001, caused global disruptions to transportation. Local events such as strikes, although likely to be short-lived, may also disrupt supply channels. The floods in Queensland in January 2011 damaged a pharmaceutical distribution centre, but supplies were obtained from other centres.

Demand

Unexpected increases in demand may occur due to sudden unavailability, or restrictions to the indications, of competitor products. Unexpected disease outbreaks, such as influenza pandemics, also stretch supply. Overcoming shortages or demand surges is particularly challenging if the product lead times are long, as with products manufactured by biotechnology. An example may be that a major supplier of one brand of a multi-brand product becomes unable to supply its product. The unexpected increase in demand for the remaining brands may cause shortages which could take some time to overcome while schedules are altered and manufacturing quantities increased. The planning of manufacturing schedules requires relatively long lead times, therefore unplanned stockpiling of products, for instance, by governments or pharmacies could adversely impact on supply in other regions.

Maintaining supply

The industry's predictive mechanisms do not generally account for unforeseen surges in demand, or for unintended breakdowns in supply. However, extended shelf lives, careful adherence to storage recommendations and maintenance of a reserve stock may compensate for short-lived, unexpected incidents.

There is a fine balance between the holding of safety stock to cover potential shortages and keeping inventory as low as is practicable to avoid wastage caused by stock expiring. As soon as the likelihood of a shortage is confirmed, companies endeavour to establish its probable duration. This will enable the company to determine if safety stocks are sufficient or whether the product can be supplemented from alternative sources.

Vaccines have their own specific challenges and continuation of supply is a constant concern due to the complexity of the production process. Demand is also variable, for example with the uptake of seasonal vaccines. This requires careful stock management and mechanisms for rapid redirection of international supplies.

Sponsors may implement systems whereby stock is assigned and packaged for particular countries at the last minute to enable redirection of supplies at short notice to areas of need. This is a common means of managing the drugs used in clinical trials where recruitment rates may be uncertain.

Cooperation with regulators

When a product is predicted to be out of stock for only a short time, the wholesaler is informed. However, if the shortage is likely to affect the availability of the product to the public, then the Therapeutic Goods Administration (TGA) and Pharmaceutical Benefits Division of the Department of Health and Ageing are advised and a collaborative response is established where necessary. It is a condition of listing on the Pharmaceutical Benefits Scheme (PBS) that sponsors have stock available. They must report any problems that will affect supply of a listed product. There is no requirement for companies to ensure supplies of drugs which are not listed on the PBS.

Under existing exemption mechanisms within the *Therapeutic Goods Act 1989*, pharmaceutical companies may apply to access medicines from alternative sources to cover product shortages. For example, international versions of a product in other strengths, doses or dosage forms, or supplies approved and packaged for countries other than Australia (with non-Australian labelling) may be granted an exemption to enable supply in Australia.[4]

The time needed to resolve the regulatory requirements for alternative supplies can be prolonged. It is therefore imperative for companies to establish transparent and early communication with the TGA in the event of supply problems when expedited assessment of exemption applications may be desired. Similarly, communication within the company, with wholesalers and customers needs to be clear and timely.

In many cases supply problems are resolved without difficulties so widespread notification of potential shortages may be premature. However, prompt notification to the TGA will facilitate a coordinated response to localised or widespread shortages. There are examples where the TGA stipulates that relevant clinicians, colleges, professional bodies and applicable consumer groups are notified of a potential shortage and advised of the proposed contingency strategies. Wider publication of these issues is beneficial when clearly in the

public interest and may be recommended by the Department of Health and Ageing.

In 2008, recalls of batches of heparin-based products led to widespread shortages. The response to this scarcity was closely coordinated between the Department of Health and Ageing and the manufacturers of the affected products. Consensus guidelines for Australian clinicians were developed to provide advice on the use of anticoagulants during the shortage. Substitute treatment regimens with alternative products were established which prioritised patients according to clinical need.[5]

In 2009 supplies of imiglucerase for the treatment of Gaucher's disease, and agalsidase-beta for the treatment of Fabry's disease were significantly depleted due to manufacturing problems. This resulted in a worldwide shortage of these products. The coordinated global and local response recommended rationing the use of remaining product to extend existing supplies for as long as possible.[6] The manufacturer of these products continues to work with government and patient support organisations for the ongoing management of supply.[6]

Conclusion

Medicines manufacturers and suppliers try to prevent shortages of products wherever possible. To achieve this effectively they rely on accurate forecasting, maintenance of appropriate levels of safety-stock and identification of backup supply routes. The TGA has a number of powers under the Therapeutic Goods Act, to permit supply of unapproved products in critical situations.[4]

Early identification of potential stock shortages and early engagement with the TGA enables a coordinated response to assist in managing interruptions or changes to patient care. Both the companies and the TGA will endeavour to provide a product, or appropriate alternative therapies, to ensure that patient care is not appreciably diminished.

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References

1. Department of Health and Ageing. National Medicines Policy 2000. Canberra: Commonwealth of Australia; 1999. www.health.gov.au/internet/main/publishing.nsf/Content/National+Medicines+Policy-1 [cited 2011 Jul 4]
2. Therapeutic Goods Administration. www.tga.gov.au
3. Department of Health and Ageing. Pharmaceutical Benefits Scheme. www.pbs.gov.au
4. Commonwealth of Australia. Therapeutic Goods Act 1989. www.comlaw.gov.au/Details/C2010C00430 [cited 2011 Jul 4]
5. Department of Health and Ageing. Office of Health Protection. Consensus guidelines for Australian clinicians for the use of anti-coagulants during heparin-based product shortages. 2008. www.health.gov.au/internet/main/publishing.nsf/Content/heparin-guidelines.htm [cited 2011 Jul 4]
6. Department of Health and Ageing. Alternative arrangements for medicines: Other supply arrangements outside the Pharmaceutical Benefits Scheme (PBS). www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-info [2011 Jul 4]

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Medicines Safety Update

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Medicines Safety Update is the drug safety bulletin of the Therapeutic Goods Administration (TGA). It is published in each issue of *Australian Prescriber*. You can also read it on the TGA website and sign up for free Medicines Safety Update email alerts at www.tga.gov.au/newsroom/subscribe-msu.htm

In this issue:

Cramps, quinine and thrombocytopenia

Summary

The TGA continues to receive reports of thrombocytopenia in people taking quinine to treat muscle cramps. Health professionals are reminded that quinine is not approved for the treatment of nocturnal cramps because of its low efficacy and the risk of thrombocytopenia. Non-pharmacological interventions, such as stretching, should be considered for preventing cramps.

In 2004, the Product Information (PI) for quinine tablets was amended and the indication for nocturnal cramps removed. Quinine tablets (Quinbisul, Quinate and Quinsul) are now only approved for treatment of malaria due to strains of *Plasmodium falciparum* resistant to chloroquine and the related 4-aminoquinolines.

Thrombocytopenia continues to be reported

Up to 2004, the TGA had received 228 reports of thrombocytopenia in people taking quinine, six of which were fatal.[1] Since 2004, the TGA has received a further 21 reports of thrombocytopenia in people taking quinine, including several in the past few years (see table). In most cases, patients were prescribed quinine to treat leg cramps.

In 2010, a case reported to the TGA involved a 73-year-old woman who had been taking one quinine tablet every two days for muscle cramps for one year. She presented with a history of three days of bleeding gums, nose bleeding and multiple bruises and was found to have a platelet count of 4 x 10^9/L. Quinine was ceased and her platelet count recovered to normal.

Utilisation data show that although Pharmaceutical Benefits Scheme (PBS) prescribing of quinine has reduced substantially since removal of the indication and PBS listing for muscle cramps, private prescribing of quinine continues.[2] It is likely that 'off label' prescribing for muscle cramps occurs.

