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CONTENTS

EDITORIAL

Diagnostic tests and litigation 106
S Bird

LETTERS TO THE EDITOR 108

ARTICLES

Long-acting beta$_2$ agonists for childhood asthma PP van Asperen 111

Medical management of endometriosis K Black, IS Fraser 114

Management of cystic fibrosis in adults P Masel 118

FEATURES

Abnormal laboratory results: Tumour markers 125
D Faulkner, C Meldrum

Medicines Safety Update 122

Patient support organisation 121
Cystic Fibrosis Australia

Dental note 107
Diagnostic tests and litigation

NEW DRUGS

Abiraterone for prostate cancer 128
Cabazitaxel for prostate cancer
Rasagiline for Parkinson's disease
Rilpivirine for HIV
Telaprevir for hepatitis C
Terlipressin for hepatorenal syndrome
Vemurafenib for metastatic melanoma

EDITORIAL

Diagnostic tests and litigation

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Key words
abnormal laboratory results

Aust Prescr 2012;35:106–7

The most common category of litigation against general practitioners is an allegation of diagnostic error. This accounts for approximately 45% of the claims against Australian general practitioners, based on analysis of MDA National's data since 2000. A study of medical negligence claims in which patients alleged a missed or delayed diagnosis in the ambulatory setting found a median of three errors in the diagnostic process. The most common errors were:

- failure to order an appropriate diagnostic test (55%)
- failure to create a proper follow-up plan (45%)
- failure to obtain an adequate history or perform an adequate physical examination (42%)
- incorrect interpretation of diagnostic tests (37%).[1]

The underlying causes of diagnostic error are complex and multifactorial. They typically involve both cognitive and system-related factors.[2]

Cognitive errors involve faults in the clinical reasoning process. The cognitive factors related to investigations generally involve either a failure to consider the correct diagnosis, or a failure to order the appropriate investigation as part of the diagnostic process. A common example of a claim arising from a cognitive error is a failure to consider pulmonary embolus in the differential diagnosis of a patient presenting with dyspnoea. This results in a failure to order appropriate diagnostic tests to confirm or exclude this diagnosis. Another example is a patient presenting with a breast lump who has a normal mammogram, but the doctor fails to order fine needle aspiration cytology as part of the recommended 'triple test' process.

System-related factors generally involve either a failure to follow up the performance or receipt of an investigation, or a failure to inform the patient of a clinically significant test result. These errors often arise when there is not an explicit discussion or shared understanding about how the patient will obtain the results of their investigations. A common example of this type of error is when a prostate specific antigen test is ordered as part of a screening process, but the patient does not contact or attend the practice to obtain the result. If the prostate specific antigen is markedly elevated and there is a breakdown in the recall system in the practice then the patient will not be informed of the abnormal result or provided with recommendations about further investigations.

The courts have confirmed that if a patient undergoes a diagnostic test ordered by a doctor, then it is the doctor's responsibility to review the results and consider if further action is required. The case of *Kite v Malycha* [1998] involved an allegation of failure to diagnose breast cancer in a 31-year-old patient. The surgeon performed fine needle aspiration cytology which revealed cancer, but as a result of a system-related error, the fine needle aspiration result was not received and reviewed by the surgeon. The court found that 'irrespective of any initiative taken by the patient, [the surgeon] owed a duty to find out what the outcome of the pathological examination of the fine needle aspiration was … it is unreasonable for a professional medical specialist to base his whole follow-up system, which can mean the difference between death or cure, on the patient taking the next step'.[3]

If the result of an investigation is clinically significant for the patient, a medical practitioner has a legal duty to follow up or 'recall' the patient to inform them of the result and any recommendations for future management. Notwithstanding a patient's failure to contact the practice or return for a follow-up appointment, it is ultimately the medical practitioner's responsibility to inform the patient. The number and types of attempts to recall the patient will depend on the circumstances. Depending on the likely harm to the patient, three telephone calls at different times of the day and follow-up by mail may be needed.[4]

Importantly, the courts have also found that in some circumstances general practitioners and their staff have a duty either to ensure a patient undergoes a recommended investigation, or to satisfy themselves that the patient has made an informed decision not to undergo the recommended investigation. In

From the Editor

Current prescribing patterns suggest that long-acting beta agonists are being overused in childhood asthma. Peter van Asperen discusses where these drugs fit in therapy.

Cystic fibrosis is a less common respiratory disease, but has many complications. Phillip Masel reviews the current treatments.

Like cystic fibrosis, endometriosis can contribute to infertility. Kirsten Black and Ian Fraser say that infertility is usually an indication for referring a woman with endometriosis to a specialist.

The diagnosis of endometriosis is often delayed. Similar delays in the diagnosis of cancer may have medicolegal implications, as discussed by Sara Bird. It will therefore be important to follow up the results of tests for the tumour markers reviewed by David Faulkner and Cliff Meldrum.

Young v Central Australian Aboriginal Congress Inc [2008] a general practice was found negligent in failing to follow up a patient who had been referred by a general practitioner for blood tests and also referred to a specialist within the practice for investigation of suspected ischaemic heart disease. When the patient failed to attend the appointment for a stress test, the practice did not follow up the patient due to a system-related error, where the medical record of another patient with the same name was reviewed. Interestingly, in this case the general practitioner who provided the patient with the referral for the investigations was found not to have been negligent because the court concluded the general practitioner had 'explained the potential seriousness of ischaemic heart disease and the importance of the follow-up appointments'. The court also found the patient had contributed to the outcome because he 'failed in his own interests to attend either the appointment or to ever raise the issue of these tests when he subsequently attended [the practice] for other unrelated conditions'. The compensation awarded was reduced by 50% to account for the patient's contributory negligence.[5]

Once a patient has been properly informed of their results and the management recommendations, it is up to the patient to decide whether or not to follow this advice. The law recognises that there is legally effective informed consent, but also legally effective informed refusal.

So what does this mean for medical practitioners? The law does not impose a duty to ensure patients undergo all of the investigations a doctor has ordered. If the patient does undergo the recommended tests, then there is a duty on the doctor to review the results and consider what action, if any, is required. While there is some evidence that Australian medical practitioners order more tests as a result of medicolegal concerns,[6] the key to minimising litigation related to investigations should involve attention to cognitive factors, such as ordering the correct investigations during the diagnostic process, and having rigorous recall systems to ensure the appropriate follow-up of patients and their test results.[4] The importance of good communication to ensure the patient understands the reasons for, and the consequences of not, undertaking a recommended investigation and also how to obtain their investigation results cannot be overemphasised. Good documentation is also essential. ◀

Conflict of interest: none declared

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Dental note

Diagnostic tests and litigation

General practice dentists in Australia usually undertake any diagnostic tests within the confines of their clinic and the results are immediately relayed to the patient. Simple vitality testing, percussion tests and intra-oral radiographs are usually sufficient for immediate diagnosis and treatment planning. Occasionally there is a need for further investigations, such as an orthopantomogram or cone-beam CT and conveying these results to patients should be done in a timely manner. When dentists order a test it is their responsibility to ensure that the result, with interpretation, is directly communicated to the patient.

Of concern is our professional responsibility when referring patients for further specialist investigation and care, particularly for the management of a potentially malignant oral lesion. On the one hand, there can be a failure in thoroughly examining patients and not recognising abnormalities. However, this can be greatly compounded if there is a lack of communication, emphasising the importance of the recommended referral and following up to ensure the patients proceed with our recommendations. Simple procedures for referral, communication with the specialist practice and documenting communication should not delay diagnosis which could adversely affect the outcome for the patient.

