Australian Prescriber

CELEBRATING 30 YEARS

VOLUME 28 | NUMBER 5 | AN INDEPENDENT REVIEW | OCTOBER 2005

1975–1977

1977–1978

1979

CELEBRATING 30 YEARS

1980

1981–1983

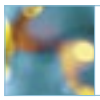
1984–1993

1994–1999

2000–2003

2004

CONTENTS



Editorials

Suicide and antidepressants in children

Jon N. Jureidini, Head, Department of Psychological Medicine, Women's and Children's Hospital, North Adelaide, and Anne L. Tonkin, Associate Professor, Department of Clinical and Experimental Pharmacology, University of Adelaide, Adelaide

Key words: children, depression.

(Aust Prescr 2005;28:110–11)

- Antidepressants are not first-line treatment for children and adolescents.
- They cause a small but significant increase in suicidal thinking and self-harm behaviour.
- Unless there is acute risk, consider education and 'watchful waiting'.
- Report all possible adverse events to the Australian Adverse Drug Reactions Advisory Committee.

Although selective serotonin reuptake inhibitors (SSRIs) have not been approved for use in children under 18 years old, they are widely used in general practice. Until 2003, most authorities argued that these drugs, which are relatively non-toxic in overdose, were without significant undesirable adverse effects, and therefore safe for childhood depression. It is now apparent that the data were biased, giving an overly positive view of efficacy and underplaying adverse effects including increased suicidal risk.[1] Having re-examined the data, UK regulators have contraindicated all antidepressants other than fluoxetine for children. In the USA, the Food and Drug Administration (FDA) applied a 'black box warning' to the product information of all antidepressants to warn prescribers and consumers of the increased suicide risk in children.

There have been eight published and 16 unpublished randomised controlled trials of newer antidepressants in children.[2] None of the unpublished and only half of the published studies have shown any advantage over placebo on the pre-specified primary outcomes. Only one-third of all published measures (all of these physician-rated rather than self- or parent-rated) favour drug over placebo. In most of these cases placebo accounted for about 85% of the overall response, suggesting that the benefit of the antidepressant drugs was of dubious clinical significance. Although trials such as the Treatment of Adolescents with Depression Study[3] have supported claims that antidepressants are beneficial, these claims are often based on flawed interpretations of data.[4]

If evidence for effectiveness is weak, what of harm? FDA analysis (and re-analysis by Columbia University) showed that during the 6–12 weeks of the randomised controlled trials, the risk of suicidal activity/thinking was 4% for those on medication and 2% for those on placebo. This is a statistically significant difference.[5] Two studies[2,6] exempted fluoxetine from conclusions that the harm:benefit ratio was unfavourable; our analysis did not.[1] Subsequently, the FDA deemed that no individual antidepressant is exempt from concerns about suicide.[7] There is no evidence that older adolescents are less at risk than younger. Studies showing no overall increase in suicide in response to these drugs in adults cannot reassure us that the risks for adolescents decrease as they approach 18 years of age. If young adults on antidepressants had a higher risk of suicide than older people, this might not be detected as a change in the suicide risk in the adult population as a whole. The UK product information warns that paroxetine carries 'a possibility of an increased risk of suicide related behaviour in young adults ages 18–29'.

There is a plausible argument that any increased risk in the short time frame covered by randomised controlled trials is outweighed by subsequent reduction in suicide due to effective treatment of depression. Some have attributed reductions in suicide rates over the last decade to the increased availability of SSRIs, but there are reasons to doubt this association.[8]

Many adverse effects of new drugs (especially those not

In this issue…

Australian Prescriber was first published 30 years ago. Although the journal had a turbulent development, it survived to become an important part of Australian practice.

Unfortunately, some Australian children do not survive their adolescence because of depression. Awareness of childhood depression is increasing, but its management is controversial. Joseph Rey, Jon Jureidini and Anne Tonkin take two views of the evidence concerning antidepressants, while Philip Hazell gives an overview of the role of psychotropic drugs in children.

Despite improvements in the last 30 years, the health of Indigenous Australians remains a problem. Although medicines are only part of the solution, it is important to use them appropriately. Cathy Larkin and Richard Murray provide advice on how to achieve this.

predictable from the mechanism of action of the drug) do not emerge until well after marketing approval. As the number of people involved in randomised controlled trials (in this case, just over 4000) is so much smaller than the number of patients who ultimately take the drug, infrequent adverse events often only emerge after years of widespread use. Unfortunately, postmarketing surveillance is poorly implemented internationally. It is the weakest function of the FDA (as shown by the withdrawal of rofecoxib). In Australia reporting of adverse events to the Adverse Drug Reactions Advisory Committee (ADRAC) is voluntary, yet SSRIs rate among the highest for adverse events notified (5% of the total number of notifications since 1972).

So we have poor evidence of efficacy, small but significant increases in suicide risk, and significant, probably underestimated, adverse events. The evidence therefore shows us that antidepressants are not demonstrably 'better than nothing' and may be worse. This conclusion will be at odds with many general practitioners' clinical experience in using these drugs. The discrepancy arises because prescribers who have seen apparently positive responses to antidepressants have not realised that much of the observed benefit would have occurred in response to a placebo.

So what should general practitioners do when faced by an apparently depressed adolescent? Recent recommendations from the UK National Institute for Clinical Excellence confirm that antidepressants are not appropriate for the treatment of mild depression in any age group.[9] Their proposed strategy of 'watchful waiting' is appropriate for children with mild–moderate depression. Where acute risk is low, a general practitioner might offer a brief explanation about depression, sleep hygiene, the usefulness of finding a confidante, the benefits of exercise and of gradually resuming any activities set aside because the individual is 'too depressed'. The general practitioner should then arrange to see the patient again in about two weeks but offer to talk to them earlier if they are worried.

In more severe cases, referral to or consultation with a child and adolescent mental health service or a child psychiatrist is recommended. The limited availability of such services is an indication for advocacy; it does not mandate prescribing against available evidence. Such prescribing, based on faith or hope that antidepressants may actually be better than the evidence indicates, risks contravening the injunction to 'first do no harm'.

References

1. Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL. Efficacy and safety of antidepressants for children and adolescents [clinical review]. Br Med J 2004;328:879-83.
2. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 2004;363:1341-5.
3. Treatment for Adolescents with Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression. JAMA 2004;292:807-20.
4. Jureidini J, Tonkin A, Mansfield PR. TADS study raises concerns [letter]. Br Med J 2004;329:1343-4.
5. http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf [cited 2005 Aug 22]
6. http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/ssrioverview_101203.pdf [cited 2005 Aug 22]
7. FDA Statement on Recommendations of the Psychopharmacologic Drugs and Pediatric Advisory Committees. US FDA; 2004. http://www.fda.gov/bbs/topics/news/2004/NEW01116.html [cited 2005 Aug 22]
8. Gunnell D, Ashby D. Antidepressants and suicide: what is the balance of benefit and harm [clinical review]. Br Med J 2004;329:34-8.
9. The National Collaborating Centre for Mental Health. Depression in children: identification and management of depression in children and young people in primary, community and secondary care. Draft for first consultation. November 2004. http://www.nice.org.uk/pdf/Depn_child_1stcons_Fullguideline.pdf [cited 2005 Aug 22]

Conflict of interest: none declared

Children, serotonin and suicide

Joseph M. Rey, Professor of Child and Adolescent Psychiatry, Northern Clinical School, University of Sydney, Sydney

Key words: depression, cognitive behaviour therapy, fluoxetine, paroxetine.

(Aust Prescr 2005;28:111–13)

Controlled trials show that psychosocial treatments such as cognitive behaviour therapy[1] and interpersonal psychotherapy are effective in mild to moderate paediatric depression. However, effectiveness in severe depression (when symptoms are serious and last more than six weeks in at least two of three contexts – home, school, peers) is questionable.[2] This raises the question of drug treatment.

Tricyclic antidepressants are not more effective than placebo in children and adolescents.[3] They are cardiotoxic, particularly in overdose, and are therefore not recommended. A meta-analysis of data from published and unpublished randomised controlled

trials (practically all company-sponsored) that evaluated a selective serotonin reuptake inhibitor (SSRI) versus placebo in patients aged 5–18 years concluded that only fluoxetine had evidence of effectiveness.[4] A recent randomised trial funded by the US National Institute of Mental Health also showed response rates were higher with fluoxetine (61%) than placebo (35%) or cognitive behaviour therapy (43%) in severely depressed adolescents when global clinical improvement was considered. Combined fluoxetine and cognitive behaviour therapy worked best (71%).[2]

SSRIs are less toxic and have fewer unwanted effects than tricyclic antidepressants, but it has been suggested that, paradoxically, SSRIs may induce suicidal behaviour in the young. Ascertaining whether this is true is not easy because depression also increases the risk of suicide. So far, data are contradictory. On the one hand, pharmacoepidemiological and ecological studies suggest that increased use of SSRIs may have resulted in a reduction in youth suicide and that SSRIs are not found more often than expected in young suicide victims. On the other hand, a review[5] by the US Food and Drug Administration of 24 controlled trials involving more than 4400 children and adolescents showed a robust if small (2%) short-term increase in the incidence of suicidality (suicidal thoughts, attempts) in those receiving antidepressants, mostly SSRIs, compared with placebo. There were no suicides. The mechanisms underlying increased suicidality are unclear. SSRIs, particularly paroxetine[5], can induce akathisia, agitation and irritability (so-called 'activation'). Symptoms of 'activation' may be an indicator of increased suicide risk. Like other antidepressants, SSRIs can also trigger manic switches.

This is a rapidly evolving field in which new data are becoming available all the time and clinicians need to change their practice accordingly, considering that the balance between benefit and harm is neither simple nor static. Conclusions derived from clinical trials may not apply to individual patients for methodological, genetic, physiological, psychosocial and cultural reasons. Also, the weight given to the evidence may vary in line with changes in personal and social values. Electroconvulsive therapy is a case in point.[6] (Ironically, electroconvulsive therapy could become an increasingly attractive treatment option for youth depression due to concerns about antidepressants.) Hence, clinical practice should be guided by a careful appraisal of benefit and harm based on best evidence, clinical experience, and the needs, circumstances and wishes of each individual patient.