Quinine is not approved for treatment of muscle cramps

When a patient presents with leg cramps, consideration should be given to non-pharmacological interventions for cramps such as stretching. An NPS factsheet describes suitable stretches for people who experience nocturnal cramps.[3]

References

1. Quinine indications – cramps deleted. Aust Adv Drug React Bull 2004;23:5.
2. Department of Health and Ageing. PBS Statistics. Australian Statistics on Medicines. www.pbs.gov.au
3. Quinine: Poor efficacy in muscle cramps outweighed by risks of harm. Sydney: NPS; 2009 Dec 18. www.nps.org.au

Table

Reports to the TGA since 2005 of thrombocytopenia in patients taking quinine

Year	Number of reports in which quinine was suspected
2011*	1
2010	1
2009	0
2008	5
2007	2
2006	3
2005	9

*to 2 June 2011

Venlafaxine and stress cardiomyopathy

Summary

Published case reports have suggested that stress cardiomyopathy may be an adverse effect of venlafaxine. There is currently insufficient evidence to confirm an association, although a biologically plausible mechanism exists. Clinicians are reminded to report suspected adverse reactions of all types, even for drugs that have been available for many years.

Venlafaxine is a potent selective serotonin-noradrenaline reuptake inhibitor. It also exhibits rate-dependent sodium channel blocking activity. Venlafaxine is approved for the treatment of major depression, generalised anxiety disorder, social anxiety disorder and panic disorder, including prevention of relapse.

Features of stress cardiomyopathy

Stress cardiomyopathy, or Taka-Tsubo cardiomyopathy, is characterised by an acute transient left ventricular dysfunction with akinesia of the left ventricular apex and a hypercontractile base, occurring predominantly in women in the context of emotional distress.[1] Accompanying transient electrocardiographic changes may mimic an acute coronary syndrome. It is thought the findings are due to catecholamine-mediated neurogenic myocardial stunning caused by emotional stress. Elevated plasma catecholamines are a typical finding.

Reported cases

Following a literature report[1] and routine pharmacovigilance activities, the TGA has undertaken a review of stress cardiomyopathy in association with venlafaxine use. To March 2011, the TGA had received three case reports of stress cardiomyopathy in patients taking venlafaxine: one in the context of overdose, and two in patients over the age of 70 with normal dosing. All three cases had the diagnosis confirmed with echocardiography and noradrenaline levels. For the same time period there were six other cases of cardiomyopathy and one case of cardiac failure reported in patients taking venlafaxine. These numbers are very small in the context of use of venlafaxine in Australia. Approximately 21 million PBS prescriptions for venlafaxine have been dispensed.

Two additional cases of stress cardiomyopathy in patients taking venlafaxine, both in the context of overdose, are identified in the database of the World Health Organization's Programme for International Drug Monitoring. Thirty-nine patients were reported to have a cardiomyopathy, nine had congestive cardiomyopathy, and 58 patients had cardiac failure in association with venlafaxine use. The WHO database provides insufficient information about the diagnosis and features of the reported cases of cardiomyopathy to confirm an underlying causal relationship beyond a temporal association.*

By increasing plasma catecholamine levels, possibly by the inhibition of noradrenaline reuptake, a potential mechanism exists for venlafaxine to cause stress cardiomyopathy.

Cardiovascular precautions

The PI states that venlafaxine causes a dose-related increase in resting heart rate and is associated with hypertension and increased serum cholesterol, which are presumed to be additive to other cardiovascular risk factors, and that venlafaxine should be used with caution in patients with unstable heart disease.[2] In these patients, assessment of the cardiovascular system (e.g. ECG, serum electrolytes during diuretic treatment) should be considered during treatment with venlafaxine, particularly when the dose is increased beyond 150–200 mg daily.

The TGA continues to monitor the potential association between venlafaxine and stress cardiomyopathy. Clinicians are reminded to report all adverse events that are potentially medication-related.

References

1. Christoph M, Ebner B, Stolte D, Ibrahim K, Kolschmann S, Strasser RH, et al. Broken heart syndrome: TakoTsubo cardiomyopathy associated with an overdose of the serotonin-norepinephrine reuptake inhibitor venlafaxine. Eur Neuropsychopharmacol 2010;20:594-7.
2. Pfizer Australia Pty Ltd. Efexor XR (venlafaxine) Product Information. 2011 May 19.

* The information in adverse event reports in the WHO database is not homogeneous with respect to the sources of the information or the likelihood that the pharmaceutical product caused the suspected adverse reaction. The information in this article does not represent the opinion of the WHO.

In utero antipsychotic exposure and neonatal extrapyramidal and withdrawal adverse effects

Summary

Neonates exposed to antipsychotic medications during the third trimester of pregnancy may be at risk of experiencing extrapyramidal signs and/or withdrawal symptoms. Neonatal drug withdrawal symptoms may occur when drug exposure ceases at birth. All registered antipsychotics are now classified as Australian pregnancy category C.

The safety of antipsychotic use in pregnancy and lactation has not been thoroughly studied. The antenatal management of serious mental illnesses, such as schizophrenia and bipolar affective disorder, involves clinical decision-making about the continuation, commencement or discontinuation of psychotropic treatments. If the use of an antipsychotic in a pregnant woman is clinically indicated, avoid unnecessarily high doses and duration of treatment.[1] The decision about using antipsychotics should be made on a case-by-case basis, taking into account the woman's individual characteristics, her mental health history and tendency to relapse, the risk to the fetus or infant, and the risk – to both mother and fetus – of not treating the disorder.[2]

The potential risks to the fetus or infant from antipsychotic exposure include structural teratogenicity, pregnancy complications (e.g. inducing maternal diabetes), effects on fetal growth, neonatal toxicity/withdrawal and long-term adverse neurodevelopmental outcomes. There is growing evidence that psychiatric disorders themselves appear to independently elevate the risk of spontaneous abortion, pre-eclampsia, premature birth, low birth weight, smaller head circumference and long-term adverse neurodevelopment.[1,3]

Reported cases

When used in pregnancy, many typical antipsychotics are known to be associated with the development of reversible extrapyramidal signs (EPS), such as dyskinetic movements, in the neonate. Although the incidence of EPS tends to be lower in patients treated with some atypical antipsychotics, this may not necessarily translate to a lower risk to neonates exposed *in utero*. Fetal exposure is largely dependent on placental transfer which can vary depending on the placental permeability of different antipsychotics. Spontaneous adverse event reporting provides evidence of both EPS and withdrawal symptoms occurring in the neonate following chronic *in utero* exposure to atypical antipsychotics.

To May 2011, the TGA had received 19 reports of EPS or withdrawal symptoms in neonates. Of these, an atypical antipsychotic was suspected in 18 reports. Many reported cases were confounded by concomitant use of other psychotropic medication (e.g. antidepressants), obstetric complications (e.g. fetal distress) or tobacco and alcohol exposure. However an antipsychotic alone was suspected in four reports.

In the cases reported to the TGA, adverse events included jitteriness, agitation, tremor, feeding problems, somnolence, breathing difficulties, hypertonia, hypotonia, pronounced startle reflex and myoclonus. Although the term 'neonatal drug withdrawal' was specifically identified in 14 reports, it was not possible to definitively determine whether these were related directly to antipsychotic toxicity or to withdrawal. Reported time to onset ranged from birth to seven days. Where outcome was described, most neonates recovered within a few days although some required supportive therapy and prolonged hospitalisation. An analysis of adverse events reported in the United States described similar findings.[4]

Changes to PI for antipsychotics

PI documents for all antipsychotics are being updated with warnings about neonatal EPS and withdrawal symptoms. All registered antipsychotics are Australian pregnancy category C. Category C refers to: 'Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.'

See page 111 for information about the TGA's new 'Prescribing medicines in pregnancy' database.