Michael McCullough
Chair
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Australian Dental Association

LETTERS

Letters to the Editor

New drugs for osteoporosis

Editor, – I read 'New drugs for osteoporosis' by Peter Ebeling with interest (Aust Prescr 2011;34:176-81). I must compliment him on a lucid, comprehensive and informative article about a very common disease. The comparative table about the new drugs gives almost all the information at a glance. I understand that these drugs are to be given when usual treatment is ineffective. However, I have a few questions to ask the author:

1. Which is the drug of first choice amongst the new drugs, especially in refractory cases?
2. In some countries or ethnicities menopause starts early. Does the line of management change?
3. For therapeutic menopause, which invariably is earlier than usual, what should be the management since oestrogen is missing and replacement therapy is contraindicated?

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Peter Ebeling, author of the article, comments:

I would like to thank Professor Yadav for her thoughtful questions. In response, I would say that in Australia three of the four osteoporosis medications mentioned in my article are first-line treatments for osteoporosis – zoledronic acid, denosumab and strontium ranelate. They are all used as alternative options to the other first-line treatments – oral bisphosphonates or raloxifene. However in patients with severe osteoporosis, teriparatide is used when fractures occur after 12 months of therapy with other medications or when intolerance to these medications occurs.

In answer to question 1, if fractures have occurred on oral bisphosphonates it could be because the medications have been taken incorrectly or they are ineffective in patients with severe osteoporosis. If compliance or correct dosing is thought to be the main issue, parenteral therapy with either zoledronic acid or denosumab would be best. However, if the treatment was truly ineffective, teriparatide would be a better option for patients with severe osteoporosis.

In answer to question 2 about early menopause, most specialists would reserve treatment with these drugs until later in life when the absolute fracture risk is higher (calculated using the FRAX or Garvan Institute tools). However if the absolute fracture risk was already high, all would be options for treatment with the exception of teriparatide.

With therapeutic menopause (question 3), it would depend on whether the absolute fracture risk was elevated. Oral or intravenous bisphosphonates, denosumab or strontium ranelate could all potentially be used to prevent bone loss in these younger postmenopausal women.

Dental notes: Bisphosphonates and osteonecrosis of the jaw

Editor, – As a clinician I was concerned to read the dental note by Michael McCullough (Aust Prescr 2011;34:181), in which the incidence of osteonecrosis of the jaw in bisphosphonate users was quoted as being 1/500 to 1/1500. The reference quoted is a retrospective survey of 13 946 individuals. It is worth noting that other studies, in some cases with much larger sample sizes, have concluded that the incidence is rather lower. One review estimated the risk with oral bisphosphonates for osteoporosis to be between 1/10 000 and less than 1/100 000 patient-treatment years.[1] Another study of medical claims from 714 217 individuals concluded that intravenous, but not oral, bisphosphonates seem to be strongly associated with adverse outcomes in the jaws.[2] This conclusion was reiterated by Canadian guidelines.[3] It also appears that the risk of osteonecrosis of the jaw is substantially higher in patients being treated for cancer than it is in patients with senile osteoporosis.

My concern is that patients may be discouraged from using bisphosphonates because of concerns about osteonecrosis of the jaw. I understand that clinical experience with a patient suffering from this condition is likely to have a powerful effect on a practitioner, but we should aim to help our patients make quality decisions based on objective assessments of the risks and benefits.

Let us use the example of a 70-year-old woman who is estimated to have a 5% risk of sustaining a fractured neck of femur over five years, using a tool such as FRAX or the Garvan calculator. If we assume a 20% death rate in the 12 months following

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such a fracture, then the absolute risk of death is 1%. Intravenous zoledronate has been shown to reduce the incidence of hip fracture by 41%. Treating the patient would reduce the five-year hip fracture risk to 2.95%, in turn reducing the risk of death to 0.59%. This absolute reduction of the risk of hip fracture of 2.05% equates to a number needed to treat of 49 to prevent a hip fracture, or 243 to prevent a premature death subsequent to a hip fracture. This compares very favourably with the potential harms of bisphosphonate use, even assuming the higher rates quoted by Dr McCullough.

It is entirely appropriate to use bisphosphonates carefully, preferably having estimated absolute fracture risk, and to take steps to optimise oral health before starting treatment.

Simon Vanlint
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Michael McCullough, author of the dental note, comments:

Dr Vanlint raises some very interesting points regarding the risk of bone fracture and osteonecrosis of the jaw. We agree that the careful use of bisphosphonates after clinical assessment and estimation of fracture risk is entirely appropriate and can have significant benefits for patients.

The discussion regarding the incidence of bisphosphonate-associated osteonecrosis of the jaw continues and it was once thought to be low and of an order of 1/10 000 to 1/100 000. More recent studies show the risk to be more likely around 1/1000 (95% confidence interval 1/500 to 1/1500).[1] This was previously quoted in an information pamphlet produced for Australian doctors and dentists by both Osteoporosis Australia and the Australian Dental Association. Interestingly, some specialist single centre studies show the risk following dental extraction to be of the order of 1/300.[2] Other ongoing studies will shed more light on the true incidence and risk factors for delayed dental healing and its association with bisphosphonate use.

Irrespective of the exact incidence of this adverse event, Dr Vanlint is entirely correct in stating that optimising oral health before bisphosphonate treatment is ideal, and will diminish the likelihood of osteonecrosis of the jaw occurring.

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Medicinal mishap: Dabigatran – a new safe drug to replace an old poison?

Editor, – Boehringer Ingelheim suggests an alternative title for the feature about dabigatran (Aust Prescr 2012;35:64-5) – Medicinal mishap: Always read the product information before prescribing.

Given the case history of the elderly woman with nephropathy (creatinine clearance (CrCl) 29 mL/min), she should clearly not have been prescribed dabigatran. This serves to reinforce the need for appropriate patient selection consistent with the approved product information which includes the contraindication 'severe renal impairment (CrCl <30 mL/min)'.

Prescribers should always read the product information before prescribing, regardless of whether a drug is new or old. As the sponsor for dabigatran, we are concerned the authors of this article did not include the dabigatran product information as a reference. The product information provides information pertinent to many of the issues raised in this case history.

On presentation to hospital, the patient was reported as having an INR of 2.5. As the authors mention later in the article, interpretation of an INR 2–3 weeks after starting dabigatran is meaningless. This information is provided in the product information. Further, and very importantly, when switching from warfarin to dabigatran, prescribers should only commence dabigatran once the INR is under 2. It is not clear whether this was confirmed in this clinical scenario.

The authors quote the Queensland Health guidelines for managing patients on dabigatran who present to hospital.[1] These recommendations appear broadly consistent with the product information for dabigatran. Interventions recommended for the reversal of moderate-to-severe or life-threatening bleeding by the Queensland Health document

LETTERS

and the product information include platelets, oral charcoal, recombinant factor VIIa, activated prothrombin complex concentrates (for example, factor eight inhibitor bypassing activity FEIBA), haemodialysis and charcoal haemofiltration. These were not used in this case.