SSRIs have been widely used 'off-label' from the early 1990s, but none is formally approved for paediatric depression in Australia. The data about effectiveness are not great. The risks are small, but real. Conversely, depression is a serious illness that produces much personal suffering and can lead to social problems, poor physical health and suicide. Given a high recurrence rate, the effects of depression can be particularly harmful during childhood and adolescence, the stage when personality, professional and social skills are developed. Yet, youth depression is often ignored, not diagnosed, and not treated. For example, an Australian national household survey showed that of all depressed adolescents, 11% had seen a GP or paediatrician, 17% had used mental health services, and only 3% had been prescribed antidepressants.[7] The current evidence suggests that psychosocial treatments, not medication, should be used in mild and moderate depression, but they are no panacea.[2] Delivering them can pose challenges because clinicians may lack skills and confidence in using these therapies. Psychosocial treatments may also be unavailable in public sector services or be difficult to access because of cost, long waiting lists, or lack of services (for example, in rural areas). Further, depressed young people may be more reluctant to become engaged in these treatments because of anger, lack of motivation or insight, and demoralisation. Fluoxetine has a place in the treatment of severe depression in the young.[2,4] Fluoxetine and cognitive behaviour therapy should be the preferred option because the combination may be more effective and may reduce suicidal risk.[2]

When treatment with SSRIs is begun, the patients (and their families when appropriate – for example in younger adolescents) must be informed of the risk of increased suicidal thoughts and attempts, and adverse effects, so that they can detect 'activation', a manic switch, or an increase in suicidality, as well as discussing practical ways of dealing with them and enhancing patients' safety. This may require a reduction of the dose, because the adverse effects are dose-related. It is imperative to review patients often and monitor them closely for adverse effects, particularly during the first few weeks of treatment.

The Royal Australian and New Zealand College of Psychiatrists, the Royal Australasian College of Physicians and the Royal Australian College of General Practitioners have recently issued a statement about the use of antidepressants in children. This provides further guidance about the prescription of these drugs.[8]

References

1. Compton SN, March JS, Brent D, Albano AM, Weersing R, Curry J. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. J Am Acad Child Adolesc Psychiatry 2004;43:930-59.
2. Treatment for Adolescents with Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression. JAMA 2004;292:807-20.
3. Hazell P, O'Connell D, Heathcote D, Robertson J, Henry D. Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis. Br Med J 1995;310:897-901.

4. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 2004;363:1341-5.
5. Hammad T. Results of the analysis of suicidality in pediatric trials of newer antidepressants. In: Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research. Joint Meeting of the CDER Psychopharmacologic Drugs Advisory Committee and the FDA Pediatric Advisory Committee, September 13, 2004. p. 152-200. http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4065T1.pdf [cited 2005 Aug 22] http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1.htm [cited 2005 Aug 22]
6. Rey JM, Walter G. Half a century of ECT use in young people [review]. Am J Psychiatry 1997;154:595-602.
7. Rey JM, Sawyer MG, Clark JJ, Baghurst PA. Depression among Australian adolescents. Med J Aust 2001;175:19-23.
8. Royal Australian and New Zealand College of Psychiatrists, Royal Australian College of General Practitioners, Royal Australasian College of Physicians. Clinical guidance on the use of antidepressant medications in children and adolescents. http://www.racgp.org.au/folder.asp?id=1180 [cited 2005 Aug 22]

Further reading

Tiller J. Cognitive behaviour therapy in general practice. Aust Prescr 2001;24:33-7.

Professor Rey was a member of the advisory committees for atomoxetine (Eli Lilly) and methylphenidate (Janssen-Cilag) and was funded by Eli Lilly to attend an international conference.

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Varicella vaccine

Editor, – Despite the risks, the article 'Frequently asked questions about varicella vaccine' (Aust Prescr 2005;28:2–5) recommends widescale immunisation. There are three arguments against this strategy. Firstly, vaccine immunity may wane over time leaving susceptible adults. Secondly, immunising part of the population may shift the disease burden to those who are not vaccinated and because they will be less likely to acquire chickenpox in childhood they risk more severe disease in adulthood. Thirdly, the effect of vaccination on the incidence of herpes zoster is unknown.

The data so far show that chickenpox in immunised individuals is less severe. However, it is too early to know how this will change as immunised infants reach adulthood.

In 2000 mathematical modelling showed that immunising 90% of infants would produce an initial 'honeymoon' period of low incidence, one or more post-honeymoon epidemics in adolescents and young adults 10–20 years later, and an equilibrium reached after 20–40 years in which the incidence in adults is similar to that in the pre-vaccine years.[1] The evidence from the USA on reduced incidence in all age groups covers only five years of experience, which is within the honeymoon period predicted by the modelling. This is insufficient time for epidemics in adults to occur through the build-up of susceptible people, as partial population immunity increases the interepidemic interval.

The impact of varicella vaccine on herpes zoster is complex. There is reasonable evidence that adults exposed to children, or exposed to chickenpox, have less chance of developing zoster, through presumed immunologic boosting by exposure to varicella zoster virus.[2] Modelling shows that immunisation causes an increase in herpes zoster for up to 50 years until immunised infants reach old age.

Due to the infectivity of reactivated herpes zoster it is not possible to eliminate varicella zoster virus in the way measles or polio could be eliminated completely. The aim of immunisation is therefore to reduce the burden of varicella disease rather than disease elimination. Since the burden of serious disease, particularly mortality, is in adults, and the modelling shows that in the long term the incidence in adults will not be affected by even high levels of vaccination coverage, the logic of universal vaccination has to be questioned.

Vaccination undoubtedly reduces childhood disease and saves the costs of medical care, childcare costs and lost income for parents while they look after sick children. Health decisions, however, should be primarily based on health considerations rather than economics.

The current low burden of disease from varicella means that it would take only a small rise in varicella in adults for us to be worse off than we were without the vaccine.

Ben Ewald
General practitioner and Lecturer in epidemiology
Centre for Clinical Epidemiology and Biostatistics
University of Newcastle
Newcastle, NSW

References

1. Brisson M, Edmunds WJ, Gay NJ, Law B, De Serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. Epidemiol Infect 2000;125:651-69.
2. Thomas SL, Wheeler JG, Hall AJ. Risk factors for herpes zoster in immunocompetent adults. J Epid Community Health 2001;55(Suppl 1):108.

Associate Professor Jonathan Carapetis, one of the authors of the article, comments:

Dr Ewald raises the question of how mathematical modelling should be used in determining public health policy. Should we refrain from using a vaccine that can bring immediate reductions in morbidity and mortality because of predictions that there might be ill effects in the future? Some reassurance comes from US data, which have failed to show any change in rates of zoster up to seven years after introduction of varicella zoster virus immunisation.[1] It is still early days, and this study may have taken place during the initial 'honeymoon' period. Even if the models prove correct and we begin to see early increases in adult zoster followed by later increases of varicella in adolescents and young adults, there is an obvious solution: booster doses. We already give booster doses of pertussis, diphtheria and tetanus vaccine in adolescence, and regular influenza and pneumococcal immunisation is recommended for high-risk adults.

A recent study of more than 38 000 elderly people in the USA found that a live attenuated varicella zoster virus vaccine reduced the incidence of zoster by 51%.[2] This provides reassurance that vaccination of adolescents or adults will be an effective countermeasure to the model predictions, if they eventuate.

The models of post-varicella zoster virus vaccine disease patterns are important in highlighting the need for better surveillance of varicella and zoster, the longer-term questions relating to duration of immunity, and the importance of a flexible immunisation policy that can react quickly to changes in the epidemiology of vaccine preventable diseases. The uncertainty surrounding predictions from models means that they should not be used as a reason to withhold an intervention that can prevent illness and death and save health dollars at the same time.

References

1. Jumaan AO, Yu O, Jackson LA, Bohlke K, Galil K, Seward JF. Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992-2002. J Infect Dis 2005;191:2002-7.
2. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352:2271-84.

First-line medicines in the treatment of hypertension

Editor, –The article by Hill and Smith (Aust Prescr 2005;28:34–7) states that when the blood pressure, on at least three separate occasions, exceeds the threshold pressures which predict an increased cardiovascular risk, treatment is required. They quote systolic and diastolic figures for triggering treatment, but then state that the patient's predicted cardiovascular risk should determine the time for intervention.

When does cardiovascular risk become 'increased'? Over what acceptable level? How is the 'predicted cardiovascular risk' used to delay the time for active intervention when one of the measurements has crossed the red line?

Why is there no reference in the entire article to discussion with the patient of their acceptable risk levels? The New Zealand Cardiovascular Risk Calculator to which they refer us has numbers needed to treat ranging from <10 to >120. The result of treatment is prevention of one cardiovascular event in five years.

This would suggest that even in a high risk 'herd' of patients, drenching all of them delivers benefits to very few. When the 'herd' consists of autonomous fellow human beings, should they not be involved in the good shepherd's calculations?

Warwick Ruse
Gastroenterologist
Cannington, WA

Dr S. Hill and Professor A.J. Smith, authors of the article, comment:

Our article's focus was first-choice medicines for hypertension. We could not embark on this without a brief, but not a full, account of the assessment of absolute cardiovascular risk and its application to treatment decisions.

Blood pressure is continuously associated with cardiovascular risk and therefore there is no discrete point at which treatment is mandated. Blood pressure should not be viewed in isolation from accompanying risks such as age, gender, ethnicity, smoking, lipids, glucose, family history and body mass index – the ingredients currently used for calculating absolute cardiovascular risk.[1]

What is an 'acceptable' level of risk? The New Zealand guidelines, and our own National Heart Foundation, recommend lifestyle advice alone for individuals whose risk of a cardiovascular event over the next five years is less than 15%. Any threshold for treatment is a compromise between unnecessary intervention (the 'Number needed to treat (needlessly)'[2], culpable inactivity and economic feasibility. If, however, the approach of establishing absolute cardiovascular risk is taken it is **impossible** to leave the patient out of the discussion. We agree that this is essential for any intervention and particularly one that will last a lifetime.

References

1. The New Zealand Cardiovascular Risk Calculator. In: The assessment and management of cardiovascular risk. Best practice evidence-based guideline. Wellington, NZ: New Zealand Guidelines Group (NZGG); 2003. p. xxii. http://www.nzgg.org.nz/guidelines/0035/CVD_Risk_Full.pdf#page=33 [cited 2005 Aug 22]
2. Bogaty P, Brophy J. Numbers needed to treat (needlessly?). Lancet 2005;365:1307-8.