References

1. Psychotropic Expert Group. Therapeutic guidelines: Psychotropic. Version 6. Melbourne: Therapeutic Guidelines Limited; 2008.
2. Austin M-P, Highet N; Guidelines Expert Advisory Committee (2011). Clinical practice guidelines. Depression and related disorders – anxiety, bipolar disorder and puerperal psychosis – in the perinatal period. A guideline for primary care health professionals. Melbourne: beyondblue; 2011. www.beyondblue.org.au/index.aspx?link_id=6.1246&tmp=FileDownload&fid=1626 [cited 2011 Jul 4]
3. Gentile S. Antipsychotic therapy during early and late pregnancy. A systematic review. Schizophr Bull 2010;36:518-44.
4. US Food and Drug Administration. FDA drug safety communication: Antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. 2011. www.fda.gov/Drugs/DrugSafety/ucm243903.htm [cited 2011 Jul 4]

Prescribing medicines in pregnancy – new TGA database

As part of the recent website upgrade, the TGA has developed a new, searchable database for use by health professionals prescribing medicines to pregnant women. The database can be found at www.tga.gov.au/hp/medicines-pregnancy.htm.

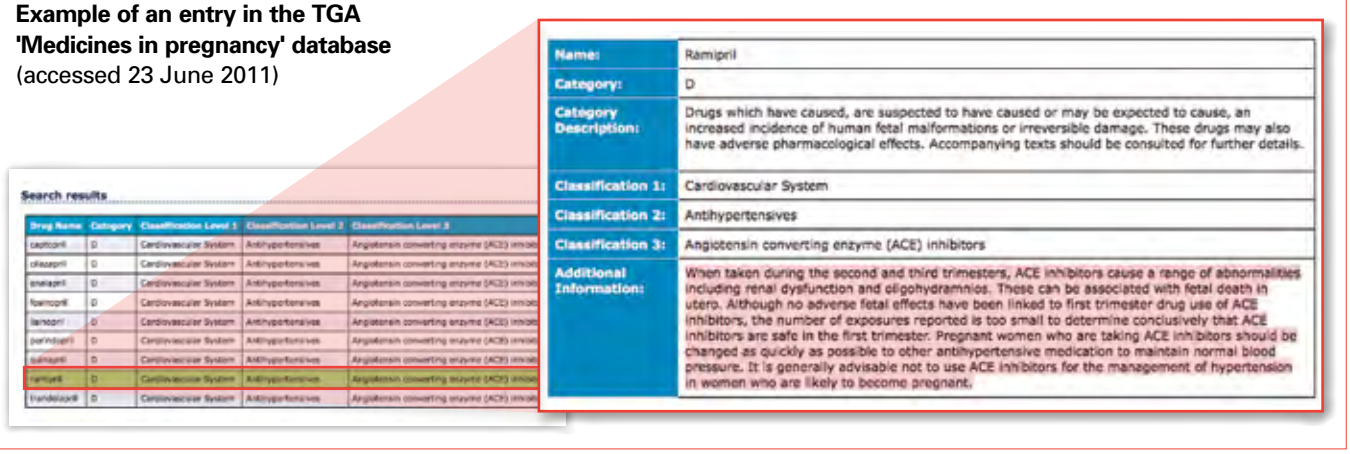
The 'Prescribing medicines in pregnancy' database replaces the booklet 'Prescribing medicines in pregnancy – an Australian categorisation of the risk of drug use in pregnancy'. The booklet was first published in 1989, with the latest edition published in 1999, and subsequent updates added as amendments on the TGA website. Unlike the booklet, the new database is searchable by generic name (or part of the generic name), and by classification using a drop-down list.

Once the user finds the relevant medicine, clicking on the medicine name will display the pregnancy category, an explanation of the category and, if available, a safety statement specific for the medicine or medicine group (see figure).

The database contains over 1200 individual entries, including all new medicines and any changes of pregnancy category for existing medicines. A separate page lists the therapeutic goods exempted from pregnancy classification.

Other pages on the TGA website with information relevant to prescribing medicines in pregnancy include the PI documents (www.ebs.tga.gov.au) and the Australian Public Assessment Reports (www.tga.gov.au/industry/pm-auspar.htm).

Example of an entry in the TGA 'Medicines in pregnancy' database
(accessed 23 June 2011)



Medicines Safety Update is written by staff from the Office of Product Review of the TGA. Editor: Ms Elspeth Kay. Principal Medical Advisor: Dr Megan Keaney. Contributors to this issue include Dr Kevin Dodd, Dr Kaye Robertson, Dr Jennifer Elijah, Dr Manuel Navarro-Gonzalez and Dr Jin Zhu. For correspondence or further information about Medicines Safety Update, contact the TGA's Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114.

What to report? You do not need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. We particularly request reports of all suspected reactions to new medicines, all suspected medicines interactions, and suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website and with the April, August and December issues of *Australian Prescriber*
- **online** on the TGA website
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Office of Product Review on 1800 044 114.

Pharmaceutical excipients – where do we begin?

***Alison Haywood**, Senior lecturer, School of Pharmacy, Griffith University, Gold Coast Campus; and **Beverley D Glass**, Professor of Pharmacy, James Cook University, Townsville, Queensland*

Summary

Excipients have been defined in many ways, including as inert substances used as vehicles and diluents for drugs. The problem with this definition is that in recent years excipients have proved to be anything but inert, not only possessing the ability to react with other ingredients in the formulation, but also to cause adverse and hypersensitivity reactions in patients. These range from a mild rash to a potentially life-threatening reaction. Different brands of the same drug may contain different excipients, especially preservatives and colourants. The Consumer Medicines Information provides a list of excipients, and information on the safety of individual excipients can be found in drug reference guides.

Key words: adverse reactions, drug labelling, inactive ingredients, hypersensitivity.

(Aust Prescr 2011;34:112–4)

Introduction

The word *excipient* is derived from the Latin *excipere*, meaning 'to except', which is simply explained as 'other than'. Pharmaceutical excipients are basically everything other than the active pharmaceutical ingredient. Ideally, excipients should be inert, however, recent reports of adverse reactions have suggested otherwise.

What are excipients doing in medicines?

The best new therapeutic entity in the world is of little value without an appropriate delivery system.[1] Today, medicines are available in many dosage forms including tablets, capsules, oral liquids, topical creams and gels, transdermal patches, injectable products, implants, eye products, nasal products, inhalers and suppositories. Pharmaceutical excipients are substances that are included in a pharmaceutical dosage form not for their direct therapeutic action, but to aid the manufacturing process, to protect, support or enhance stability, or for bioavailability or patient acceptability. They may also assist in product identification and enhance the overall safety or function of the product during storage or use.[2]

Thousands of different excipients are used in medicines and make up, on average, about 90% of each product. They represent a market value of €3 billion (almost $4 billion) accounting for 0.5% of the total pharmaceutical market according to industry experts.[3]

Common excipients used in tablets

The list of purposes for which excipients are used, as defined in international pharmacopoeias, is extremely long. Many excipients have more than one use, which can be an advantage since it reduces the number of excipients needed and minimises the risk of interactions between them.

Tablets are the most widely used dosage form. Their manufacture can be a complex process and considerable ingenuity and formulation expertise are required to produce a product that will be stable during storage, transport and handling, yet will release its active pharmaceutical ingredient as required once ingested.[4] Various excipients are used to achieve this (Table 1).[2]

Adverse reactions to excipients

Ideally, an excipient is pharmacologically inactive, non-toxic, and does not interact with the active ingredients or other excipients. However, in practice few excipients meet these criteria. Toxicity may relate to compounds used as excipients in the final dosage form, or to residues of compounds (such as solvents) used during the manufacturing process.[2] Table 2 shows examples of adverse reactions that have occurred with excipients.