Lastly, the authors incorrectly assert 'Currently, no assay of dabigatran's effect on coagulation is available'. A direct thrombin inhibitor assay (Hemoclot) is commercially available in Australia for assessing the anticoagulant activity of dabigatran.[2]

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Joel Iedema, one of the authors of the medicinal mishap, comments:

We thank Boehringer Ingelheim for highlighting the importance of patient selection. This principle underlies safe and effective prescribing of all medicines, but is particularly critical for medicines such as anticoagulants. This patient was not a suitable candidate for dabigatran and we reinforce the need to read the product information and other independent literature for unfamiliar medicines before prescribing.

In response to the letter, the Australian product information states that the INR is 'too insensitive' to be used for therapeutic monitoring. A problem with inconsistent INR results related to certain assays was described post-marketing.[1] While a dabigatran assay is now available, it is provided by select pathology providers and evidence-based guidelines for rational use are lacking.

Evidence for dabigatran reversal is very limited. Inactivated prothrombin complex has no effect in dabigatran reversal[2] and no human data are available for other treatments.[3] Many of these treatments carry significant risks of their own and the costs are considerable. Anticoagulant reversal is critical to the management of bleeding and the current lack of specific reversal should be included in harm-benefit discussions with patients.[4]

These issues further reinforce the key message of our article that the real-world risk of any medicine is often not fully appreciated until considerable post-marketing experience has been gained. Regrettably, real-world risk does include inappropriately prescribed medication. Postmarketing surveillance may identify other patient groups at increased risk of adverse events, which would only reinforce the need for careful patient selection.[5]

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Editorial note:

The Editorial Executive Committee believes that the approved product information is an important document for all drugs and should be consulted before prescribing. It is therefore unnecessary to cite it as a reference for every drug mentioned in *Australian Prescriber*. Our editorial practice is therefore to not reference the product information at the end of every article. The authors of the Medicinal mishap included the product information for dabigatran in their original draft, but it was deleted in accordance with our usual practice.

ARTICLE

Long-acting beta$_2$ agonists for childhood asthma

SUMMARY

Long-acting beta$_2$ agonists are currently overprescribed in children. They are also often used inappropriately as first-line therapy and are not recommended for children aged five years or less.

Due to the paucity of paediatric clinical trials, the evidence for the efficacy and safety of long-acting beta$_2$ agonists in children is limited. There is little evidence that they reduce the risk of severe exacerbations and some evidence that they may actually increase the risk.

The regular use of long-acting beta$_2$ agonists may also result in a loss of protection against exercise-induced bronchoconstriction, and the development of tolerance to short-acting beta$_2$ agonists.

Long-acting beta$_2$ agonists are only one option for children whose asthma is not adequately controlled with inhaled corticosteroids alone – the other options being an increase of inhaled corticosteroid dose or the addition of a leukotriene receptor antagonist. For children whose major ongoing symptoms are activity related, the addition of a leukotriene receptor antagonist is the preferred option.

Introduction

Australian guidelines for persistent childhood asthma advocate a stepwise approach to therapy with preventer drugs.[1] These guidelines highlight that the vast majority of children requiring preventer therapy will be well controlled on either low-dose inhaled corticosteroids or a leukotriene receptor antagonist. Long-acting beta$_2$ agonists should be given only to children who remain symptomatic on optimal doses of inhaled corticosteroids.

There is limited evidence for the efficacy of long-acting beta$_2$ agonists in children,[2] but combination therapy (inhaled corticosteroids and long-acting beta$_2$ agonists) is commonly prescribed as first-line when preventer therapy is needed. Combination therapy now represents over 40% of prescribed preventer therapy in children. Based on the frequency of asthma patterns in children and the stepwise approach advocated by the current National Asthma Council of Australia guidelines,[1] combination therapy should represent no more than 10% of prescribed preventer therapy in children and probably less, given the availability of alternative step-up options.

A greater concern is that combination therapy now represents 20% of **all** prescribed asthma medication (preventers and relievers) in pre-school children.[3] This is outside the prescribing indications for combination therapy and no evidence exists for the efficacy or safety of long-acting beta$_2$ agonists in this age group. Combination therapy is also often inappropriately prescribed for intermittent, rather than regular, use.

Efficacy of long-acting beta$_2$ agonists in children

A Cochrane review has assessed the addition of long-acting beta$_2$ agonists to inhaled corticosteroids for persistent asthma in children.[2] It included 25 randomised trials, representing 31 control–intervention comparisons, in 5572 children. Importantly, no studies included children less than four years of age.

There were 24 comparisons of adding long-acting beta$_2$ agonists or placebo to a constant dose of inhaled corticosteroids. These trials showed a predictable small and probably not patient-important improvement in lung function. There was no significant reduction in exacerbations in the children taking regular long-acting beta$_2$ agonists.

No trials of long-acting beta$_2$ agonists have been conducted in pre-school children

Seven studies compared the addition of long-acting beta$_2$ agonists with an increased dose of inhaled corticosteroids. The children on long-acting beta$_2$ agonists had significantly improved lung function and short-term linear growth when compared to those on higher dose inhaled corticosteroids. However, there was a non-significant increase in exacerbations requiring oral corticosteroids and hospitalisation (which the authors concluded required further examination).

Another Cochrane review highlighted the difference in the effectiveness of long-acting beta$_2$ agonists

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Key words
inhaled corticosteroids, leukotriene receptor antagonists

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in children versus adults.[4] This review compared the addition of long-acting beta$_2$ agonists to inhaled corticosteroids versus higher dose inhaled corticosteroids, in both adults and children with suboptimal asthma control despite low-dose inhaled corticosteroids. In adolescents and adults the combination of long-acting beta$_2$ agonists and inhaled corticosteroids was modestly more effective in reducing the risk of exacerbation requiring oral corticosteroids than a higher dose of inhaled corticosteroids. However, in children, combination therapy did not lead to a significant reduction, but rather a trend toward an increased risk of severe exacerbations and hospital admission.[4]

A further Cochrane review examined the addition of long-acting beta$_2$ agonists to inhaled corticosteroids versus inhaled corticosteroids alone as first-line therapy for persistent asthma in adults and children who had previously taken steriods. This review concluded that the 'current evidence does not support the use of combination therapy as first-line preventive treatment, without a prior trial of inhaled corticosteroids'.[5] While the combination of budesonide and eformoterol is approved for patients aged 12 years and over, there are limited paediatric data.

Safety of long-acting beta$_2$ agonists in children

The Cochrane reviews raised safety concerns about an increased risk of severe exacerbations and hospitalisation with long-acting beta$_2$ agonists.[2,4] These observations are consistent with a recent meta-analysis which found an increased risk of severe and life-threatening asthma exacerbations associated with long-acting beta$_2$ agonists, even when they were used with concomitant inhaled corticosteroids.[6] This finding contradicts previous suggestions that the increased risk of severe exacerbations with long-acting beta$_2$ agonists is only seen in patients treated with long-acting beta$_2$ agonists alone.