Antibiotics for surgical prophylaxis

Editor, – I read with interest the article 'Antibiotics for surgical prophylaxis' (Aust Prescr 2005;28:38–40) and the accompanying Dental notes (Aust Prescr 2005;28:41). While I do agree that surgical removal of the third molar (most often impacted) may be technically classified as 'contaminated', I think we should be more cautious with regards to routine use of antibiotic prophylaxis for this procedure.

Jawbones somehow behave differently when exposed to oral flora as compared to other bones in the body. By experience, we know that the jawbones may be exposed to oral flora as a result of periodontal disease (bony involvement may be severe in advanced cases) or as a result of dental extractions, yet they hardly get infected. I believe these exposures somehow make jawbones more resistant to infection by the oral flora, at least in healthy patients. Most patients can therefore avoid infection following routine dental extraction from a 'contaminated' area without the need for antibiotics. This 'resistance' may also explain the rareness of osteomyelitis in the jawbones even though they are frequently exposed to various dental causes such as trauma, abscesses and severe periodontal disease. A review of the need for antibiotic prophylaxis in third molar surgery concluded that there is no justification for routine prophylaxis.[1]

In view of the popularity of dental implants (technically categorised as insertion of prosthetic material), I would like to highlight a Cochrane review, mentioned in the Australian Dental Journal[2], on the use of prophylaxis to prevent complications following insertion of dental implants. It has been suggested that there is no appropriate scientific evidence to recommend or discourage the use of prophylactic systemic antibiotics. As such, we are still left in the dark on the appropriateness of prophylactic antibiotics for dental implantation. If we were to follow the criteria for surgical prophylaxis, antibiotics would be used because a dental implant is a prosthetic device and is inserted in a 'contaminated' environment.

W.C. Ngeow
Department of Oral & Maxillofacial Surgery, Faculty of Dentistry
University of Malaya
Kuala Lumpur, Malaysia

References

1. Martin MV, Kanatas AN, Hardy P. Antibiotic prophylaxis and third molar surgery. Br Dent J 2005;198:327-30.
2. Esposito M, Coulthard P, Oliver R, Thomsen P, Worthington HV. Antibiotics to prevent complications following dental implant treatment. Aust Dent J 2004;49:205.

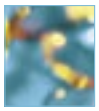
Valediction

Robert Moulds

In April this year Professor Robert Moulds stood down as the chairman of the Editorial Executive Committee of *Australian Prescriber*. Professor Moulds first wrote for *Australian Prescriber* in 1982 and 10 years later he joined the Executive Editorial Board of the journal. The Board appreciated Professor Moulds' pharmacological knowledge and in 2000 he became the chairman.

Under Professor Moulds' chairmanship the journal made the transition from the Department of Health and Ageing to the National Prescribing Service. Professor Moulds helped to ensure that the journal's editorial independence was maintained after this transition.

The Editorial Executive Committee became truly international when Professor Moulds became the Professor of Medicine at the Fiji School of Medicine. Despite the travel involved he remained committed to *Australian Prescriber* and regularly returned to Australia to chair the editorial meetings. His valuable contribution over the years is greatly appreciated.



Prescribing psychotropic medication to children in general practice

Philip Hazell, Conjoint Professor of Child and Adolescent Psychiatry, University of Newcastle, Newcastle, New South Wales

Summary

Child and adolescent mental health problems are common in the community, but the scientific basis for the treatment of many of these conditions is still in its infancy. Conditions for which a moderate level of skill in pharmacological management is required include obsessive-compulsive disorder, tic disorders, attention deficit hyperactivity disorder in the primary school-aged child, and persistent enuresis. Greater skill is required in the treatment of anxiety disorders, depression, attention deficit hyperactivity disorder in teenagers, and aggressive behaviour associated with autism and intellectual disability. Only clinicians with advanced skills should consider treating juvenile onset bipolar affective disorder, children with psychotic-like symptoms, and attention deficit hyperactivity disorder in preschoolers or in children with intellectual disability.

Key words: antidepressants, attention deficit hyperactivity disorder.

(Aust Prescr 2005;28:116–18)

Introduction

> 'You are always on your own when prescribing psychotropic medication to children.'

This statement was made, not by a general practitioner or a paediatrician, but by a leading paediatric psychopharmacologist. It is a pithy reminder that the scientific basis to the pharmacological management of children with psychiatric conditions is limited and that institutional support for such prescribing is qualified. This said, there is good evidence for the pharmacological management of some childhood disorders.

Psychiatric disorders in childhood are too common for treatment to be the exclusive domain of specialist services. Several conditions can be managed by general practitioners depending on their level of skill. However, many general practitioners report limited exposure to child and adolescent psychiatric problems in their undergraduate and postgraduate training.

General considerations

Many childhood problems can be resolved without drugs. If prescribing is being contemplated there are some important considerations[1]:

- be clear what you are prescribing for
- do not allow yourself to be rushed into a treatment decision
- follow the published mg/kg dose recommendations, but be prepared to use doses in the upper range if there is a poor response to treatment
- be familiar with the drug's adverse effect profile
- give a drug an adequate trial in time and dose before considering a change in treatment
- when stopping treatment, pay attention to whether doses should be tapered to avoid the development of a discontinuation syndrome (examples include the selective serotonin reuptake inhibitors (SSRIs) and clonidine)
- if multiple medications seem necessary, it is time to obtain a specialist review.

Conditions requiring a moderate skill level

These conditions are usually easy to recognise and have proven treatments.

Obsessive compulsive disorder

The content of the obsessions, particularly if they are of a sexual nature, can be distressing and may lead to secondary depression. Obsessive compulsive disorder can be very disabling.

Obsessive compulsive disorder responds well to cognitive behaviour therapy, the selective serotonin reuptake inhibiting drugs such as sertraline and fluvoxamine, and the serotonergically active tricyclic clomipramine.[2] The doses required to achieve remission may be higher than those used in the treatment of childhood depression. Once symptoms are suppressed treatment should be continued for at least 12 months to minimise relapse.

Tourette's syndrome

This syndrome and other chronic tic syndromes are more likely to cause embarrassment than impairment. Associated problems such as obsessionality or hyperactivity may cause the patient most difficulty.

Tics can be suppressed with clonidine, low doses of high potency antipsychotics such as haloperidol, or one of the atypical antipsychotics such as risperidone. Tics fluctuate in intensity and frequency, therefore the recurrence of tics following adequate suppression is not an automatic indication for a dose increase or a change in treatment. Owing to the chronic nature of the condition, treatment is usually required for many years.

Attention deficit hyperactivity disorder (ADHD)

In carefully selected children aged 6–12 years ADHD responds well to the psychostimulants methylphenidate or dexamphetamine. These are well-researched medications and are relatively safe if used appropriately.[3] In many states general practitioners are not permitted to prescribe them. Other non-stimulant treatments include atomoxetine and clonidine. Atomoxetine was released in Australia in 2004, so clinicians are still becoming familiar with prescribing the drug. Early experience suggests a longer lead time to clinical response than is seen with psychostimulant drugs. Clonidine is more commonly prescribed in Australia in combination with a psychostimulant than it is alone.

Enuresis

Bedwetting that has not responded to behavioural treatments, including the 'bell and pad', may respond to medication. Although tricyclic antidepressant drugs are effective for this condition, their benefit does not justify the risk when safer alternatives, such as intranasal desmopressin, are available.

Conditions requiring a medium to high skill level

These conditions may have a wide differential diagnosis or require complex therapy.

Anxiety

Anxiety disorders are common in children, but often cause only mild impairment and respond well to psychological treatments. They therefore rarely warrant pharmacological treatment. Indications for medication include school refusal that is unresponsive to other treatments and the incapacitating anxiety that occurs in panic disorder.

Fluoxetine, fluvoxamine and sertraline have all proven superior to placebo in randomised controlled trials. Benzodiazepines are discouraged in children with anxiety because they have no significant benefit over placebo. For cases of overwhelming distress arising from acute psychological trauma I would, in the past, have recommended short-term treatment with the relatively sedating antipsychotic thioridazine. As its use is now restricted, the atypical antipsychotics are reasonable alternatives.

Depression

Depression in children and adolescents can be overlooked as it often has an insidious onset and is characterised by irritability rather than low mood. By the time the patient is evaluated by a doctor the symptoms may have been present for many months. There is no need to rush into treatment. It is wise to review the mood state of the patient on at least two occasions before recommending pharmacotherapy. The Adverse Drug Reactions Advisory Committee recommends that drugs should only be used as part of a comprehensive management program.[4]

Fluoxetine is the only antidepressant considered from trial evidence to possibly have a satisfactory risk:benefit ratio in this age group.[5] Patients should be monitored regularly during the first weeks of treatment for the emergence of agitation, suicidal thoughts or intent, or self-harming behaviour, as one in 20 will develop problems. Remission of depressive symptoms may take up to three months. Treatment should be continued for at least nine months after remission has been achieved.

ADHD in adolescents

ADHD persisting into adolescence is the rule rather than the exception, but patients may find it difficult to access specialist services for treatment. Psychostimulant drugs remain the first-line treatment, but some patients complain of adverse effects including dysphoria. Teenage patients may be pressured to give or sell their tablets to peers. For such reasons some adolescent patients need to switch to one of the non-stimulant treatments. ADHD presenting for the first time in adolescence is atypical and warrants a specialist assessment.

Aggressive behaviours associated with autism and intellectual disability

Aggression arises from a combination of limited problem-solving skills and a low threshold to arousal. Medicines are not first-line treatment, however controlled trials have found risperidone superior to placebo in treating such symptoms.[6] In my experience, while the initial impact on behaviours can be dramatic, the effectiveness of risperidone usually declines over time. For this reason the benefit of continuing treatment should be reviewed every three to six months. Other atypical antipsychotics and pericyazine are prescribed for the same indication, but the evidence is less robust. Clonidine as a monotherapy offers an alternative strategy for reducing arousal. Patients whose aggression arises in the context of obsessive compulsive disorder-like behaviour may respond to SSRIs.