Colouring agents

Owing to their widespread and relatively large use in food, a number of colours in current use have been associated with adverse effects, although in a relatively small number of people.[5] The role of food additives in hyperactive behaviour has been debated for many years. In 2007 a study was published linking the use of six colours (tartrazine, quinoline yellow, sunset yellow, carmoisine, ponceau 4R and allura red) with behavioural problems in children. However, after reviewing the results of the study, the European Food Standards Agency concluded that no change in legislation was needed.[5]

Identifying reactions to excipients in practice

When presented with a patient who has an adverse reaction, it is important to be aware that reactions may not always be due

Table 1

Common excipients used in tablets

Excipient	Function	Examples
Diluents	Provide bulk and enable accurate dosing of potent ingredients	Sugar compounds e.g. lactose, dextrin, glucose, sucrose, sorbitol Inorganic compounds e.g. silicates, calcium and magnesium salts, sodium or potassium chloride
Binders, compression aids, granulating agents	Bind the tablet ingredients together giving form and mechanical strength	Mainly natural or synthetic polymers e.g. starches, sugars, sugar alcohols and cellulose derivatives
Disintegrants	Aid dispersion of the tablet in the gastrointestinal tract, releasing the active ingredient and increasing the surface area for dissolution	Compounds which swell or dissolve in water e.g. starch, cellulose derivatives and alginates, crospovidone
Glidants	Improve the flow of powders during tablet manufacturing by reducing friction and adhesion between particles. Also used as anti-caking agents.	Colloidal anhydrous silicon and other silica compounds
Lubricants	Similar action to glidants, however, they may slow disintegration and dissolution. The properties of glidants and lubricants differ, although some compounds, such as starch and talc, have both actions.	Stearic acid and its salts (e.g. magnesium stearate)
Tablet coatings and films	Protect tablet from the environment (air, light and moisture), increase the mechanical strength, mask taste and smell, aid swallowing, assist in product identification. Can be used to modify release of the active ingredient. May contain flavours and colourings.	Sugar (sucrose) has now been replaced by film coating using natural or synthetic polymers. Polymers that are insoluble in acid, e.g. cellulose acetate phthalate, are used for enteric coatings to delay release of the active ingredient.
Colouring agents	Improve acceptability to patients, aid identification and prevent counterfeiting. Increase stability of light-sensitive drugs.	Mainly synthetic dyes and natural colours. Compounds that are themselves natural pigments of food may also be used.

Table 2

Common examples of adverse reactions to excipients [2,5]

Excipient	Function	Caution in practice
Tartrazine	Colouring agent	Reported cases of hypersensitivity, and hyperkinetic activity in children
Aspartame	Sweetener	Caution in patients with phenylketonuria
Benzalkonium chloride	Preservative	Bronchoconstriction (nebuliser solutions) and ocular toxicity (soft contact lens solutions)
Sodium metabisulphite	Antioxidant	Hypersensitivity, including bronchospasm and anaphylaxis, are reported for all sulphites
Propyl gallate	Antioxidant	Contact sensitivity and skin reactions
Lactose	Tablet filler	Caution in patients with galactosaemia, glucose-galactose malabsorption syndrome, or lactase deficiency
Sesame oil	Oil (injections)	Hypersensitivity reactions reported
Lanolin (wool fat)	Emulsifier (topical products)	Skin hypersensitivity reactions, caution in patients with known sensitivity

to the active ingredient (Fig. 1). They are more likely to occur if the patient has an existing sensitivity to similar ingredients, or is on multiple medicines, or when the quantity of excipients may be high relative to body weight, for example in premature babies.[6] Excipients present in their current and past medication history should also be considered. This will help to rule out which ingredients may be causing the adverse effects.

Finding information on excipients

The Consumer Medicine Information leaflet, which is often readily available online (www.nps.org.au/search_by_medicine_name), will have a list of the excipients included in the medicine. This list can be found under 'Product description' and may be titled 'Other ingredients' or 'This product also contains...'

The Pharmacopoeias (US Pharmacopoeia, British Pharmacopoeia) contain monographs for many excipients. However, not all excipients reach these texts due to companies withholding data because of concerns about releasing proprietary information. The Handbook of Pharmaceutical Excipients contains monographs for 340 excipients, with each monograph including a 'Safety' section that presents adverse reactions that have been reported.[5] Martindale[2] has safety information on excipients and is a required text for hospital and community pharmacists. The monographs for each excipient contain a section on adverse effects reviewed from the literature.

Conclusion

Medicines contain ingredients other than the active drug that are essential for their manufacture, stability and function. These ingredients should be inert, however they do have the potential to cause adverse effects in sensitive individuals. Identifying such reactions and finding the appropriate safety information will help to ensure a safe outcome for the patient.

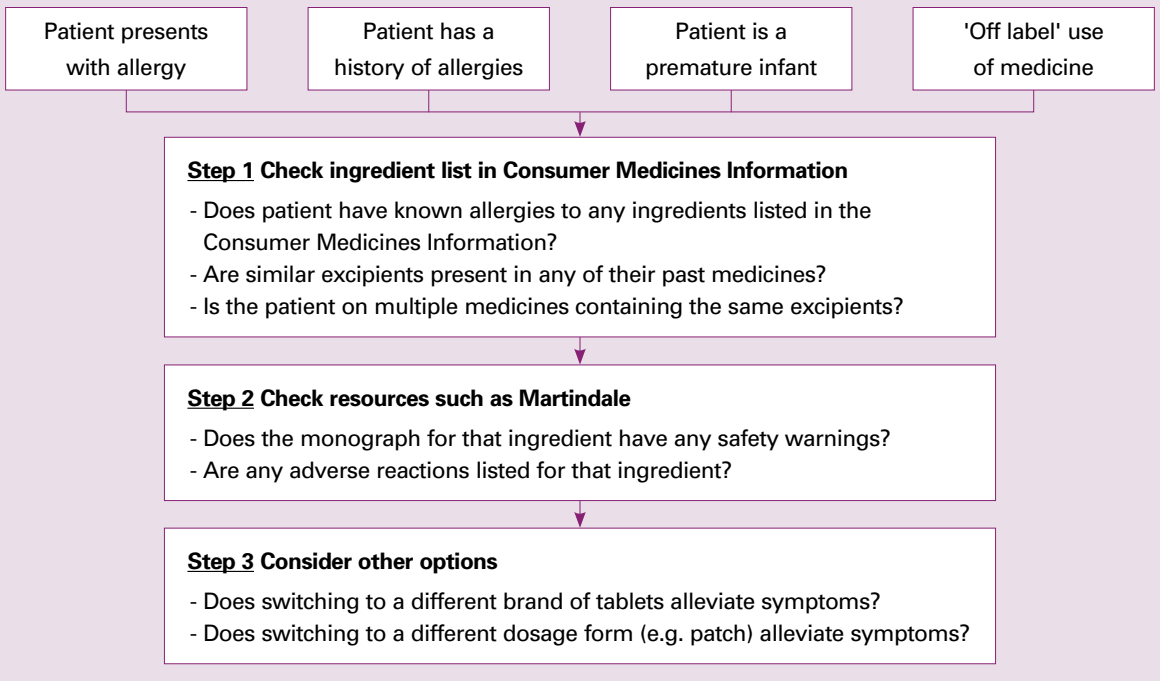
References

1. Augsburger LL, Zellhofer MJ. Tablet formulation. In: Swarbrick J, Boylan JC, editors. Encyclopedia of pharmaceutical technology. 3rd ed. New York: Marcel Dekker; 2006.
2. Martindale: The complete drug reference. 37th ed. London: Pharmaceutical Press; 2011. (electronic and hard copy available)
3. International Excipients Certification Project: minimize risks – maximize benefits. London: Pharmaceutical Quality Group; 2009.
4. Armstrong NA. Tablet manufacture. In: Swarbrick J, Boylan JC, editors. Encyclopedia of pharmaceutical technology. 3rd ed. New York: Marcel Dekker; 2006.
5. Rowe RC, Sheskey PJ, Quinn ME, editors. Handbook of pharmaceutical excipients. 6th ed. London: Pharmaceutical Press; 2009.
6. What are excipients doing in medicinal products? Drug Ther Bull 2009;47:81-4.