A possible explanation for the increased risk of severe exacerbations is the development of tolerance to short-acting beta$_2$ agonists, resulting in a diminished response to the child's normal rescue therapy. This assumption is supported by a recent study in children with poorly controlled exercise-induced asthma, despite inhaled corticosteroids. The trial compared montelukast versus long-acting beta$_2$ agonists as add-on therapy to inhaled corticosteroids. Long-acting beta$_2$ agonist therapy was associated with the development of tolerance to both protection against exercise-induced bronchoconstriction and the response to short-acting beta$_2$ agonists.[7]

These safety concerns have led the US Food and Drug Administration (FDA) to recommend that long-acting beta$_2$ agonists should only be used as combination therapy to ensure that children continue to receive an inhaled corticosteroid. To limit exposure, the long-acting beta$_2$ agonist should be withdrawn once good asthma control has been achieved.[8] More recently the FDA issued a requirement for further trials in children, adolescents and adults, to 'provide data in a timely fashion that will clarify the safety risks associated with long-acting beta$_2$ agonists when used concurrently with inhaled corticosteroids, and to inform the safe use of these medications for the treatment of asthma'.[9]

Comparison with other treatments

The currently recommended options for children whose asthma is not adequately controlled on inhaled corticosteroids alone are:

- adding a long-acting beta$_2$ agonist
- adding a leukotriene receptor antagonist
- increasing the dose of inhaled corticosteroids.

Before intensifying the treatment of poorly controlled asthma it is important to first exclude other factors contributing to poor control. These include incorrect diagnosis, poor adherence, inappropriate delivery device and poor inhaler technique.

When comparing the addition of long-acting beta$_2$ agonists to an increased dose of inhaled corticosteroids, current evidence suggests that while regular use of long-acting beta$_2$ agonists will predictably improve lung function, the risk of exacerbation appears, if anything, to increase.[2,4]

A randomised triple crossover study in 182 children aged 6–17 years of age who had uncontrolled asthma on 100 microgram of fluticasone propionate twice daily also provides relevant comparative information.[10] These children received 16 weeks on each of the following therapies, in random order:

- 250 microgram of fluticasone twice daily (inhaled corticosteroid step-up)
- 100 microgram of fluticasone plus 50 microgram salmeterol twice daily (long-acting beta$_2$ agonist step-up)
- 100 microgram of fluticasone twice daily plus 5 or 10 mg montelukast daily (leukotriene receptor antagonist step-up).

The response was assessed by a composite index comprising exacerbations requiring oral corticosteroids, asthma-control days and forced expiratory volume in one second. Overall the probability of the long-acting beta$_2$ agonist step-up providing the best response was higher (45%), but the probability of having a best response to leukotriene receptor antagonist (28%) or inhaled corticosteroid

(27%) step-up was also significant. This highlights the variability of children's responses to these drugs, plus the need to regularly monitor and appropriately adjust each child's therapy.[9]

What is clear is that leukotriene receptor antagonists are superior to long-acting beta$_2$ agonists in protecting against exercise-induced bronchoconstriction as add-on therapy in children already receiving inhaled corticosteroids.[7] Further, in contrast to regular use of long-acting beta$_2$ agonists, leukotriene receptor antagonists are not associated with the development of tolerance to either protection against exercise-induced bronchoconstriction, nor responsiveness to short-acting beta$_2$ agonists.[7] Montelukast has now been listed in the Australian Pharmaceutical Benefits Scheme for add-on treatment (as an alternative to long-acting beta$_2$ agonists) for children aged 6–14 years, who despite inhaled corticosteroids, have ongoing activity (exercise)-related asthma.

Box **Recommendations on step-up options** [11]

In situations where effective control of asthma cannot be achieved with doses of 400 microgram/day budesonide, or 200 microgram/day fluticasone or hydrofluoroalkane-beclomethasone dipropionate or 160 microgram/day ciclesonide, the main step-up options include increasing the inhaled corticosteroids dose or adding a long-acting beta$_2$ agonist or a leukotriene receptor antagonist. In the absence of evidence of safety and efficacy, the use of long-acting beta$_2$ agonists is not recommended in children aged five years or younger. (Strong recommendation, moderate quality evidence)

In children with ongoing exercise-induced symptoms, despite inhaled corticosteroids, adding leukotriene receptor antagonists has been shown to be effective and superior to long-acting beta$_2$ agonists, and does not have the problem of the development of tolerance. (Strong recommendation, moderate quality evidence)

Recommendations

There are few efficacy trials of long-acting beta$_2$ agonists in children with asthma, and no trials have been conducted in children under four years of age. There are ongoing safety concerns with long-acting beta$_2$ agonist use, particularly in children, which require further clarification. Based on current evidence the Thoracic Society of Australia and New Zealand has made recommendations on 'The role of corticosteroids in the management of childhood asthma'[11] (see Box).

In brief, there are three step-up options for children not adequately controlled on inhaled corticosteroids:

- adding a long-acting beta$_2$ agonist
- adding a leukotriene receptor antagonist
- increasing the dose of inhaled corticosteroids.

The addition of a leukotriene receptor antagonist is the preferred option for children with ongoing activity-related asthma. Long-acting beta$_2$ agonists are not recommended for children five years or younger. <

Professor Peter van Asperen is currently a member of the MSD (Aust) Paediatric Respiratory Physician Advisory Board and has received speaker fees from MSD for presentations on management of asthma and wheeze in children. He is a member of the GlaxoSmithKline Paediatric Respiratory Taskforce which has been convened to ensure appropriate prescribing of Seretide in children. His department has received research funding in the past from GlaxoSmithKline, Astra Zeneca, MSD, Boehringer Ingelheim and Altana for involvement in clinical trials but is not currently receiving funding from these companies.

Q:

SELF-TEST QUESTIONS

True or false?

1. Long-acting beta$_2$ agonists may induce tolerance to short-acting beta$_2$ agonists in children with asthma.
2. In childhood asthma, the combination of a long-acting beta$_2$ agonist with an inhaled corticosteroid significantly reduces severe exacerbations.

Answers on page 135

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ARTICLE

Medical management of endometriosis

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Key words
dysmenorrhoea, laparoscopy, menstruation, pelvic pain

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SUMMARY

Endometriosis is increasingly being recognised as a disease which commonly affects women through the reproductive years.

It is the commonest cause of chronic pelvic pain in developed countries, and frequently begins in adolescence.

Endometriosis is a highly variable condition, and diagnosis can be difficult. Confirmation of diagnosis still requires laparoscopy in most situations, but successful therapy of many, especially milder, cases can be based on a presumptive diagnosis. A careful history needs to be taken to try and exclude other common causes of pelvic pain.

Medical management requires treatment of pain with analgesics, and suppression of disease activity mainly with hormonal preparations. This needs to be integrated with the potential need for surgery.

Patients with persistent pain unresponsive to hormonal treatments and analgesics should be referred for specialist care.

Introduction

Endometriosis is a complex condition of great variability and presentation (see Box 1).[1] In many cases, this variability leads to difficulty and delay in making the diagnosis.[1,2] Most studies report a mean duration of 8–10 years between the onset of symptoms and the diagnosis. Longer delays can occur when the symptoms begin in adolescence.[3,4] Aside from the variability in presentation, the major reasons for delays in diagnosis include the prevalence of pelvic pain symptoms in the community and a lack of awareness by many health professionals that the onset of symptoms often occurs in adolescence. However, it is widely recognised around the world that endometriosis is now the commonest cause of chronic pelvic pain in women in most industrialised societies.

Early recognition of endometriosis

Early recognition of the signs and symptoms (especially in those with a family history) will allow medical management to reduce disease progression and its consequences, including infertility and endometriosis-associated health problems. Educating health professionals and the community to consider the diagnosis of endometriosis in young women with dysmenorrhoea and pelvic pain is important.

Assessing women with suspected endometriosis

Diagnosis based purely on clinical features may have a high rate of error so an important aspect of managing women with suspicious symptoms (Box 2) is knowing when to refer them for a specialist opinion (Box 3). If classic combinations of symptoms are present, especially in the presence of a family history, a diagnosis of endometriosis is highly likely.