Conditions requiring advanced skills

General practitioners should only consider these treatment options if they have had specific training or if they work in close collaboration with child mental health services.

ADHD in preschoolers and the intellectually disabled

The evidence base for the efficacy of pharmacological treatments in preschool children is limited. Young children are more prone than older children to experience adverse effects with methylphenidate. Psychostimulant medication will alleviate hyperactive behaviours in children with autism or intellectual disability, but may exacerbate obsessive compulsive disorder-like behaviours.

Juvenile onset bipolar affective disorder

This diagnosis is controversial, yet most people with bipolar disorder have the onset in adolescence. Children identified with the condition usually have severe and complex problems that are better managed by a specialist team. Pharmacological treatment typically comprises a mood stabiliser such as sodium valproate, lithium or lamotrigine augmented with one of the atypical antipsychotics. Antidepressant medications are usually avoided owing to the risk of precipitating mania.

Psychotic symptoms

Psychotic-like symptoms in young people are as likely to arise from non-psychotic conditions such as substance abuse, dissociative states, post-traumatic stress disorder and obsessive compulsive disorder as they are from schizophrenia or severe mood disorder. For this reason specialist evaluation is recommended. Some younger or intellectually disabled children who engage in antisocial behaviour will report that a voice in their head commanded them to act in that manner. Such children are usually describing their own thoughts.

Conclusion

Psychiatric disorders are common in childhood. While many problems can be managed without drugs, some conditions require pharmacotherapy. However, the evidence supporting this therapy in children is often limited. Some conditions can be successfully managed by the general practitioner provided they have the appropriate level of skill.

References

1. Nunn KP, Dey C, editors. The clinician's guide to psychotropic prescribing in children and adolescents. Newcastle: Child and Adolescent Mental Health Statewide Network; 2003.
2. Rapoport JL. Child psychopharmacology comes of age. JAMA 1998;280:1785.
3. Hazell P. Stimulant treatment for attention deficit hyperactivity disorder. Aust Prescr 1995;18:60-3.
4. Australian Drug Evaluation Committee. Use of SSRI antidepressants in children and adolescents – updated 15 October 2004. Canberra: Therapeutic Goods Administration; 2004. http://www.tga.gov.au/adr/adrac_ssri.htm [cited 2005 Aug 22]
5. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 2004;363:1341-5.
6. Hollander E, Phillips AT, Yeh CC. Targeted treatments for symptom domains in child and adolescent autism. Lancet 2003;362:732-4.

Further reading

Lask B, Taylor S, Nunn KP. Practical child psychiatry: the clinician's guide. London: BMJ Books; 2003. p. 290-349.

Professor Hazell has received a speaker fee from Pfizer to talk to general practitioners about the evidence for treatment of child and adolescent depression. He has received travel funds from Eli Lilly to attend a conference and present a paper on attention deficit hyperactivity disorder (ADHD). His service has been in receipt of payment from Eli Lilly for speaker fees, his participation in advisory boards, and research on atomoxetine for ADHD. His service has received funds for his participation in research on extended-release methylphenidate for ADHD. His service has received payment from Novartis for his participation on an advisory board for ADHD.

Self-test questions

The following statements are either true or false (answers on page 131)

1. Benzodiazepines are recommended for the treatment of severe anxiety in childhood.
2. Irritability may be a sign of childhood depression.

Wallchart

Copies of the wallchart 'Medical management of severe anaphylactoid and anaphylactic reactions' are still available from *Australian Prescriber*. This A3-sized chart was published as an insert to *Australian Prescriber* Vol 24 No. 5, 2001. It was endorsed by the Australasian College for Emergency Medicine, the Australasian Society of Clinical Immunology and Allergy, the Australian and New Zealand College of Anaesthetists, the Royal Australasian College of Physicians, the Royal Australian and New Zealand College of Radiologists, and the Royal Australian College of General Practitioners.

Your questions to the PBAC

Aprepitant – recommendations for PBS listing

In April 2005 the Pharmaceutical Benefits Advisory Committee (PBAC) approved the listing of aprepitant as a pharmaceutical benefit. Aprepitant is available as an authority item for the management of nausea and vomiting associated with cytotoxic chemotherapy being used to treat malignancy, in combination with a 5-HT_3 antagonist and dexamethasone, where any one of the following chemotherapy agents are to be administered:

- altretamine
- carmustine
- cisplatin
- cyclophosphamide at a dose of 1500 mg/m^2/day or greater
- dacarbazine
- procarbazine or
- streptozocin.

Aprepitant was approved by the Therapeutic Goods Administration (TGA) for use in combination with other antiemetic agents for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin. This TGA approval is broad, yet the PBAC has restricted the use of aprepitant as a pharmaceutical benefit to certain cancer chemotherapy.

The only phase III trial data available for aprepitant are from patients receiving cisplatin chemotherapy. Presumably the PBAC selected drugs that had an emetogenic risk similar to that of cisplatin.[1,2] If this were true, why were drugs such as dactinomycin, lomustine, mechlorethamine or pentostatin omitted?[1]

Combinations of chemotherapy increase the emetogenic potential.[3] The National Comprehensive Cancer Network's 2005 antiemesis guidelines include the combination of doxorubicin or epirubicin with cyclophosphamide as having the same high emetogenic risk as cisplatin.[2] Aprepitant is not available for this combination. How did the PBAC decide which cytotoxic drugs would qualify patients for subsidised treatment with aprepitant?

Jim Siderov
Senior Pharmacist
Cancer Services
Austin Health
Melbourne

References

1. Jordan K, Kasper C, Schmoll HJ. Chemotherapy-induced nausea and vomiting: current and new standards in the antiemetic prophylaxis and treatment. Eur J Cancer 2005;41:199-205.
2. National Comprehensive Cancer Network. Antiemesis practice guidelines in oncology. Version 1, 2005. http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf [cited 2005 Aug 22]
3. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-9.

PBAC response:

It was the sponsor who requested that only specific highly emetogenic drugs be included in the restriction. Although dactinomycin, lomustine, mechlorethamine and pentostatin are generally considered highly emetogenic, they were not included in the requested restriction. Further, mechlorethamine and pentostatin are not currently approved by the TGA for use in Australia.

The PBAC recommended listing on the basis of acceptable cost-effectiveness when aprepitant is used with certain highly emetogenic cytotoxic chemotherapy agents, either in isolation or in combination with other agents. The PBAC considered that even though there were some uncertainties around the cost-effectiveness of the product, the extent of incremental effectiveness of antiemetic therapy involving aprepitant was of substantial clinical importance. There are likely to be cost off-sets from reduced use of extended regimens of 5-HT_3 drugs and the total cost to the Pharmaceutical Benefits Scheme would be small.

An additional consideration for the PBAC was the pack size proposed for listing. The PBAC noted that the pack size will result in wastage of the 80 mg capsules if used to prevent nausea and vomiting in patients undergoing multidose chemotherapy. It therefore restricted listing to single-dose cycles of chemotherapy.

The PBAC would welcome a re-submission from the sponsor to address whether other highly emetogenic drugs should be included in the restriction.

Australian Prescriber – the first 30 years

John S. Dowden, Editor, Australian Prescriber

Key words: drug information, medical journals.

(Aust Prescr 2005;28:120–2)

As Australia slipped towards a constitutional crisis in late 1975, a new medical journal slipped into letter boxes across the country. *Australian Prescriber* had arrived.

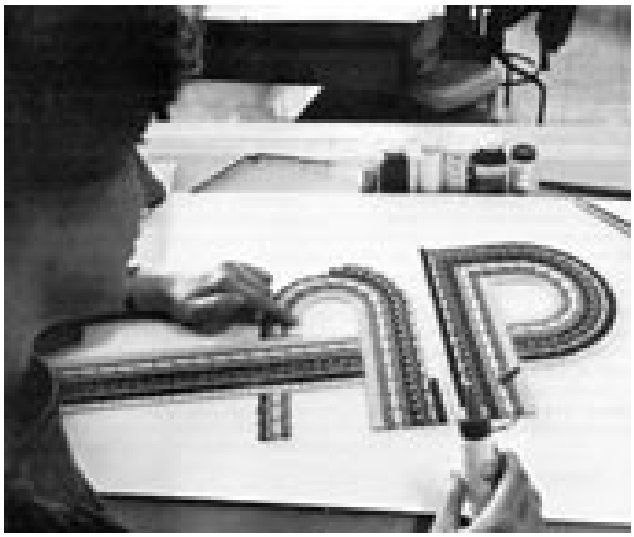
Health professionals had previously received the Prescribers' Journal published by the UK Department of Health, but by 1975 it was time for an Australian publication. With Dr Robert Hodge, the Senior Adviser in Clinical Pharmacology to the Australian Department of Health, as its editor, the journal set out for its 'lofty, but attainable aims'. The Executive Editorial Board was going to fill the need for a 'concise, authoritative, unimpeachably unbiased journal giving guidance to treatment'.[1]

This set the pattern for the 30 years to come. Each issue features a variety of articles about drugs and therapeutics with occasional papers on other influences on prescribing. From its inception, the journal was distributed free to doctors, dentists, pharmacists and perhaps most importantly students of these professions.

The first issue announced that only metric units would be used in the journal. It also stressed the importance of clearly written prescriptions. This simple advice was to land the new journal in immediate trouble.

To illustrate the illegibility of some prescriptions the first issue included a copy of a scrawled prescription from the 1950s. Unfortunately someone who could read the prescription was the doctor who wrote it. With rumblings of litigation the Executive Editorial Board had to apologise for publishing something illegible!

Creating the 1977 cover



Just as there was no electronic prescribing in the 1970s, there was no computer-assisted design. The new cover of 1977 required hundreds of tablets and capsules to be laid out by hand to spell out the journal's initials. This colourful concept was to reappear in different forms until 1994.

In 1979 *Australian Prescriber* asserted its independence by refusing to provide 'interested parties' with copies of articles before publication.[2] The journal's ability to make independent unbiased comments, particularly about new drugs, is one of the reasons for its success.

Dr Rod Hall, who became the editor in 1980, demonstrated this independence by publishing an article criticising the Federal Government's decision in 1982 to discontinue *Australian Prescriber* as a cost-cutting measure.[3] By then health professionals had recognised the educational value of the journal and lobbied to reverse the government's decision.[3] There was even comment in the Lancet about the folly of closing the journal.[4]

There was a possibility that *Australian Prescriber* would be taken over by a private publisher. The Medical Journal of Australia was a possible contender, but this privatisation did not take place. The second issue of 1982 seemed destined to be the last.