Conflict of interest: none declared

Fig. 1

Pharmaceutical excipients – managing the risk in practice



Managing aggressive and violent patients

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Summary

All healthcare workers, especially general practitioners and staff in emergency departments, are likely to encounter aggression and violence. This behaviour may be caused by a medical illness, a psychiatric illness or drug intoxication or withdrawal. These problems can occur in combination. It is important that a diagnosis is made, but in some cases the patient may need sedation before they can be examined. If non-drug management, such as de-escalation techniques, does not work, a benzodiazepine or antipsychotic can be considered. It is essential that sedated patients are monitored for signs of oversedation. Practice design and policies as well as staff training can help to reduce the risk of violence.

Key words: antipsychotics, benzodiazepines, de-escalation, sedation.

(Aust Prescr 2011;34:115–8)

Introduction

Aggression and violence may be a manifestation of underlying psychiatric disorders. These include drug psychosis, delusional states, mania and personality disorder. Some patients try to use aggression as means of achieving a particular goal, such as being seen earlier or obtaining drugs.

Medical illness may result in behaviour disturbance. It can also coexist in patients with mental health, drug and alcohol problems or other conditions (see Box 1).

Prevention

Some simple preparatory steps may be helpful in averting trouble or in dealing with difficult situations as they arise. A sign should make clear that aggression and violence are not tolerated. The practice or emergency department should have a functioning duress system and protocols for responding. Ideally the assessment area should have no dangerous objects easily at hand and should have more than one exit. Some medical practices and hospitals have systems to alert staff that a presenting patient may be difficult to manage, or pre-agreed management plans for particular patients.

A number of studies have found benefits from education and training programs to help healthcare workers develop skills and increase confidence in managing these situations. Staff should be advised that their personal safety is a priority. They should not see patients for a late appointment when they are alone. It is appropriate to avoid confrontation and to call for help if they feel at risk. Keeping patients informed of waiting times and providing a comfortable waiting area is helpful.

Clinical scenarios

An elderly woman with known mild dementia is brought in by her family as she has become increasingly agitated and is confused and aggressive. A calming low stimulus environment assists the initial assessment. The underlying cause turns out to be a urinary tract infection, dehydration and hyponatraemia. Treatment with antibiotics and appropriate fluids in hospital returns her to her usual state.

A drug-affected young man is brought in by friends as he has become increasingly irrational and aggressive. An ambulance

Box 1
Medical conditions which can cause aggression

Hypoxia, hypercarbia – pneumonia, worsening chronic airway disease

Hypoglycaemia – diabetes, malnourished alcoholic

Cerebral insult – stroke, tumour, seizure, encephalitis, meningitis, trauma

Sepsis – systemic sepsis, urine infection in the elderly

Metabolic disturbance – hyponatraemia, thiamine deficiency, hypercalcaemia

Organ failure – liver or renal failure

Withdrawal – alcohol, benzodiazepines

Drug effects – amphetamine, steroids, alcohol, prescribed medications and interactions

and police are called, a schedule is written, he is taken to the emergency department for a short-stay mental health and drug and alcohol admission, and sedated. The diagnosis is methamphetamine intoxication.

A middle-aged man with a long-standing brain injury is often threatening and disruptive while in the waiting room for his regular attendances. His future visits are always scheduled as an early long appointment and it is made clear he must be accompanied by his carer.

A 65-year-old man is tremulous, agitated and aggressive. He seems irrational and is experiencing visual hallucinations. He is admitted to hospital where the diagnosis is acute alcohol withdrawal. He is given fluids, nutrition, thiamine and diazepam in relatively high doses according to an alcohol withdrawal protocol. Antipsychotics and other drugs which lower the seizure threshold are avoided.

Managing an acute episode

Before treating the behavioural disturbance consider what may be causing it.

Assessment

Look for clues that the behaviour disturbance may be due to an organic cause, for example a previously stable elderly patient presenting with behaviour change may have sepsis, stroke, trauma or a drug interaction. The history is relevant, for example a patient with known epilepsy may present with post-ictal confusion, or a patient who is taking long-term anticoagulation may have had a head injury.

A general physical examination including neurological examination looking for higher function, orientation, meningism and localising signs should be performed as soon as possible. Measure the pulse, blood pressure, temperature, respiratory rate and if possible, oxygen saturation and blood glucose.

The clinical scenario will determine the extent of investigation required to exclude an organic cause or contributing comorbidity. Initial basic blood tests such as a full blood count, chemistry, blood sugar, liver and renal function are appropriate if results can be quickly obtained. Further tests including blood alcohol level, urine drug screen, urinalysis and culture and cerebral CT scanning may be required if the patient is hospitalised.

Common clues that a psychiatric cause is likely include past history of mental illness, drug use or alcoholism, current medications, general physical appearance including self-care, appropriateness of mood and engagement, manner and content of speech, posture and movement. Wherever possible collateral and corroborating history should be sought from family, friends and healthcare providers.

Box 2

De-escalation

- Use an empathic non-confrontational approach, but set boundaries
- **Listen** to the patient, but avoid giving opinions on issues and grievances beyond your control
- Offer food, drink and a place to sit
- Avoid excessive stimulation
- Avoid aggressive postures and prolonged eye contact
- Recruit family, friends, case managers to help
- Address medical issues especially pain and discomfort
- Try to ascertain what the patient actually wants and the level of urgency

Non-pharmacological management

Some basic verbal de-escalation and distraction techniques can be used (see Box 2). It is often safer to call for help early and to remain at a safe distance until support, such as police and ambulance, arrives. A show of force may persuade the patient to cooperate.

Suspected or identified medical problems must be addressed before treating the behavioural disturbance. If the patient is uncooperative they may need to be scheduled if they are a danger to themselves or others and mental illness is suspected. While there are state by state differences in the Mental Health Act the principles are very similar. When involuntary care is needed, an initial schedule is written to allow safe care and transport to a mental health unit (this may be an emergency department, psychiatric unit or hospital). It should be remembered that in some jurisdictions a Mental Health Schedule can now be written by police and ambulance officers as well as by a doctor, and that it is a legal order that a patient be taken to a place where they can be assessed by a mental health specialist. If there is a potentially serious medical emergency it may be necessary to provide treatment without immediate scheduling of an uncooperative patient. Restraint and forced sedation should be considered a last resort.

Pharmacological management (Table 1)

In some situations sedation may be appropriate. The choice of drug and dosage used is influenced by the patient's age, size, other prescribed or non-prescribed drugs taken, known illness such as long-term benzodiazepine abuse, alcoholism, liver or renal failure.

Physical signs such as hypotension and hyperthermia indicate a need for resuscitation as well as adjustment of drug choice and dosage. Position the patient appropriately, for example lay them

Table 1

Drugs for sedation

Drug	Usual adult dose	Adverse events and management
Diazepam	5–10 mg oral or intravenously. Max 30 mg per event. Longer acting than midazolam.	Oversedation – maintain airway, coma position, provide oxygen Hypotension – lay down, intravenous fluids Airway or respiratory compromise – support airway, give oxygen Parodoxical reactions
Lorazepam	2 mg. Max 10 mg in 24 hours.	
Midazolam	5–10 mg intramuscularly. Max 20 mg per event. Rapid onset.	
Olanzapine	5–10 mg oral. Max 30 mg per event.	Hypotension – lay down, intravenous fluids Seizure – coma position, clear airway, benzodiazepines
Haloperidol	5–10 mg intramuscularly. Max 20 mg per event.	Acute dystonia – benztropine 2 mg oral or intramuscularly or intravenously Hypotension – lay down, intravenous fluids

Note: Lower doses (titrate to effect) should be used in those who are elderly, have low body weight, are dehydrated, have significant other medical illnesses or have ingested significant amounts of alcohol or other drugs. All sedatives can cause oversedation.

flat, elevate their legs if hypotensive, and ensure a safe airway position if they are post-ictal. When possible administer oxygen, intravenous fluids and glucose (plus thiamine if Wernicke's encephalopathy is a possibility). Gather information, continue to manage clinically and arrange transfer if indicated.