The initial assessment involves taking a detailed history of the duration and nature of pelvic pain. Ask about its relationship to the menstrual cycle, the presence of bowel and bladder symptoms and the impact of posture and movement on pain.

There may be overlap between the symptoms of irritable bowel syndrome, pelvic inflammatory disease and endometriosis and it can sometimes be difficult to distinguish clinically between these conditions.[5] There are also a number of co-existing pain conditions in women with endometriosis, such as interstitial cystitis, which should be considered in the assessment of a woman with pelvic pain. Women with irritable bowel syndrome will usually experience relief following a

Box 1 **Variable factors leading to a heterogeneous clinical picture of endometriosis**

The age of symptom onset – from adolescence through to later reproductive years

The delay to diagnosis – often 8–10 years with onset in adolescence

The types of symptoms experienced – usually much more complex than just pain, including infertility, abnormal menstrual bleeding patterns, exaggerated and painful abdominal bloating, other gastrointestinal symptoms, urinary symptoms, extreme lethargy

The anatomical sites of ectopic lesions – there are possibly different 'phenotypes' of endometriosis (peritoneal, ovarian endometriomas, deep invasive lesions)

The response to medical or surgical treatment

The likelihood of early recurrence of disease

The variable 'natural' history of disease progress over years

bowel motion, whereas this relief does not usually occur with endometriosis.

Initial investigations may include urinalysis, screening for sexually transmitted infections and a transvaginal ultrasound scan. Transvaginal ultrasound scanning by a specialist in pelvic sonography has a reasonably high sensitivity and specificity for diagnosing ovarian endometriotic cysts and deep infiltrating bowel endometriosis,[6,7] but is of little use in identifying the commoner types of peritoneal disease. Diagnostic laparoscopy by an experienced gynaecological endoscopist remains the best way of confirming or excluding most types of endometriosis as there is no consistently reliable non-invasive test.[8]

When no diagnosis is evident

When uterine, adnexal or cervical motion tenderness is present in sexually active young women and no other cause is identified, guidelines recommend treatment for presumptive pelvic inflammatory disease.[9] However, other possible diagnoses may need to be pursued. Endometriosis is under-diagnosed in this group of young women and having a low threshold for referral is important.

When examination and investigations reveal no definitive diagnosis, women should be offered simple analgesia to control their pain, beginning with non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol in effective doses. Patients with persistent pain unresponsive to these analgesics should be referred for specialist care, including a gynaecologist for diagnostic laparoscopy.

Management of women with confirmed endometriosis – factors to consider

The management of endometriosis may be influenced by the woman's presenting complaint, for example pain or infertility.

Endometriosis is a chronic condition that may require lifelong management. Medical treatment is usually based on suppressing ovulation and inducing a steady hormonal environment. Commonly used drugs and their mechanisms of action are listed in Table 1. Both oral progestogens and combined oral contraceptives may be effective in relieving pain. They are generally well tolerated and are initially preferable to danazol, gonadotrophin releasing hormone agonists and aromatase inhibitors.[10] In our clinical experience, in most women progestogen-only methods that induce decidualisation of the endometrial lesions are

Box 2 Symptoms suspicious of endometriosis

- Dysmenorrhoea (moderate to severe in 60–80%)
- Chronic pelvic pain (troublesome in 40–50%)
- Deep dyspareunia (troublesome in 40–50%)
- Infertility (30–50%)
- Premenstrual spotting lasting 1–2 days (common)
- Dyschezia, tenesmus, painful abdominal bloating (10–40%)
- Dysuria, haematuria (5%)
- Heavy menstrual bleeding (10–20%)

Box 3 When to refer women for specialist opinion

- Unexplained persistent pelvic pain
- Symptoms unresponsive to initial supervised hormonal or analgesic treatment
- Primary infertility of greater than one year (or less in older women)
- Finding a pelvic mass or nodule, especially if tender, on bimanual vaginal examination

Table 1 Treatment options for endometriosis (in addition to necessary analgesia)

Medical treatment	Mechanism of action	Adverse effects
Combined oral contraceptives	Inhibit ovulation, decidualise endometriotic tissue	Mood changes, nausea, headaches, hypertension, deep venous thrombosis (rare)
Oral progestogens	Decidualisation and atrophy of lesion tissue	Irregular bleeding, mood changes, weight gain, acne
Levonorgestrel intrauterine system	Decidualisation and atrophy of lesion tissue	Irregular bleeding, mood changes, breast tenderness
Etonogestrel implants	Inhibit ovulation, decidualise lesion tissue	Irregular bleeding, mood changes, weight gain, acne
Gonadotrophin releasing hormone agonists	Down-regulate the pituitary-ovary axis and produce a hypo-oestrogenic state, with lesion atrophy	Hot flushes, change in libido, vaginal dryness, headaches, emotional lability, acne, myalgia, decreased breast size
Aromatase inhibitors	Inhibit oestrogen synthesis with lesion atrophy	Hot flushes, arthralgia, myalgia, osteoporosis
Androgens (danazol)	Complex effects on the hypothalamic-pituitary-ovarian axis and uterus, including mild, impeded androgenic action, resulting in lesion atrophy	Acne, hirsutism, voice changes, emotional lability

more effective than combined oral contraceptives. There is a trend towards use of the delivery systems like the levonorgestrel intrauterine system, which has evidence of efficacy,[11,12] and the subdermal etonogestrel implant, where the benefit has been documented so far mainly in case reports. It is not logical to give an oestrogen-containing preparation (combined oral contraceptive) to a woman with an oestrogen-sensitive disease, but all modern combined oral contraceptives have a strong progestogenic balance and many women do well with this treatment. There is no evidence that one combined oral contraceptive is superior to another.

Fertility

In a woman wishing to conceive, medical treatment will relieve symptoms but there is strong evidence that it does not improve fecundity. The recommended approaches are surgical excision of macroscopically recognisable lesions on the peritoneal surface, deep lesions or ovarian cyst linings by a specialist, or referral for assisted fertilisation techniques.[13]

Management by a gynaecologist

Specialist management of endometriosis involves judicious use of laparoscopy for diagnosis, well-planned laparoscopic surgery and medical management. Excisional surgery is usually the initial treatment of choice, as it confirms the diagnosis, significantly reduces painful symptoms and improves quality of life in 67–80% of patients compared to techniques using diathermy or laser to coagulate or vaporise visible lesions. Such surgery can be difficult but complete excision is the goal. Postoperative medical preventive therapy should always be considered, unless pregnancy is immediately desired. Deep infiltrating pelvic endometriosis involving the bowel requires a multidisciplinary approach with colorectal surgery.

In women with minimal to mild endometriosis-associated infertility, there is evidence that surgery that excises visible deposits, divides adhesions, and normalises pelvic anatomy may enhance fertility.[14] Although there are no randomised controlled trials or meta-analyses available to answer the question of whether surgical excision of deep invasive endometriosis enhances pregnancy rates, observational studies provide some support.[15] Laparoscopic cystectomy for ovarian endometriomas greater than four centimetres in diameter improves fertility, compared to drainage and coagulation of the cysts, but the presence of a small asymptomatic endometrioma may not require surgical intervention before *in vitro* fertilisation.

There is usually amelioration of symptoms during pregnancy and there may sometimes be long-term improvement in pain after pregnancy. However, many women with endometriosis will experience recurrence of symptoms as soon as pregnancy and breastfeeding have been completed.