The journal was gone, but not forgotten. No publication of comparable quality emerged to fill the gap left by *Australian Prescriber*, yet there was still a need to provide health professionals with objective and independent information about new treatments. In 1983, the government concluded that the cost of publishing the journal was minimal compared to the costs of prescribing and therefore *Australian Prescriber* was resurrected after an absence of 18 months.

Under the direction of Dr Hall, the journal settled into a regular pattern of four issues a year. The Australian Adverse Drug Reactions Bulletin which had been incorporated into the original journal, but survived the cuts of 1982, continued as a separate publication.

The importance of independent information about drugs was becoming increasingly recognised internationally. In 1986 *Australian Prescriber* became one of the founding journals of the International Society of Drug Bulletins (ISDB).

In 1988 *Australian Prescriber* began a long-running series called 'Pharmacokinetics made easy'. This series, written by Professor Don Birkett, a member of the Executive Editorial Board,

eventually became an international textbook which is now in its second edition.[5] During this time the journal also published a booklet collecting together the articles in the series 'Abnormal laboratory results'. This is now available as a separate publication and a new edition is expected later this year.[6]

Editing the journal remained the responsibility of the senior medical advisers in the Therapeutic Goods Administration (TGA), but with the growth in drug evaluation it was becoming clear the dual roles were unsustainable. After returning to the editor's chair, which was capably filled by Dr John McEwen between 1988 and 1989, Dr Hall began the process which eventually led to the recruitment of a dedicated editor.

The first issue officially under my editorship was published in 1990. It contained the results of a readership survey which highlighted a problem which was to plague the Executive Editorial Board and production staff for years. The mailing list was found to be disturbingly inaccurate and the Board could never comprehend why the Department of Community Services and Health, as it was then known, was unaware of how many doctors there were and where they practised.

Questioning the Department was made easier once the Executive Editorial Board appointed an independent chairman. Until 1990 the editor had chaired the Board. Having a chairman who was not paid by the publisher enhanced the journal. Professors Peter Fletcher and Rob Moulds have both been strong independent chairmen willing to support and defend *Australian Prescriber* when necessary.

One threat to the independence of the journal came in 1990 when the TGA toyed with the idea of funding the journal by selling advertising space in *Australian Prescriber*. Fortunately the proposal did not progress. Accepting drug company advertising could have compromised the journal's independence and resulted in its expulsion from the ISDB.

When the TGA started to receive funding from the pharmaceutical industry, it was decided to transfer responsibility for *Australian Prescriber* to the Pharmaceutical Benefits Branch of what was then called the Department of Health, Housing and Community Services. This move was appropriate as the new policy on the quality use of medicines (QUM) was being implemented.[7] *Australian Prescriber* had already published the proceedings of a seminal conference about rational prescribing convened by the unlikely alliance of the Consumers' Health Forum of Australia and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists.[8] This was the first of a series of supplements reporting the beginnings of activities which are now part of practice. The academic detailing workshop[9] paved the way for the educational visiting activities of the National Prescribing Service and the Drug and Therapeutics Information Service, while the Australian National Formulary Workshop[10] foreshadowed the development of the Australian Medicines Handbook.

With all this activity, the demand for the journal increased. One way of meeting this demand was to explore the nascent technology of electronic publication. Following the original idea in 1994 an application was made to the Australian Vice-Chancellors' Committee for funding to develop an *Australian Prescriber* website. A grant was awarded in 1995 and Dr Darren Williams, with the help of Dr Andrew Dawson of the Executive Editorial Board, established the website at the University of Melbourne in 1996. Although the website has subsequently been hosted in different locations its popularity continues to grow. By 2000 there were 100 000 hits a month on the site rising to over a million in 2004.

Australian Prescriber was one of the first medical journals in the world to make its full text freely available on the internet. As it could be accessed by anyone, there was a need to explain some of the articles to a lay audience. Many of the articles in the electronic journal are now accompanied by comments for consumers which briefly summarise important messages from the articles.

Editorial teams

1975: From left, Emilio Maculan (secretary), Dr Robert Hodge (editor), Linda Turner (designer) and Dennis Blewett (journalist)

2005: From left, Cherie Graham (administrative support officer), Dr John Dowden (editor), Susan Reid (production manager) and Maureen Ryan (editorial assistant)

The electronic version of *Australian Prescriber* is an important way of providing independent information to an international audience. In 2002 the website was accredited by the international Health On the Net Foundation for the quality of the information in *Australian Prescriber*.

The international role of the journal was further underlined when it was chosen to produce a publication for the World Health Organization. The proceedings of the International Conference on National Medicinal Drug Policies, held in Australia, were published as a supplement to *Australian Prescriber* in 1997.[11]

Despite the success of the journal and other QUM initiatives, funding for pharmaceutical education was reduced in 1996. A review was announced to look at 'the future role (if any) for the *Australian Prescriber*'.

The review consisted of market research and also a nationwide consultation by Dr Andrew Herxheimer. When Dr Herxheimer reported in 1997 he found that *Australian Prescriber*'s resources were 'tiny and precarious' and had been 'whittled away over the years'. As the staff had by now been reduced to two there was a danger that '*Australian Prescriber* would collapse'. Dr Herxheimer found that there was a need for an independent Australian drug bulletin and that *Australian Prescriber* should be published more, not less, frequently. The report was accepted and by 1999 sufficient funds were available to allow *Australian Prescriber* to be published six times a year.

Despite this reprieve the Department of Health and Aged Care, as it was then called, decided in 2000 that it would no longer be the publisher of *Australian Prescriber*. There then followed almost a year of uncertainty which led the Executive Editorial Board to once again fear for the journal's existence.[12] After some difficult negotiations, the journal became part of the National Prescribing Service (NPS) in 2002.

Once the initial anxieties were overcome, the journal settled well into the NPS. There are many opportunities for *Australian Prescriber* to assist the NPS to promote the quality use of medicines, while continuing its tradition of editorial independence. The continued funding of *Australian Prescriber*, as an integral part of the NPS, in the Federal budget of 2005 confirms the success of the partnership and augurs well for the future.

Australian Prescriber would not have survived for three decades without the hard work and goodwill of many people involved in its production. Ultimately, however, a journal will only survive if people read it. The fact that *Australian Prescriber* has the widest readership of any Australian medical publication suggests that the journal is giving health professionals the information they need. If this helps to improve the care of patients then *Australian Prescriber* will celebrate many more anniversaries.

References

1. Pargiter RA. Lofty, but attainable, aims? Aust Prescr 1975;1:2.
2. Independence of *Australian Prescriber* [editorial]. Aust Prescr 1979;3:26.
3. Harris R. The *Australian Prescriber* [editorial]. Aust Prescr 1982;6:27.
4. Threat to the *Australian Prescriber*. Lancet 1981;2:1222.
5. Birkett DJ. Pharmacokinetics made easy. 2nd ed. Sydney: McGraw-Hill; 2002.
6. Dunstan R, editor. Abnormal laboratory results. Sydney: McGraw-Hill; 2001.
7. Pharmaceutical Health and Rational Use of Medicines Committee. A policy on the quality use of medicines. Canberra: Commonwealth Department of Health, Housing and Community Services; 1992.
8. Rational prescribing: the challenge for medical educators. Aust Prescr 1991;14 Suppl 1:S1-59.
9. Academic detailing. Aust Prescr 1993;16 Suppl 1:S1-105.
10. Australian National Formulary Workshop. Aust Prescr 1993;16 Suppl 3:S1-46.
11. International conference on national medicinal drug policies – the way forward. Aust Prescr 1997;20 Suppl 1:S1-272.
12. Executive Editorial Board. Changes at *Australian Prescriber* [editorial]. Aust Prescr 2002;25:2.

Reflections from a past editor

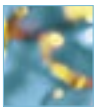
Editor, – Congratulations on reaching this distinguished milestone. It raises many memories for me – mostly fond. In my time as Editor I was critically dependent on the highly professional input to the journal from the Executive Editorial Board (EEB). Without their input the journal would have 'gone under' at the first of the several hurdles you discuss. As a public servant the journal brought me into contact with many colleagues across Australia and opened new contacts overseas. This should not be underestimated in what could have been an isolated existence in the 'wastes of Canberra'.

The first major hurdle, possible extinction, was an opportunity to prove the value of the journal. While lobbying to maintain the journal went on, in parallel, the EEB was holding 'clandestine' meetings to ensure continued publication. I well recall one such meeting at Sydney University which, at the time, reviewed material for what seemed to be the last issue. Volume 6 Issue 2 of 1982 marked the expected demise of the journal, however, thanks to all the lobbying, the journal was restored in 1983.

I now look forward to the 40th and 50th anniversary celebrations.

Rod Hall

Editor, *Australian Prescriber*, 1980–88



Assisting Aboriginal patients with medication management

Cathy Larkin, Pharmacist Academic, Kimberley Aboriginal Medical Services Council, Broome, Western Australia, and Richard Murray, Planning Director, Rural Clinical School, James Cook University, Townsville, Queensland

Summary

The burden of acute and chronic disease in the Aboriginal and Torres Strait Islander population is well documented. Medicines are important for treatment and prophylaxis, but there are many factors which continue to impede medication management in Aboriginal populations. These include access and financial barriers, the nature of the therapeutic regimen and cultural, socioeconomic and geographic factors. The patient-clinician interaction and the organisational aspects of healthcare practices also have an impact. Solutions may include the selection of appropriate formulations, simple dose regimens, tailored use of medication aids, local formularies and a greater role for Aboriginal health workers.

Key words: compliance, drug utilisation.

(Aust Prescr 2005;28:123–5)

Introduction

There are many challenges to the delivery of effective drug therapy in Aboriginal communities.[1] One challenge is the patient adhering to the prescribed course of treatment. Aboriginal people are often said to be 'poorly compliant'. This seems unfair; Aboriginal people may face difficulties managing medicines, but approximately 50% of the general population also do not take their medicines as directed.[2] There is also limited literature documenting medication adherence rates in the Australian Aboriginal population.