For disturbed patients, in the first instance an oral sedative should be offered in a non-threatening collaborative way: 'I know you feel very distressed and this will help while we work out what to do next'. Oral diazepam 5 mg or olanzapine 5 mg are common choices.

The dosage should be titrated to clinical effect whilst watching for over-sedation and other adverse effects such as hypotension in the patient who has ingested other drugs or alcohol, is dehydrated or has a medical illness.

Parenteral sedation is more difficult although a number of patients may accept this if it is offered: 'You will feel better far more quickly if I can give you this now'. Forced parenteral sedation is not usually possible outside hospital. It requires trained staff in numbers (usually five or more) to either convince the patient to accept without violent struggle or to restrain the patient while medication is given. This needs training and equipment such as gowns, gloves and face masks and requires some skill to avoid injury to the patient or staff.

All patients who have been given parenteral sedation will require a level of monitoring and ambulance transfer to hospital should be arranged as soon as possible. The need for transfer and monitoring becomes even more urgent when higher doses of benzodiazepines are used or when other drugs such as haloperidol have also been given.

Benzodiazepines

Increasing doses of benzodiazepines produce a progressive spectrum of effect from anxiolysis and anticonvulsant effects to amnesia, sedation and eventually hypnosis and anaesthesia. Toxicity is usually related to very high doses and results in excessive sedation and airway obstruction. While benzodiazepines are essentially safe drugs, at very high doses or when given to a patient with hypovolaemia or other significant physiological compromise, they may contribute to cardiovascular and respiratory depression. Extra care should be taken if there is a possibility that the patient has consumed other sedating drugs (for example methadone).

Diazepam is used as an oral or intravenous preparation (not for intramuscular injection). It is quickly absorbed, but has a long half-life (up to 36 hours or more) so it can accumulate after repeated doses. Lorazepam has a shorter half-life (12–16 hours).

Midazolam is water-soluble and can be given intravenously or intramuscularly. It has a rapid onset, an elimination half-life of 2–4 hours and a much steeper dose-response curve than diazepam.

Antipsychotics

Olanzapine is an 'atypical antipsychotic' which can be given orally or as an intramuscular injection. It has a rapid onset of action with a half-life of about 30 hours. In clinical trials doses of 5–10 mg have been effective. A second dose should not be given for at least two hours. Olanzapine should not be given with benzodiazepines because of the risk of cardiorespiratory

depression. Extrapyramidal effects may occur but are less likely than with typical antipsychotic drugs. Other potential adverse effects include excessive drowsiness, hypotension and tachycardia.

Haloperidol can be given as an intramuscular injection. It has a rapid onset of action with effects lasting two to four hours. Toxicity manifests as over-sedation or hypotension. There may be extrapyramidal adverse effects such as dystonia (or even neuroleptic malignant syndrome) and it may lower the seizure threshold.

Post-sedation management

In almost all circumstances the patient will need to be transferred for further medical and then psychiatric assessment as soon as possible. After sedation the patient must be closely observed and monitored. They should be managed in a safe position with a clear airway and if possible supplemental oxygen given. The degree of sedation (for example as assessed by the Glasgow Coma Score), pulse, temperature, blood pressure, respiratory rate and pupils should be checked. If equipment is available check the blood glucose (or give glucose if hypoglycaemia is possible but glucose cannot be checked), ECG rhythm and oxygen saturation. A physical examination looking for possible organic medical illness should be performed.

Arranging urgent transfer and managing a patient post-sedation is critical. An awareness of the potential adverse effects and possibility of overdosage is essential. Documentation including recorded observations is required.

Conclusion

Preparedness involves a level of awareness and some planning for the possibility of aggression and violence, in particular facility design, policies and procedures and staff training. It should always be remembered that organic illness can mimic or coexist with psychiatric illness and that both may cause behaviour disturbance. Verbal de-escalation is a useful technique.

In the uncommon situation that sedation is needed in a non-hospital setting, an early call for police and ambulance assistance should be made. Oral sedation can be effective, but intramuscular or intravenous medication is needed in some cases. Post-sedation physical assessment and monitoring is essential. A review of practice preparedness and staff debriefing should be undertaken after an event.

Further reading

Mental health for emergency departments: a reference guide. NSW Health. 2009. www.health.nsw.gov.au/resources/mhdao/pdf/mhemergency.pdf [cited 2011 Jul 5]

Isbister GK, Calver LA, Page CB, Stokes B, Bryant JL, Downes MA. Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study. Ann Emerg Med 2010;56:392-401.

Nobay F, Simon BC, Levitt MA, Dresden GM. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. Acad Emerg Med 2004;11:744-9.

Kynoch K, Wu CJ, Chang AM. The effectiveness of interventions in the prevention and management of aggressive behaviours in patients admitted to an acute hospital setting: a systematic review. JBI Lib of Syst Rev 2009;7:175-223.

Nisselle P. Difficult doctor-patient relationships. Melbourne: Royal Australian College of General Practitioners; 2000. www.racgp.org.au/runningapractice/relationships [cited 2011 Jul 4].

Krakowski M. Violent behavior: Choosing antipsychotics and other agents. Curr Psychiatr 2007;6;63-70.

Therapeutic Guidelines: Psychotropic. Version 6. Melbourne: Therapeutic Guidelines Limited; 2008.

Caplan G. Managing delirium in older patients. Aust Prescr 2011;34:16-8

Conflict of interest: none declared

Self-test questions

The following statements are either true or false

(answers on page 123)

5. When sedation is indicated for an aggressive patient, an oral drug should be considered first.
6. Parenteral diazepam should not be used intramuscularly to sedate a disturbed patient.

Anaphylaxis – new wallchart with this issue

Included with this issue, for Australian readers, is a laminated A3 wallchart titled 'Anaphylaxis: Emergency management for health professionals'.

The *Australian Prescriber* anaphylaxis wallchart is revised and published every few years. As in previous editions, it is published with the assistance and endorsement of several specialist Colleges.

Copies can be printed from the website. For further laminated A3 copies, Australian readers can contact the *Australian Prescriber* office.

Online anaphylaxis training is available free of charge from the website of the Australasian Society of Clinical Immunology and Allergy (www.allergy.org.au)

New drugs

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

Fampridine

Fampyra (Biogen)

10 mg modified release tablets

Approved indication: multiple sclerosis

Australian Medicines Handbook section 16.6

Fampridine is a potassium channel blocker indicated for symptomatic improvement of walking in adults with multiple sclerosis, including relapsing remitting, secondary progressive, progressive relapsing and primary progressive. Currently there are no other drugs for this indication.

Fampridine is thought to increase conduction in demyelinated nerves by inhibiting potassium channels. It can be used on its own or with other treatments for multiple sclerosis, including immunomodulatory drugs.