It is important to recognise that the extent of endometriosis may not correlate with the presenting symptoms, and some women with mild peritoneal endometriosis may have severe debilitating pain while others with severe disease and gross distortion of pelvic anatomy may experience minimal or no symptoms. Further, if endometriosis is found at laparoscopy it may not always be the major cause of pain in an individual, and pain symptoms attributed to endometriosis occur in some women without obvious laparoscopic evidence of endometriosis.

Recurrence after surgery

Endometriosis has a propensity to recur with time after conservative surgery (excision of visible lesions, rather than removal of the ovaries and uterus). At least 10–20% of treated patients developed signs and symptoms of persistent or recurrent endometriosis within one year.[16]

Secondary prevention

There is good evidence that hormonal treatments after surgery reduce symptoms and disease recurrence. The combined pill and oral progestogens have been found to reduce the frequency and severity of recurrent endometriosis-related dysmenorrhoea[17] and endometriomas after surgery.[18] Local pelvic release of levonorgestrel via an intrauterine system is an effective way of delivering progestogen therapy and has been found to be as effective at relieving dysmenorrhoea as gonadotropin releasing hormone agonists[19] or injectable progestogens, without the same degree of systemic symptoms.[20] The role of the subdermal etonogestrel implant in this situation has not yet been clarified.

Treatment

If recurrence occurs, initial treatment should be appropriate analgesics and hormonal treatment. Repeat surgery has the same limitations as primary surgery in terms of disease recurrence. In the most severe and troublesome symptomatic endometriosis, combined off-label use of the two progestogen delivery systems (levonorgestrel intrauterine system and etonogestrel subdermal implant used simultaneously) may have a major beneficial impact on quality of life, but there is only one case report to support this line of management.[21] It also needs to be recognised that a minority of severe

ARTICLE

endometriosis sufferers experience persistent pelvic pain, which has a major impact on quality of life. Ongoing management may require involvement of a specialised pain management clinic.

Conclusion

As a greater understanding of the pathophysiology of endometriosis emerges, new targets for treatment will become available. Until then the best approach combines both medical and surgical modalities. The single significant barrier to good management of endometriosis is still timely recognition of the disease, especially in adolescents.

A greater awareness of the variability in the clinical presentation of endometriosis could potentially reduce the social, health and economic impact of this condition on women.

Dr Black is a consultant for Bayer HealthCare on an international advisory board (Bayer is the maker of Mirena). Professor Fraser has undertaken consultancies, lectures and research projects for Bayer Pharmaceuticals, Merck/MSD, Daiichi Sankyo and Vifor Pharma and has received honoraria, lecture fees and expenses. These honoraria and lecture fees are directed to his research program.

Q:

SELF-TEST QUESTIONS

True or false?

3. Medical treatments for endometriosis usually improve fertility.

4. Danazol is one of the first-line treatments of choice for endometriosis.

Answers on page 135

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ARTICLE

Management of cystic fibrosis in adults

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Key words
antibiotics, corticosteroids, mucolytics

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SUMMARY

Cystic fibrosis is the most common lethal autosomal recessive disease. Mutations in a membrane protein cause secretions such as mucus and digestive juices to be abnormally thick and sticky.

Respiratory symptoms tend to dominate the course of the disease but other complications include gastrointestinal disorders, male infertility, osteoporosis, diabetes and rhinosinusitis.

Due to improved treatments in childhood, the life expectancy of patients with cystic fibrosis has increased. Doctors are now more likely to encounter adults with this disease so being aware of current and emerging therapies used in their management is important.

Introduction

The management of patients with cystic fibrosis has improved over the past 30 years and most people now survive into adulthood. In an Australian study, the mean age at death in 2005 was 26.6 years.[1] As a result doctors other than paediatricians are managing the complications of this disease.

Cystic fibrosis is the most common lethal autosomal recessive disease and occurs in 1 in 2000 people. A defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which regulates the transport of chloride and other electrolytes, causes secretions to be abnormally thick and sticky. These secretions build up in the upper airways and the ducts of various organs affecting the lungs, gastrointestinal tract, pancreas, liver, sinuses, sweat glands and reproductive system. Respiratory problems, such as chronic infection and inflammation, tend to dominate the clinical course and a patient's respiratory status ultimately determines their prognosis.

Managing respiratory disease

There are a number of respiratory complications including acute pulmonary exacerbations, asthma, haemoptysis, pneumothorax and pneumonia. *Pseudomonas aeruginosa* is the predominant organism, however other organisms may colonise the respiratory tract and warrant therapy on occasions.

Non-drug treatments

Because sputum of increased viscosity will lead to worsening airway obstruction, patients are strongly encouraged to perform active airway clearance techniques such as autogenic drainage or positive expiratory pressure to maintain their health. A flutter device can be effective in some patients. This is a hand-held oscillating positive pressure device (see Fig. 1). The patient breathes out through the device against an alternating resistance. Back pressure leads to small airway opening which in turn promotes increased airway clearance.

Mucolytics

Mucolytics are given to improve the viscosity of mucus and aid its clearance. Nebulised dornase alpha (2.5 mg) acts by breaking down DNA, which contributes to the high viscosity of the sputum.[2] Responses are variable so patients can only continue this treatment on the Pharmaceutical Benefits Scheme if their lung function improves by 10% (forced expiratory volume in 1 second – FEV_1) after a one month trial. There are very few adverse effects although haemoptysis has been reported.

Nebulised hypertonic saline, typically 5 mL of 6% solution twice a day, is also used to reduce mucus viscosity. The high salt content is thought to cause water to influx into the airway lumen and assist with mucus clearance. Many patients benefit from using this medication.[3] However, some patients may not tolerate it because of severe bronchospasm or cough.

Inhaled mannitol powder has recently become available for cystic fibrosis.[4] A standard dose is 400 mg twice a day. Its high sugar content elevates the osmolality within the airway leading to water influx into the lumen. Cough can be a limiting factor in adherence.

Antibiotics

Antibiotics are administered for several possible purposes:

- to eradicate or delay the onset of *P. aeruginosa* colonisation
- to maintain lung function
- to intensify treatment of a pulmonary exacerbation.

Eradication protocols contain intravenous antipseudomonal antibiotics followed by a prolonged course of nebulised colistin and oral ciprofloxacin.

Fig. 1 **Flutter device**

Picture courtesy of the author

Maintenance strategies include long-term treatment with oral azithromycin.[5,6] Nebulised tobramycin or colistin cycling over some months to years, and other oral antibiotics sometimes given in a rotating fashion, are commonly used. However, there is no evidence for this practice.

Exacerbations

An exacerbation is difficult to define. One definition[7] requires the patient to have two out of a possible seven symptoms – including fever, increased sputum volume (by 50%) and increased cough frequency (by 50%) as well as at least one of three additional clinical criteria such as a drop of 10% in forced vital capacity.

As the majority of adult patients are colonised with *P. aeruginosa*, therapies are directed at this organism. For mild exacerbations, oral ciprofloxacin (2 week course) and nebulised aminoglycoside (2–4 week course) are used. Typically, nebulised tobramycin 80–160 mg twice a day is given. Nebulised colistin (for example 1–2 million units twice a day) could be used as an alternative to tobramycin. This trial switch in therapy would be indicated if the patient was not responding to nebulised tobramycin or was intolerant (for example developing bronchospasm). Nebulised antibiotics rarely cause systemic adverse effects but with time can cause hearing impairment or balance problems in some patients.