Several strategies can be used to improve adherence to medication regimens. These strategies range from patient specific approaches, such as effective communication and simplifying drug regimens, to adopting a regional focus on medication management.

Tailoring drug regimens

Traditional bush medicines are commonly used as an immediate dose or linked to a symptomatic response. For people who are familiar with traditional remedies, the concept of taking tablets every day in the absence of symptomatic sickness may not be consistent with their understanding of the use of medicines. The need to take medicines regularly should be emphasised in patient education.

Consideration of the dosing intervals and appropriate combinations is important in tailoring dosage regimens. Simple regimens are easier to adhere to.

- Atorvastatin is an HMG-CoA reductase inhibitor which has a long half-life and therefore can be taken at any time of the day, without concern about the diurnal variation of cholesterol production. All other statins are best dosed at night which may mean an additional dosing time for the patient.
- Consider long-acting preparations that reduce the number of daily doses for patients. (For example, once-daily sulfonylureas, however they have a risk of prolonged hypoglycaemia, particularly in patients with renal impairment.)
- Appropriate combinations of drugs can reduce the dosing interval or the number of tablets people have to take. For example, using probenecid in combination allows twice a day dosing of flucloxacillin for serious staphylococcal infections instead of four times a day dosing.
- Implant and depot preparations reduce the frequency of dose administration (for example, etonogestrel).

Dose forms

Adherence may be compromised by the selection of an administration route that is not ideal for the patient. For example, using a patch for transdermal administration of medications may be inappropriate in hot and humid localities.

The selection of drug delivery devices is particularly relevant to inhaled therapies and insulin. Dry powder inhalers are portable and easy to use by patients who are having problems co-ordinating a metered dose inhaler, or where transportation and maintenance of a spacer is difficult. However, there is limited information about the stability of dry powder inhalers in humid environments.

Innolets are a useful device for the delivery of insulin in visually impaired patients.[3]

Storage considerations

A lack of refrigeration or frequent power cuts can be a problem for the storage of some medications and this may be a barrier to medication adherence. Antibiotic liquids are common medications that require refrigeration. Consideration may have to be given to chewable or injectable preparations where appropriate storage conditions are limited.

In some cases, medication regimens have to be tailored to accommodate available storage conditions. There have been situations where patients have kept their supply of insulin at the community clinic, while keeping one pen/vial/innolet at home in an insulated container with an ice pack (allowing at least room temperature to be maintained).

Using formulations that have less stringent storage requirements is beneficial. For example, after opening, glyceryl trinitrate sublingual spray is stable for longer than glyceryl trinitrate sublingual tablets and is therefore a more suitable option in regions of heat and humidity.

Dose administration aids

Problems with medication adherence may involve taking a higher or lower dose than prescribed, taking medicine at the wrong time, just forgetting or making a conscious decision not to follow the prescribed treatment. Although often useful, dose administration aids are not a panacea for all such problems.

In discussing possible use of a dose administration aid with a patient, important issues to be considered include:

- the suitability of the medications for repackaging
- the logistics involved in filling and collecting the pack
- cost to the patient and/or the health service
- the additional risk of human error
- the most suitable type of device
- how inhaled, as required, or liquid preparations are to be managed.

There are a number of preparations that should not be removed from the manufacturer's package and therefore they are unsuitable for use in a dose administration aid. Examples include wafer and sublingual preparations (such as olanzapine wafers), dispersible preparations (such as soluble aspirin), drugs that degrade when exposed to light (such as nifedipine) and hygroscopic preparations (such as sodium valproate tablets).

Warfarin therapy often presents a conundrum for prescribers. Although adherence is critical, a fixed dose is often not possible so orders for dose administration aids may need alteration. Frequent changes to a dose administration aid may be difficult to manage, particularly if the preparation of the aid is outsourced to a pharmacy which may be hundreds of kilometres away. Prescribers need to ensure strategies are in place for patients to manage such scenarios.

Beware the practical problems not anticipated by professionals. Complaints from the Kimberley region include the aid not fitting into a handbag (commonly one of the only relatively secure places for medicines storage), insomnia from crinkling blister-packs under the pillow at night and the backing card disintegrating and disgorging soggy medicines after sitting in a bag with a moist plug of 'ngunju' (chewing tobacco).

The Tiwi Islands provide an example of where on-site preparation of dose administration aids and the availability of a pharmacist to provide drug counselling (with the support of local pharmacy assistants) allowed more timely access to medicines. This resulted in a documented increase in the collection rates of dose administration aids.[4]

Discussing administration of medications

Failing to achieve a shared understanding of health concepts between patients and clinicians is a problem in the delivery of effective health care.[5] A simple message can be lost by using culturally ambiguous words to describe the time of a dose (for example 'dinner'). Clarification of the terminology used to describe daily meals can be a simple but important step in working towards adherence. For example, Kimberley Aboriginal people usually refer to lunch as dinner and the evening meal as supper.

Furthermore, administration in relation to food can cause confusion for patients. A common misconception is that all medicines should be taken with food. The corollary is that patients will not take their medicines because they did not have anything to eat. For example, a patient may be told to take their medication at breakfast time and therefore believe that it should not be taken if breakfast is not eaten.

Educational tools

Finding better ways to communicate key messages about medicines and improve understanding can assist in improving medication adherence. It is important to remember that educational tools should not be developed with the intent of simplifying the message, but rather transferring the key message in a manner that it is consistent with the learning processes of the target audience.[6]

Successful strategies for improving adherence in the Gapuwiyak community in East Arnhem Land have included the use of anatomical models, 'key language concepts' (that is, phrases that were developed by Aboriginal health workers and used when showing certain illustrations), and a microscope with a video monitor to show patients the bacteria in their urine specimen.[7]

In the Kimberley, a picture of the human body has been used to explain medicines. Tablets are placed on the organ that they are 'keeping healthy' or protecting. This is particularly useful for asymptomatic chronic diseases where greater emphasis on education may be required.

The National Aboriginal Community Controlled Health Organisation (NACCHO) is currently working on a quality use of medicines project to develop medication management tools. This includes the development of medicine information sheets with plain language information and pictures that are intended to supplement the Consumer Medicine Information sheets to better meet the information needs of many Aboriginal patients.

Regional strategies to assist in improving medication adherence

The challenges associated with non-standard approaches to treatment were the impetus for the development of the Kimberley Standard Drug List (KSDL). The KSDL is a rationalised drug list for use in all Kimberley clinics (remote Government clinics and Aboriginal community-controlled health services). This list will be reflected in hospital stock. The KSDL was developed as a joint project by regional healthcare providers based on clinical evidence, existing patterns of use and multidisciplinary consensus.

A standard approach to treatment helps ensure that patients will be able to access the same medications in the places they live and visit. It also increases the familiarity of professionals and patients with the range of medicines used and reduces the likelihood of medication error.

Before the implementation of the KSDL, some clinics were managing over 320 medications, with significant and unnecessary duplication of therapies. With the implementation of the KSDL, fewer formulations need to be managed (approximately 168 essential formulations). The opportunity for residents to have guaranteed access to standard medicines and treatment protocols across the Kimberley will be a positive step towards improving medication adherence.

The contribution of Aboriginal health workers

In the day-to-day operations of an Aboriginal community-controlled health service, the health, cultural and social knowledge of Aboriginal health workers is in demand from patients and professionals. An understanding of how medicines work, familiarity with a range of common medicines and recognition of problems is needed for this work. The extent to which Aboriginal health workers (and registered nurses) have legal coverage for use of medicines is dependent on state and territory legislation and the letter of the law is often out of step with established practice.

In the Kimberley, Aboriginal health workers play an important role in the delivery of home medicine reviews to Aboriginal patients. Home medicine reviews have provided an opportunity for the development of medication management strategies, including strategies to improve adherence, in a collaborative, multidisciplinary context.

As pharmacists typically have minimal direct patient involvement in Aboriginal primary healthcare services, the participation of Aboriginal health workers in the interview stage is seen as a priority in ensuring appropriate communication and delivery of the review. Aboriginal health workers provide valuable information about the health of the patient and social circumstances that may influence medication management. The two-way exchange of information between the pharmacist and Aboriginal health worker is productive and useful for both participants and the patient.

Conducting the home medicine review interview with the Aboriginal health worker in the primary care setting is often preferable for patients. Not only is visiting the home inappropriate for some patients, being in the clinic allows for many recommendations to be actioned more quickly through the involvement of the primary care team.

Conclusion

The need for effective medication management strategies is obvious in the context of such a high burden of disease among Aboriginal people. Considering both the clinical and social needs of the patient is an important step in working towards improved adherence to prescribed treatment. Although there is benefit in tailoring the therapeutic regimen to the needs of the patient, prescribers are encouraged to also look beyond the medication chart and explore other strategies. Visual aids, communication strategies, engaging Aboriginal health workers and regional approaches are strategies that may be useful.

References

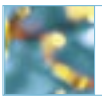
1. Murray R. Prescribing issues for Aboriginal people. Aust Prescr 2003;26:106-9.
2. Humphery K, Weeramanthri T, Fitz J. Forgetting compliance: Aboriginal health and medical culture. Darwin: Northern Territory University Press; 2001.
3. Dunning T. Insulin delivery devices. Aust Prescr 2002;25: 136-8.
4. Clarke P. Actions that made a difference: The case for a pharmacy business at a remote health clinic. CARPA Newsletter 2004;37:14-17.
5. Cass A, Lowell A, Christie M, Snelling PL, Flack M, Marrnganyin B, et al. Sharing the true stories: improving communication between Aboriginal patients and healthcare workers. Med J Aust 2002;176:466-70.
6. Trudgen R. Why warriors lie down and die: towards an understanding of why the Aboriginal people of Arnhem Land face the greatest crisis in health and education since European contact: Djambatj Nala. Darwin: Aboriginal Resource and Development Services; 2000.
7. Bryce S. Lessons from East Arnhem Land: improving adherence to chronic disease treatments. Aust Fam Physician 2002;31:617-21.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 131)

3. Storage conditions should be considered when providing medicines for people who live in remote areas.
4. Dose administration aids are not appropriate for Aboriginal people.