The efficacy of fampridine has been studied in two phase III trials.[1,2] In the first trial, 301 patients with walking difficulties associated with multiple sclerosis were randomised to fampridine 10 mg twice daily or placebo, for 14 weeks. The primary outcome was based on changes in walking speed over 25 feet (7.6 m). A responder was defined as someone who consistently walked faster during treatment compared to baseline. In the fampridine group, 35% (78/224) of patients responded compared to only 8% (6/72) in the placebo group. The average increase in walking speed of people who responded to fampridine was 0.51 feet/second (approximately 15.5 cm/second) (25% faster).[1]

These results were confirmed in a second similarly designed trial in which 43% (51/119) of patients responded to fampridine compared to only 9% (11/118) of patients to the placebo. On average, patients who responded to fampridine walked 24.7% faster.[2]

Urinary tract infection was a very common adverse event with fampridine. Neurological effects were common and included insomnia, balance disorder, dizziness, headache and asthenia. Falls and severe anxiety were also reported. In a trial of 206 patients, serious events were more common at higher doses (4% with placebo, 0% with 10 mg, 8% with 15 mg and 12% with 20 mg fampridine). One patient discontinued the 15 mg dose of fampridine because of nausea and dizziness and five patients discontinued the 20 mg dose – two patients had seizures, one developed abnormal coordination, one had chest discomfort and headache and one patient had blurred vision, chest discomfort, balance disorder, headache and paraesthesia.[3]

Seizures have also occurred postmarketing and fampridine is contraindicated in patients with a history of seizures. Because of this potential toxicity, patients should not take a double or extra dose when a dose is missed. Tablets should be taken whole and not crushed or chewed.

Following oral administration, peak concentrations of fampridine are reached after 3–4 hours. It is primarily excreted unchanged in the urine. The elimination half-life is normally 5.2–6.5 hours, but is prolonged in patients with renal impairment. Fampridine is therefore contraindicated in moderate to severe renal impairment. If renal function has not been assessed, creatinine clearance should be estimated before starting treatment. This is particularly important in the elderly. In patients with mild impairment, monitoring of renal function should be considered.

This drug has not been tested in pregnant and lactating women. As fampridine is lipophilic, it may be excreted in human milk.

Fampridine is the first drug to help improve walking in patients with multiple sclerosis. However in the trials, less than half of the patients (35–43%) consistently walked faster (increase of 15.5 cm/second) after taking fampridine. Doctors and their patients have to consider whether this potential benefit is worth the risk of seizures and other serious neurological adverse effects. The safety and efficacy of fampridine during an exacerbation of multiple sclerosis is not known as these patients were excluded from the trials. Fampridine should only be continued if the patient responds within eight weeks of treatment.

T manufacturer provided the product information

References *†

1. Goodman AD, Brown TR, Krupp LB, Schapiro RT, Schwid SR, Cohen R, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet 2009;373:732-8.
2. Goodman AD, Brown TR, Edwards KR, Krupp LB, Schapiro RT, Cohen R, et al. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. Ann Neurol 2010;68:494-502.
3. Goodman AD, Brown TR, Cohen JA, Krupp LB, Schapiro R, Schwid SR, et al. Dose comparison trial of sustained-release fampridine in multiple sclerosis. Neurology 2008;71:1134-41.

Ferric carboxymaltose

Ferinject (Vifor Pharma)

2 mL solution containing 100 mg iron and 10 mL solution containing 500 mg iron for infusion

Approved indication: iron deficiency

Australian Medicines Handbook section 7.5.2

Intravenous ferric carboxymaltose is indicated for iron deficiency when oral preparations are ineffective or not tolerated. The molecule consists of an iron-hydroxide core chelated in a carbohydrate shell. After dilution and intravenous administration, it is found in the reticuloendothelial system of the liver, spleen and bone marrow and has a terminal half-life of 7–12 hours. Iron is incorporated into red blood cells 6–9 days after injection.

In a trial of 255 patients with chronic kidney disease and iron deficiency anaemia, ferric carboxymaltose given as an intravenous infusion (up to three doses totalling 2000 mg elemental iron over a month) was compared to oral ferrous sulfate (65 mg elemental iron three times a day). The majority of patients were not taking erythropoiesis-stimulating drugs. After eight weeks, more patients receiving ferric carboxymaltose had at least a 1 g/100 mL increase in haemoglobin than those receiving oral iron (60.4% vs 34.7% of patients). This was regardless of whether or not they were receiving erythropoiesis-stimulating drugs.[1]

Ferric carboxymaltose has also been compared to iron sucrose in patients with chronic kidney disease who were on haemodialysis. All patients were receiving stable doses of an erythropoiesis-stimulating drug. Both treatments were given at a dose of 200 mg iron intravenously two to three times a week. After four weeks, haemoglobin levels had risen by at least 1 g/100 mL in 44.1% (52/118) of patients in the ferric carboxymaltose group and 35.3% (41/116) of those in the iron sucrose group. At the time of writing, this study was not published in full.

Ferric carboxymaltose has also been assessed in other conditions. In a trial of 200 patients with Crohn's disease or ulcerative colitis, treatment with up to three intravenous infusions of ferric carboxymaltose one week apart (up to 1000 mg iron a week) was found to be non-inferior to oral ferrous sulfate (100 mg iron twice a day). After 12 weeks, median haemoglobin concentrations had increased from 8.7 to 12.3 g/100 mL with ferric carboxymaltose and from 9.1 to 12.1 g/100 mL with oral iron.[2]

Ferric carboxymaltose was also effective in treating postpartum iron deficiency.[3-5] In a six-week comparative trial of 291 women with anaemia (haemoglobin ≤10 g/100 mL) after giving birth, 91.4% of women who received ferric carboxymaltose had haemoglobin concentrations greater than 12 g/100 mL. This was compared with 66.7% of women who received oral ferrous sulfate (65 mg iron three times a day).[3]

Generally, the most common adverse reactions to ferric carboxymaltose were headache, dizziness, nausea, abdominal pain, constipation, diarrhoea, rash and injection site reaction. These were reported by less than 10% of study participants. Decreased blood phosphorus and increased alanine aminotransferase also occurred in some patients. In patients with chronic kidney disease, peripheral oedema (6.1%), hyperkalaemia (4.1%) and urinary tract infection (3.4%) were the most common events.[1] In a safety cohort of 899 patients, there were five deaths. Causes included pulmonary tuberculosis, heart failure, peripartum cardiomyopathy leading to heart failure, myocardial infarction and cardiac arrest.

Transfer into human milk is negligible (≤1%) so breastfeeding is not a contraindication. In a safety analysis of 229 breastfed infants whose mothers were receiving ferric carboxymaltose, adverse reactions included erythema (5 babies), constipation (3 babies), diarrhoea (3 babies), nasopharyngitis (2 babies), pallor and flatulence (2 babies), abdominal pain (1 baby) and upper respiratory tract infection (1 baby).

This drug is contraindicated for anaemia not caused by iron deficiency, or if there is evidence of iron overload or disturbances of iron use. It should also not be used in the first trimester of pregnancy as fetal abnormalites have been observed in preclinical studies, and caution is urged in the second and third trimesters. In patients with hepatic impairment, ferric carboxymaltose should only be used after careful assessment and monitoring.

Anaphylaxis has occurred after intravenous injections of iron preparations so resuscitation facilities should be available during administration of ferric carboxymaltose.

The cumulative dose of ferric carboxymaltose required to restore iron levels should be individually calculated for each patient. As there is a risk of iron overload, patients should have their red cell indices and serum ferritin monitored regularly.

Evidence from the trials suggests that ferric carboxymaltose is an effective alternative for treating iron deficiency when oral iron is not an option. However, it is not clear if it will have advantages over other parenteral iron formulations such as iron sucrose.

T T T manufacturer provided clinical evaluation

References A

1. Qunibi WY, Martinez C, Smith M, Benjamin J, Mangione A, Roger SD. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis-dependent chronic kidney disease patients. Nephrol Dial Transplant 2011;26:1599-607.

2. Kulnigg S, Stoinov S, Simanenkov V, Dudar LV, Karnafel W, Garcia LC, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: The ferric carboxymaltose (Ferinject) randomized controlled trial. Am J Gastroenterol 2008;103:182-92.
3. Seid MH, Derman RJ, Baker JB, Banach W, Goldberg C, Rogers R. Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial. Am J Obstet Gynecol 2008;199:435.
4. Van Wyck DB, Martens MG, Seid MH, Baker JB, Mangione A. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia; a randomized controlled trial. Obstet Gynecol 2007;110:267-78.
5. Breymann C, Gliga F, Bejenariu C, Strizhova N. Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. Int J Gynaecol Obstet 2008;101:67-73.