If *P. aeruginosa* is not commonly isolated from the patient's sputa, a course of dicloxacillin (for example 500 mg four times a day) for *Staphylococcus aureus* colonisation or amoxycillin/clavulanic acid (for example 875/125 mg twice a day) may be used. Other pathogens that are sometimes isolated and need targeted therapy include *Stenotrophomonas maltophilia* (sulfamethoxazole/trimethoprim) and *Haemophilus influenzae* (amoxycillin).

For more severe exacerbations, patients are hospitalised and given intravenous antibiotics typically with a combination of a beta lactam-derived antibiotic (for example ticarcillin/clavulanic acid or ceftazidime) with an aminoglycoside (for example tobramycin as a single daily dose). The duration of these treatments is about 10–14 days. This empirical approach is justified as studies have shown that sputum sensitivities are not a useful guide to choosing therapy.[8] Often the choice of drugs is dictated by previous allergies or intolerances of various antibiotics. Because deteriorating patients require frequent courses of these antibiotics, they should be closely monitored for long-term complications such as renal and hearing impairment.

Inhaled bronchodilators

Many patients regularly use short-acting bronchodilators, such as salbutamol, to aid airway clearance and enhance delivery of other inhaled drugs. Research on tiotropium, a long-acting anticholinergic, is just beginning.

Inhaled steroids

Some patients with cystic fibrosis take these medications regularly to assist with asthma control or lung inflammation. Adherence and effectiveness are very variable. There is limited evidence for bacterial contamination of inhaler devices but it may occur.[9]

Rhinosinusitis

Rhinosinusitis is very common in cystic fibrosis and can be managed with a combination of saline sprays, inhaled steroids and sometimes oral prednisolone. Surgery may be required in some cases.

Managing gastrointestinal disorders

Maintenance of nutrition is critical for patients with cystic fibrosis. Mechanisms for weight loss include suboptimal pancreatic function, diabetes, chronic anorexia related to chronic suppurative lung disease, the catabolic effect of chronic respiratory infections and the increased work of breathing.

Patients can suffer from a range of gastrointestinal disorders including pancreatic insufficiency, liver disease (cirrhosis in 5% of patients), bacterial overgrowth and distal intestinal obstruction syndrome. About 15% of patients who are pancreatic sufficient can develop episodes of acute pancreatitis.

Pancreatic enzymes

Most patients have pancreatic insufficiency and thus require lifelong enzyme replacement. This is titrated to the fat content in each meal or snack with the aim being to control symptoms of abdominal cramping pain and steatorrhoea and to maintain weight. A typical dose would be around 3–4 capsules with meals and 1–2 capsules with snacks, but this is highly variable.

Salt and fluids

Patients are strongly encouraged to take adequate salt and fluid throughout the whole year. Many patients take 4–8 salt tablets per day depending on the season. Fluids are generally electrolyte solutions (for example Glucolyte) with patients typically requiring 1–3 sachets per day.

Vitamins

Fat-soluble vitamins (namely vitamins A, D, E and K) are replaced by prescribing a combination therapy known as VitABDECK (2 tablets every morning).

Oral supplements

The most commonly used oral nutritional supplement is Ensure which is available as 200 mL tetrapaks. A number of patients would take about 2–4 of these per day. Other options include Ensure Plus (contains increased calories), Sustagen, Resource and Scandishakes.

Calcium and bisphosphonates

Patients with cystic fibrosis are at increased risk of osteoporosis and many take oral calcium and additional vitamin D. Osteoporosis is monitored by bone mineral densitometry twice a year and is treated with bisphosphonates (and testosterone when appropriate).

Proton pump inhibitors

Gastro-oesophageal reflux is very common and often requires chronic therapy with a proton pump inhibitor.

Enteral feeds

A significant minority of patients need to administer nutritional supplements via a self-inserted nasogastric tube (usually about 1 L per night) to maintain their body weight. Gastrostomy is occasionally required instead.

Ursodeoxycholic acid

A small percentage of patients with significant liver dysfunction are treated with ursodeoxycholic acid (500 mg twice a day) in an attempt to delay progression of liver disease to cirrhosis. However, evidence for this effect is lacking.

Diabetes

Diabetes is caused by destruction of the endocrine pancreatic glands from inflammation in the exocrine component of the pancreas. If diabetes develops, insulin is usually commenced.

Reproductive health

Male infertility is universal due to absence of the vas deferens. Men who want to start a family should be referred to a fertility centre for aspiration of sperm which can then be used to fertilise the partner's eggs via *in vitro* fertilisation.

Pregnancy

Many women with cystic fibrosis can conceive naturally and should be using contraception until they decide to try for a pregnancy. We recommend that they discuss their intentions with their doctor before attempting to conceive. Genetic counselling is also important for couples planning to start a family.

Pregnancy poses a number of challenges. Often women have an increased frequency of respiratory exacerbations as the pregnancy progresses. Nutrition is harder to maintain so often additional supplements are required. Gestational diabetes may occur.

Adherence to therapy

As with other chronic diseases, adherence is a problem for many patients who often have a complicated therapy regimen. Team members work with the patient to enhance adherence using techniques such as motivational interviewing. Ongoing monitoring of adherence and appropriate advice and encouragement to address these problems are essential in managing the many challenges inherent in this chronic disease.

New therapies

As a result of ongoing research, new therapies have been developed targeting specific genetic mutations. For example, a randomised trial with a CFTR potentiator (VX770) has shown improvements in lung function and nutrition as well as demonstrating a partial correction of the electrolyte imbalance at the cellular level (chloride levels in sweat fell significantly).[10] The compound is administered as a daily tablet which enhances the function of the abnormal CFTR in the membrane of epithelial cells throughout the body. It is used in patients with one or two G551D cystic fibrosis mutations in the genotype.

Conclusion

Cystic fibrosis is a complex multisystem disease which primarily affects the lungs and the pancreas. There are many therapies available to improve the health of the patient. Regimens tend to be quite involved so encouraging adherence is very important. Optimal management of these patients is achieved via a dedicated multidisciplinary team.

Patient survival has improved dramatically over a number of decades. However, new challenges are emerging because of antibiotic resistance and allergies. New treatments targeting the specific CFTR defect are becoming more available.

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

5. Cough may limit the use of hypertonic saline and inhaled mannitol powder in patients with cystic fibrosis.

6. Mild pulmonary exacerbations are usually managed with an intravenous combination of ticarcillin/clavulanic acid and tobramycin.

Answers on page 135

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Cystic Fibrosis Australia

Cystic Fibrosis Australia promotes health and support services for children, youth and adults with cystic fibrosis, and their families. With its state and territory organisations, it distributes information at national and international levels.

Brochures, books, videos and information packs are available via the website, and there is an online forum for people to share their experiences with managing cystic fibrosis. A trust funds research into cystic fibrosis, and promotional events include the national 65 Roses Day (www.65rosesday.org.au).

Contact

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Volume 3, Number 4, August 2012

In this issue

- Accidental paracetamol poisoning
- Strontium ranelate and venous thromboembolism and serious skin reactions
- Better information on medicine labels – have your say

Accidental paracetamol poisoning

The hepatotoxic effects of paracetamol when taken as an intentional overdose are well-known. However, paracetamol hepatotoxicity can also occur in other situations, including accidental overdose and use at normal doses.