Abnormal laboratory results

Interpreting paediatric biochemistry results

Peter Verras and Ronda Greaves, Complex Biochemistry Department, Laboratory Services, The Royal Children's Hospital, Melbourne

Summary

When interpreting biochemical test results in paediatric patients, consider a number of issues that are associated with and specific to childhood. These include the age of the patient, which may vary from 14 weeks prematurity to more than 18 years, and their body weight, which may range from 500 grams to more than 100 kg. Body size is also a factor in certain situations and is of special concern in the current epidemic of childhood obesity. Children are not miniature adults, however as they age their biochemistry becomes more like that of adults. Added to these patient factors are the effects of the collection process on the blood sample, the method used to analyse the sample, the source of the reference range quoted with the result, and the interpretation placed on the result by laboratory staff.

Key words: obesity, prematurity, puberty.

(Aust Prescr 2005;28:126–9)

Introduction

Historically, the biochemical testing of children, especially very young children, tended to be the province of dedicated 'paediatric' laboratories located in specialist paediatric hospitals. This was usually because small samples of blood were not sufficient for the methods and equipment used in general pathology laboratories at the time. Nowadays almost all of the testing equipment can be adapted to process low-volume samples, although it must be recognised that some of these instruments are more adaptable than others. Most laboratories can now competently analyse small samples without much effect on workflow and consequent productivity, but this does not guarantee that the information provided is adequate for the needs of the referring clinician. The results must be interpreted with a knowledge of the factors that affect children's biochemistry.

Age-dependent factors

Age-related variation is the single most important factor impacting on the interpretation of paediatric results (Table 1).

To make matters difficult, chronological age is not a completely reliable guide for interpretation of results, as developmental processes are not uniformly linked to the age of the patient. It is often more useful to consider results in terms of the four stages of childhood development:

- neonate – the first four weeks of life
- infant – four weeks to two years
- child – two years to puberty
- adolescent – puberty to adulthood.

Most laboratories report results with reference intervals which are applied to finite age ranges by computer data systems, sometimes causing large and sudden changes in what is considered to be 'normal' when a patient ages by only a few hours. Prematurity, age of onset of puberty and body mass index (BMI) are additional important factors that are not fully taken into account, but can impact significantly on the interpretation of selected biochemical results.

Prematurity

Despite advances in perinatal care, preterm birth remains a significant problem affecting as many as 6.3% of all pregnancies. There are more than 16 000 preterm deliveries per year in Australia.[1] Immature and developing organ systems contribute to considerable differences in the concentrations of hormones, proteins, enzymes, metabolites and therapeutic drugs in comparison with adults. It is important to attempt to correct for gestational age especially in the first six months of life. However, most laboratory information systems do not provide such a correction and often this relevant information is not included in the request for the test.

Puberty

Biochemically, puberty is characterised by the secretion of gonadal hormones. In females puberty can start as early as eight years and is usually completed by the age of 16 years, whereas in boys it generally commences around 10 to 12 years of age and is generally completed by 18 years of age. Reference ranges for biochemical tests are based on chronological age and not on Tanner staging and so results should always be interpreted carefully in this group. There are marked changes in the concentrations of gonadotrophins and steroid hormones during puberty.

Table 1

Examples of common analytes where age-related reference ranges need to be considered for the correct interpretation of paediatric results

Analyte	Reference ranges
Albumin	Lower in children, rising from lowest levels in the neonate and infant, to adult levels in adolescence
Alkaline phosphatase	Higher in neonates and until post-puberty
Bilirubin	Higher in neonates due to immature metabolic pathways
Calcium	Lower values are seen in neonates, especially in prematurity. The upper reference limit is higher in paediatric patients. Adult ranges apply at about one year.
Cortisol	No diurnal variation in neonates
Creatinine	Lower due to lower muscle mass in children. Adult ranges apply in late adolescence.
Drug concentrations – relative to dose	Concentrations may be higher in neonates due to immature metabolic pathways, and lower during childhood due to increased metabolic rates. Reference ranges are usually as for adults.
Free triiodothyronine	Higher in paediatric patients. Adult ranges apply from late adolescence.
Follicle stimulating hormone	Change to adult levels at puberty
Glucose	Lower in neonates, especially in prematurity. Adult ranges apply at one month.
Insulin-like growth factor	Change with age throughout life
Luteinising hormone	Change to adult levels at puberty
Magnesium	Lower in neonates, especially in prematurity. Adult levels apply by about one year.
Oestradiol	Change to adult levels at puberty
Steroid hormones	Change with age. Assay interference is possible in premature neonates.
Testosterone	Change to adult levels at puberty
Thyroid stimulating hormone	Slightly higher in neonates. Adult levels apply at one month.
Urea	Higher in neonates, falling to adult levels during infancy
Urine catecholamines	Vary with age until adulthood

Pre-analytical factors

The lack of availability of suitably skilled staff for collecting samples from children may affect the quality of the samples received for testing. Collection problems are encountered mainly in neonates and infants, because collecting capillary blood requires some skill and experience to obtain samples which are likely to yield accurate results for all analytes. Excessive squeezing of a capillary collection site may result in haemolysis, leading to elevation of intracellular analytes such as potassium, magnesium, phosphate and lactate dehydrogenase. Dilution of the sample with tissue fluid can have varying effects on other test results. The consequential small blood sample volume is also more susceptible to the deleterious effects of light, heat, contamination and evaporation than larger-volume venous collections. A frequently encountered problem in small samples is the loss of carbon dioxide into the remaining air space in the tube, leading to falsely low bicarbonate values. The use of inappropriately large specimen containers will exacerbate this and other problems. These factors occasionally generate aberrant results which can only be clarified by repeat collection and analysis.

Collection of timed urine specimens is also often difficult in neonates and infants, and an unusually low timed urine volume must always be viewed with suspicion. Urine output starts at around 100–300 mL per day in infants (3–10 days), increasing with age to adult volumes after puberty.[2]

Analytical factors

For the paediatric biochemist, hormone assays tend to provide the largest challenge in attempting an appropriate balance between cost, turnaround time, and method quality. This is particularly true for full-term and premature babies and for assays that attempt to cater for both the male and female population. Reference ranges provided by different laboratories may vary considerably.

Assay interference

Fetal adrenal steroids persist until at least 40 weeks post conception, that is, until at least the equivalent of term, despite early delivery. Interference by fetal steroids is not routinely assessed or accounted for by some assay manufacturers, as the premature neonate may not be their main consideration when developing the assay. The potential presence of fetal adrenal steroids should be taken into account when performing and interpreting steroid hormone assays in children less than six months of age. These steroids may interfere with the routine steroid assays available in most laboratories.[3] It is possible to mitigate these problems by adapting assay methods, but not all laboratories appear to apply these procedures. Even then, different methods may vary widely in their analytical specificity complicating interpretation even further. When in doubt, hormone assays should be repeated at an age equivalent to or greater than that of a full-term pregnancy, or alternatively the tests may be referred to a specialist paediatric laboratory.

Assay imprecision

In some instances, the choice of assay may be applicable for one section of the population, but may be less than ideal for another section of the population such as children. This was illustrated by a study examining the reliability of results of testosterone assays in females, who have testosterone concentrations comparable to those seen in childhood. The 10 assays examined were the most common assays used in clinical biochemistry laboratories, but they were found to have poor sensitivity and precision for low concentrations of testosterone.[4]

Assay bias (accuracy)

Bias is a major issue for any laboratory test, and will determine the relevance of quoted reference ranges. Routine tests such as electrolytes and lipids may be closely comparable between different laboratories. However, many others including steroids, peptide hormones, therapeutic drugs and tumour markers will show potentially misleading variation if performed by different laboratories, which may use different kits with different antibody content and specificity.

Interpretation of the results

The provision of appropriate reference ranges is crucial to the interpretation of any test result, regardless of the patient group involved. The determination of accurate reference intervals is a considerable burden to any laboratory which is increased by the variations in analyte concentrations frequently encountered in young children.

It is therefore possible that a laboratory which does not have access to a large paediatric patient base may not have the resources to determine paediatric reference intervals applicable to its own specific methods and analytical systems. In these circumstances the laboratory may have to depend upon data supplied by the manufacturer of their testing materials, or perhaps determined by other laboratories. It is possible therefore, that the ranges accompanying results may not always be entirely appropriate. Clinicians are well advised to enquire about the source of the reference range(s) when faced with diagnostic uncertainty. Published guidance on paediatric ranges at different ages is available.[5]

Examples of variations which occur in childhood are:

- In the perinatal period, the reference ranges for glucose, calcium and magnesium are lower, while that of bilirubin is higher, than those of other age groups. In addition, when measuring total calcium concentration, it is essential to correct for albumin in newborns, or preferably measure their ionised calcium.
- In the term neonate, bilirubin and drug metabolism pathways are immature and significant changes in concentrations may occur as these pathways mature during the first few weeks following birth. Urea is higher, but falls to adult levels during infancy. These effects are more pronounced in premature neonates.
- From infancy through childhood, serum creatinine and urinary catecholamine excretion are lower, eventually reaching adult levels during adolescence.
- From infancy to adolescence, alkaline phosphatase and insulin-like growth factor-1 change considerably over time.
- Hepatic drug metabolism increases from neonatal levels during childhood, eventually decreasing to adult levels after puberty. Thus, even weight-adjusted doses required to achieve a therapeutic plasma level may be different from those for adults.

Caution needs to be exercised in the interpretation of hormone results from premature babies, because apparently abnormal hormone levels in premature babies may not be indicative of an underlying pathological process. Hormone assays that have negligible interference, and the availability of age-appropriate reference ranges, are essential for correct and timely interpretation of biochemical results in this age group. More work needs to be conducted by laboratories and manufacturers to develop gestational age-appropriate reference ranges for these analytes.

The pubertal period presents considerable difficulties when assigning reference ranges, since a child may reach puberty earlier or later than may be anticipated. Results may occasionally be seen significantly outside the reference ranges without any apparent pathology. It may therefore be prudent for laboratories not to quote reference ranges for this patient group, especially if there is automated assignment of ranges. Clinicians could consider encouraging their pathology provider(s) to apply interpretative comments instead of possibly incorrect reference ranges. Provision of adequate clinical information to the laboratory will enhance the value of these comments.

Conclusion

Interpretation of laboratory results from paediatric patients may be made difficult by a number of factors. Where uncertainty remains, it may be advisable to refer further testing to a laboratory which receives relatively larger numbers of paediatric samples and which should consequently have more data and greater experience at interpreting the results.