Palonosetron hydrochloride

Aloxi (Specialised Therapeutics)

vials containing 250 microgram/5 mL

Approved indication: prevention of nausea and vomiting

Australian Medicines Handbook section 12.3.2

Patients having cytotoxic chemotherapy are likely to develop severe nausea and vomiting. To try and prevent these adverse reactions patients are given antiemetic drugs. These include the serotonin ($5HT_3$) receptor antagonists dolasetron, granisetron, ondansetron and tropisetron.

Like the other members of the class palonosetron has a high affinity for the $5HT_3$ receptor. Blocking this receptor reduces the response to the emetogenic stimulus induced by cytotoxic drugs.

To prevent the nausea and vomiting, palonosetron is given intravenously 30 minutes before chemotherapy. Plasma concentrations decline rapidly, but there is a long elimination half-life (mean 40 hours). Palonosetron is metabolised by several enzymes including cytochrome P450 2D6, but 40% of the dose is excreted unchanged in the urine. No dosage reductions are recommended for patients with hepatic or renal impairment.

The approved indication for palonosetron was mainly supported by two trials in patients having moderately emetogenic chemotherapy[1,2] and one trial in patients having highly emetogenic chemotherapy.[3]

In the highly emetogenic study, 673 patients were randomised to receive different doses of palonosetron or a single dose of ondansetron. After 24 hours, 57% of the patients given ondansetron had experienced no vomiting or had not needed rescue medication. Among the patients given 250 microgram of palonosetron, 59% had a complete response.[3]

Ondansetron was also included in a study of moderately emetogenic chemotherapy involving 570 patients. There was a complete response in 69% of the patients given ondansetron and in 81% of those given 250 microgram of palonosetron. This difference was statistically significant.[1]

The other study of moderately emetogenic chemotherapy randomised 592 patients to take dolasetron or one of two doses of palonosetron. There was a complete response in 53% of the patients given dolasetron and in 63% of those given 250 microgram of palonosetron.[2]

The pattern and frequency of adverse reactions to palonosetron was similar to that of ondansetron and dolasetron. Headache and gastrointestinal symptoms, such as constipation, were the most frequently reported problems. Although palonosetron did not cause extensive QT prolongation in the trials, caution is advised when giving the drug to patients who are at risk of QT prolongation.

The trials show that palonosetron is not inferior to other $5HT_3$ antagonists for the prevention of acute vomiting. The longer half-life may help in reducing the incidence of delayed nausea and vomiting,[4] but the safety and efficacy of repeated dosing has not been evaluated.

T manufacturer provided the product information

References *†

1. Gralla R, Lichinitser M, Van der Vegt S, Sleeboom H, Mezger J, Peschel C, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol 2003;14:1570-7.
2. Eisenberg P, Figueroa-Vadillo J, Zamora R, Charu V, Hajdenberg J, Cartmell A, et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel $5\text{-}HT_3$ receptor antagonist: results of a phase III, single-dose trial versus dolasetron. Cancer 2003;98:2473-82.
3. Aapro MS, Grunberg SM, Manikhas GM, Olivares G, Suarez T, Tjulandin SA, et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol 2006;17:1441-9.
4. Mattiuzzi GN, Cortes JE, Blamble DA, Bekele N, Xiao L, Cabanillas M, et al. Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia. Cancer 2010;116:5659-66.

Vinflunine

Javlor (Pierre Fabre Medicament)

vials containing 50 mg/2 mL, 100 mg/4 mL or 250 mg/10 mL

Approved indication: bladder cancer

Australian Medicines Handbook section 14.1.8

Vinflunine is indicated for advanced or metastatic transitional cell carcinoma of the urothelial tract. It is intended as a second-line treatment for patients whose disease has progressed despite platinum-containing therapy. The median survival of these patients is four months and currently treatment focuses on best supportive care.

Vinflunine is a vinca alkaloid. Like other drugs in this class, it works by binding to tubulin and inhibiting its polymerisation into microtubules. This ultimately leads to mitotic arrest and apoptosis of the cell.

In early phase II trials, patients who had progressing or recurring disease after treatment with a platinum-containing regimen were given intravenous vinflunine 320 mg/m^2 every three weeks. Of the 202 patients treated, 31 (15%) had a partial response and 89 (44%) had stable disease. The median progression-free survival was 2.8–3 months and overall survival was 6.6–8.2 months.[1,2]

In a larger phase III comparative trial, 370 patients were randomised to receive best supportive care with or without vinflunine (320 mg/m^2 every three weeks). Although the median survival was longer for patients receiving vinflunine compared to those receiving supportive care alone (6.9 months vs 4.6 months), the difference was not statistically significant (p=0.287). However, a *post hoc* analysis suggested a possible treatment effect (p=0.04). Significantly more people responded to vinflunine than to supportive care alone – 8.6% vs 0% had a partial response and 46.5% vs 27.1% had stable disease. Also, the median duration of disease control was significantly longer for vinflunine than for supportive care alone (5.7 vs 4.2 months), as was progression-free survival (3 vs 1.5 months). The median duration of treatment with vinflunine was 9.5 weeks. This was similar in the control group.[3]

Myelosuppression is a considerable problem with vinflunine. Approximately half of the 450 patients in the trials developed severe (grades 3–4) neutropenia or leucopenia. Anaemia and thrombocytopenia were also common but, in general, less severe. Infections were frequent and seven patients died from an infection that was a complication of neutropenia. Recent or current infection is a contraindication to vinflunine use. Complete blood counts should be measured before each infusion and the dose may need to be reduced or stopped if the patient has signs of toxicity.

Gastrointestinal symptoms are frequent with vinflunine. Severe constipation (15.3%) and ileus (2.2%) occurred in some patients and dose reduction was required. Alopecia (28.7%) and peripheral sensory neuropathy (9.8%) were also frequently reported.

Cardiovascular effects have occurred with vinflunine and it should be used with caution in patients with a pre-existing heart condition. One patient died of myocardial infarction and another of cardiopulmonary arrest. Vinflunine may prolong the QT interval and concomitant use of drugs that prolong the QT interval should be avoided.

Vinflunine should be given as an intravenous infusion. Accidental intrathecal use of this class of drug has been fatal. After infusion, vinflunine is extensively distributed in the tissues. It is metabolised by cytochrome P450 3A4 and excreted in the faeces and urine. The dose of vinflunine should be reduced in patients aged 75 and over, and in those with impaired liver (mild to moderate) or kidney function (moderate to severe). Vinflunine is not recommended in severe hepatic impairment. Concomitant use of drugs that inhibit or induce CYP 3A4 should be avoided.

Although vinflunine is indicated for second-line treatment of advanced bladder cancer, patients and their doctors have to consider whether the potential modest increase in life expectancy is worth the risk of developing severe adverse effects. A review of vinflunine from a French drug bulletin concluded that in practice 'it is better to focus on individually tailored palliative care'.[4]

T manufacturer provided the AusPAR and the product information

References †A

1. Culine S, Theodore C, De Santis M, Bui B, Demkow T, Lorenz J, et al. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. Br J Cancer 2006;94:1395-401.
2. Vaughn DJ, Srinivas S, Stadler WM, Pili R, Petrylak D, Sternberg CN, et al. Vinflunine in platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma: results of a large phase 2 study. Cancer 2009;115:4110-7.
3. Bellmunt J, Théodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454-61.
4. Vinflunine. No benefit for bladder cancer patients despite statistical manipulation. Prescrire Int 2011;20:11-3.

The T-score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

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

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

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)

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