References

1. National Health and Medical Research Council. Clinical practice guidelines: Care around preterm birth. Canberra: NHMRC; 1997.
2. Tietz NW, Burtis CA, Ashwood ER. Tietz textbook of clinical chemistry. 2nd ed. Philadelphia, PA: WB Saunders; 1994. p. 2210.
3. Greaves R, Kanumakala S, Read A, Zacharin M. Genital abnormalities mimicking congenital adrenal hyperplasia in premature infants. J Paediatr Child Health 2004;40:233-6.
4. Taieb J, Mathian B, Millot F, Patricot MC, Mathieu E, Queyrel N, et al. Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women and children. Clin Chem 2003;49:1381-95.
5. Soldin SJ, Brugnara C, Wong EC, editors. Pediatric reference ranges. 4th ed. Washington DC: American Association for Clinical Chemistry Press; 2003.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 131)

5. Automated reference ranges for biochemical tests may be inaccurate for paediatric patients.
6. Excessive squeezing of an infant's heel to obtain a sample of capillary blood may increase the reported concentration of potassium.

Book review

Therapeutic Guidelines: Respiratory. Version 3.

Melbourne: Therapeutic Guidelines Limited; 2005.

205 pages. Price: $39, students $25.30, plus postage*

Cate Howell, General practitioner, Primary Care Mental Health Unit, Department of General Practice, Adelaide

The latest Therapeutic Guidelines state that the respiratory diseases are largely unchanged but there have been new approaches to them. Since the last Respiratory edition in 2000, new drugs have been introduced and more effective delivery devices and management approaches have been developed. General practitioners require an ever-increasing knowledge base and access to comprehensive information. The Therapeutic Guidelines series are always extremely useful, and incorporate clear summary tables. This respiratory update is timely and welcome.

Given the high prevalence of asthma in Australia, it is highly relevant to have a thorough summary of asthma diagnosis and management. This topic is particularly well covered, including risk factor reduction, asthma severity classification and asthma management plans. General practitioners are commonly involved in managing long-term asthma and guidelines are provided. Clinicians will find the summary of treatment of acute asthma attacks in adults and children a useful reference.

The management of chronic obstructive pulmonary disease is well covered, outlines broad management strategies (such as addressing nutritional factors) and emphasises follow-up. The principles of oxygen therapy are outlined early in the book and in this section. Cough can be a problematic presentation and common underlying causes are discussed. Guidelines on conditions such as cystic fibrosis and pleural conditions are provided, and there is a very useful section on sleep apnoea which is increasingly being recognised.

It is important to refresh knowledge of pulmonary function tests regularly, and the section on these is easy to follow, assisted by diagrams. Fitness to fly and scuba dive are covered, as are respiratory drugs in pregnancy and breastfeeding. I would recommend this book as being vital for clinicians to update knowledge and have as a reference.

* Available from www.tg.com.au Phone 03 9329 1566

New drugs

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

Eplerenone

Inspra (Pfizer)

25 mg and 50 mg tablets

Approved indication: heart failure post-myocardial infarction

Australian Medicines Handbook section 6.4.2

Low doses of spironolactone have a role in regimens for the treatment of severe heart failure. The beneficial effects of spironolactone are probably related to its antagonism of aldosterone. As aldosterone concentrations are increased in heart failure, it is a target for drug therapy.

Like spironolactone, eplerenone is a potassium-sparing diuretic. It blocks the attachment of aldosterone to its receptor. As this can reduce blood pressure, eplerenone has been approved as an antihypertensive drug in the USA.

In a study of patients with hypertension and left ventricular hypertrophy eplerenone was found to reduce left ventricular mass, particularly if it was combined with enalapril.[1] If eplerenone can prevent ventricular remodelling it may be beneficial after acute myocardial infarction.

A multinational clinical trial enrolled several thousand patients with left ventricular dysfunction and heart failure 3–14 days after a myocardial infarction. In addition to standard therapy (excluding spironolactone), 3319 patients were assigned to take eplerenone while 3313 patients took a placebo. The dose of eplerenone was 25 mg daily increasing to 50 mg daily after four weeks. After follow-up for an average of 16 months, 478 of the patients taking eplerenone had died compared with 554 of the placebo group. This was a 15% reduction in relative risk. Most of the deaths were from cardiovascular causes, particularly sudden death.[2]

Patients taking eplerenone are at risk of hyperkalaemia. In the heart failure trial serious hyperkalaemia (6.0 mmol/L) occurred in 5.5% of patients compared with 3.9% of the placebo group.[2] Apart from hyperkalaemia, other reasons for discontinuing eplerenone include dizziness and altered renal function.

Eplerenone is mainly metabolised by the liver with most of the metabolites being excreted in the urine. The drug is contraindicated in patients with moderate to severe renal impairment. As it is metabolised by cytochrome P450 3A4 it should not be prescribed with drugs, such as ketoconazole, that inhibit this enzyme.

As eplerenone is said to have relative selectivity for mineralocorticoid receptors, it may not have as many adverse effects as spironolactone. However, gynaecomastia and breast pain can still occur. Although the trials cannot be directly compared, spironolactone reduces the relative risk of death by 30% in patients with severe heart failure.[3] Although there is a risk of hyperkalaemia[4], spironolactone is a well-known and inexpensive drug and is unlikely to be superseded until more data about eplerenone are available.

T T T manufacturer provided all requested information

References

1. Pitt B, Reichek N, Willenbrock R, Zannad F, Phillips RA, Roniker B, et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy. Circulation 2003;108:1831-8.
2. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-21.
3. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.
4. ADRAC. Evidence-based medicine: pitfalls of overlooking safety. Aust Adv Drug React Bull 2005;24:7-8.

Insulin detemir

Levemir FlexPen (Novo Nordisk)

3 mL cartridges containing 100 U/mL

Approved indication: diabetes mellitus

Australian Medicines Handbook section 10.1.1

Analogues of insulin enable patients with diabetes to be treated with regimens that follow the pattern of normal insulin secretion.[1] Insulin detemir is a soluble analogue designed to provide the basal requirements for insulin.

The genetically engineered molecule has a fatty acid side chain which delays absorption and degradation. Insulin detemir is active for 3–14 hours after subcutaneous injection. Depending on the dose, the duration of action can extend to 24 hours, so some patients can manage with a single daily dose.

An open-label study compared insulin detemir with the intermediate acting NPH insulin. The 56 patients, with type 1

diabetes, used one insulin at night for six weeks then switched over to the other insulin. Larger doses of insulin detemir were required to maintain good glycaemic control and serum glucose concentrations were higher for the first few hours after a dose. During the last week of treatment, hypoglycaemia occurred in 60% of the patients injecting insulin detemir and 77% of those injecting NPH insulin.[2]

A larger study compared twice-daily doses of the two insulins. After 16 weeks, the 267 patients given insulin detemir had a lower fasting blood glucose than the 124 patients who had taken NPH insulin. The mean concentration of glycated haemoglobin (HbA_{1c}) decreased slightly more in patients given insulin detemir (mean difference between groups 0.18%).[3]

Studies lasting up to a year show that the effect of insulin detemir on HbA_{1c} is equivalent to the effect of NPH insulin.

As insulin detemir only gradually reduces blood glucose during the night, nocturnal hypoglycaemia is less likely than with NPH insulin. However, there are no significant differences in the frequency of major hypoglycaemia.[2]

To achieve good glycaemic control, patients taking insulin detemir for their basal requirements should also be prescribed a short-acting insulin. Although insulin detemir has been studied in type 2 diabetes it is not currently approved for this indication unless there is no longer a response to oral hypoglycaemic drugs.

The activity profile of insulin detemir may have some advantages over older insulins. It is unknown if this difference will actually improve the outcomes for patients.

☒ manufacturer declined to supply data

References

1. Phillips P. Insulins in 2002. Aust Prescr 2002;25:29-31.
2. Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin. Diabetes Care 2001;24:296-301.
3. Home P, Bartley P, Russell-Jones D, Hanaire-Broutin H, Heeg J-E, Abrams P, et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes. Diabetes Care 2004;27:1081-7.

Answers to self-test questions

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

www.australianprescriber.com

Australian Prescriber is available on the internet in full text, free of charge. Go to **New issue email alert** to be sent an email each time a new issue goes online.

Australian Prescriber mailing list

Australian Prescriber is distributed every two months, free of charge, to medical practitioners, dentists and pharmacists in Australia, on request. It is also distributed free of charge, in bulk, to medical, dental and pharmacy students through their training institutions in Australia. To be placed on the mailing list contact the *Australian Prescriber* Mailing Service.

Tick ☑ whichever of the following apply:

I have access to the *Australian Prescriber* website on the internet ☐ Yes ☐ No

☐ Place me on the mailing list

☐ Delete me from the mailing list

☐ Change my address

☐ Send me all the available back issues

Name: .....

Ref no.: .....
(on the address sheet above name)

Address: .....

.....

.....

Profession: .....
(general practitioner, resident, psychiatrist, surgeon, dentist, pharmacist etc.)

Postal: *Australian Prescriber* Mailing Service
GPO Box 1909
CANBERRA ACT 2601
AUSTRALIA

Telephone: (02) 6241 6044 Fax: (02) 6241 3407

Editorial office

For general correspondence such as Letters to the Editor, please contact the Editor

Telephone: (02) 6282 6755

Fax: (02) 6282 6855

Postal: The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
AUSTRALIA

Email: info@australianprescriber.com

Website: www.australianprescriber.com

Australian Prescriber

Address correspondence to:
The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
Telephone (02) 6282 6755

Australian Prescriber is indexed by the Iowa Drug Information Service, the Australasian Medical Index and EMBASE/Excerpta Medica.

Typesetting
Barnes Desktopping and Design

Printed in Australia by
National Capital Printing
22 Pirie Street, Fyshwick, ACT 2609

Published by the
National Prescribing Service Limited (NPS), an independent Australian organisation for Quality Use of Medicines funded by the Australian Government Department of Health and Ageing

NPS
National Prescribing Service Limited

INTERNATIONAL SOCIETY OF DRUG BULLETINS

Print Post Approved PP349181/00151 • ISSN 0312-8008