Paracetamol-induced hepatotoxicity at therapeutic doses

In many patients with hepatotoxicity, the paracetamol was taken for therapeutic purposes only. In a study of 662 patients with severe paracetamol-induced hepatotoxicity, 48% had not exceeded the recommended maximum daily dose of 4g.[1]

A 45-year-old woman suffered fatal paracetamol-induced liver failure after receiving paracetamol at a therapeutic dose. She had been hospitalised for subacute bowel obstruction and treated with paracetamol 1g 'qid' for 8 days while remaining nil by mouth.[1]

Risk factors for paracetamol hepatotoxicity include fasting, regular excessive alcohol use, and concomitant use of drugs that induce cytochrome P450 (CYP) 2E1 (e.g. ethanol). Paracetamol is normally metabolised through conjugation in the liver and excreted in urine. A small proportion of paracetamol is converted by CYP enzymes 2E1 and 3A4 to the hepatotoxic compound *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is then conjugated with glutathione and excreted. Prolonged fasting depletes the substrates necessary for conjugation, including glutathione, leading to a build-up of NAPQI.[1,2]

Accidental overdose

A three-year-old chronically malnourished boy with a history of gastric dysmotility syndrome was hospitalised with fever and vomiting. Being intolerant of oral medication, he was prescribed the intravenous formulation of paracetamol, Perfalgan 150 mg (15 mL). Due to confusion between mg and mL he was given a single dose of 150 mL (1500 mg).[3] He experienced transient hepatotoxicity, which responded to treatment with *N*-acetylcysteine. To avoid this type of dosing error, specify the dose volume in mL when prescribing, particularly in neonates and infants.[4]

Concomitant administration of oral and intravenous paracetamol is another cause of hepatotoxicity. When administering paracetamol, it is advisable to check no other sources of paracetamol have been given.

Information for health professionals

Australian guidelines for the management of paracetamol overdose include an updated treatment nomogram, and recommended investigations and *N*-acetylcysteine dosing regimens.[2]

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Correction

"In a study of 662 patients with acute liver failure, 275 were cases of severe paracetamol-induced hepatotoxicity. 131 (48%) of these 275 cases were the result of an unintentional overdose and 19 (7%) of the 275 patients had not exceeded the recommended maximum daily dose of 4g". The correct reference for this paragraph is:

Larson AM, Polson J, Fontana RF, Davern TJ, Lalani E, Hynan LS, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42:1364-72 <http://www.ncbi.nlm.nih.gov/pubmed/16317692> .

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

Strontium ranelate and venous thromboembolism and serious skin reactions

Health professionals are advised of additional contraindications and precautions for strontium ranelate (Protos), to help manage the risk of venous thromboembolism (VTE) and serious skin hypersensitivity reactions.

Strontium ranelate, marketed as Protos, is indicated for the treatment of postmenopausal osteoporosis to reduce the risk of fracture, and for the treatment of osteoporosis in men at increased risk of fracture.

The European Medicines Agency (EMA) recently completed a review of Protos.[1] It concluded that while Protos remains an important treatment for osteoporosis, changes were required to the information provided to health professionals to better manage the associated risks.

Risk of VTE

The risk of VTE was found to be higher in patients with a previous history of VTE, and in patients who are temporarily or permanently immobilised. A higher rate of VTE was also identified in elderly patients aged >80 years receiving Protos, compared to placebo.

Risk of serious skin hypersensitivity reactions

Post-marketing surveillance has identified cases of severe skin reactions, such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in patients prescribed Protos. However, the overall occurrence of serious skin reactions was low. Since these conditions are best managed with early diagnosis and immediate discontinuation of any suspect medicines, it is important that health professionals are aware of the time-to-onset, signs and symptoms of these conditions.

Changes to the Product Information

The Australian Product Information has been updated to include strengthened advice for managing the risk of VTE and serious skin hypersensitivity reactions (see below).

REFERENCE

1. European Medicines Agency confirms positive benefit-risk balance of Protelos/Osseor, but recommends new contraindications and revised warnings [press release]. European Medicines Agency. 2012 Mar.

New contraindications and precautions for strontium ranelate (Protos)*

New contraindications

- Current or previous venous thromboembolic events, including deep vein thrombosis and pulmonary embolism
- Temporary or permanent immobilisation (e.g. post-surgical recovery or prolonged bed rest)

New precautions

Venous thromboembolism:

- In patients over 80 years at risk of VTE, ongoing treatment with Protos should be re-evaluated
- In the event of an illness or a condition leading to immobilisation, Protos should be discontinued as soon as possible and adequate preventive measures taken. Therapy should not be restarted until the event has resolved and the patient is mobile.
- Protos should be stopped if VTE occurs

Serious skin hypersensitivity reactions:

- Patients should be advised of the signs and symptoms and monitored closely for skin reactions
- The highest risk for occurrence of SJS or TEN is within the first weeks of treatment and usually around 3–6 weeks for DRESS
- If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. rash, fever, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease)) are present, Protos treatment should be discontinued immediately
- Early diagnosis and immediate discontinuation of the suspected drug is associated with a better prognosis of SJS, TEN or DRESS. Recovery from DRESS could be slow and recurrences have been reported in some cases after discontinuation of corticosteroid therapy.
- If the patient has developed SJS, TEN or DRESS with the use of Protos, Protos must not be re-started

* For full prescribing information, see the Protos Product Information available on the TGA website

MEDICINES SAFETY UPDATE

Better information on medicine labels – have your say

Health professionals are invited to submit comments on the TGA's consultation paper for the Medicine Labelling and Packaging Review. In particular, the TGA is interested in comments from health professionals on the relevance and impact of the proposed changes on the quality use of medicines and consumer safety.

The objective of the review is to develop appropriate regulatory solutions that effectively address the consumer safety risks posed by the following issues:

- active ingredients prominence
- look-alike medicine branding, also known as brand extension or trade name extension
- look-alike and sound-alike medicine names
- look-alike medicine packaging
- standardised formats for information included on medicines labels and packaging
- mandatory space for dispensing stickers
- information provided on blister strips
- information included on small containers
- information provided in pack inserts.

The aim of the proposed changes is to reduce the risk of errors by health professionals and facilitate consumer access to the information they need to:

- make informed choices where they are self-managing minor conditions, such as a headache or a cold
- safely use a medicine that they have been prescribed by a health practitioner for the treatment of a more serious condition.

Full details of the process and the consultation paper can be found on the TGA website: www.tga.gov.au/newsroom/consult-labelling-packaging-review-120524.htm

What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website
- **online** at www.tga.gov.au
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

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

For the latest safety information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

For correspondence or further information about Medicines Safety Update, contact the TGA's Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114

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DISCLAIMER

Medicines Safety Update is aimed at health professionals. It is intended to provide practical information to health professionals on medicine safety, including emerging safety issues. The information in Medicines Safety Update is necessarily general and is not intended to be a substitute for a health professional's judgment in each case, taking into account the individual circumstances of their patients. Reasonable care has been taken to ensure that the information is accurate and complete at the time of publication. The Australian Government gives no warranty that the information in this document is accurate or complete, and shall not be liable for any loss whatsoever due to negligence or otherwise arising from the use of or reliance on this document.

Tumour markers

SUMMARY

Doctors are faced with an increasing multitude of tumour markers, biomarkers, tissue markers and genetic markers.

Some markers will make it through years of development and evaluation to clinical trial and eventual clinical use. The majority, however, will never proceed beyond the development stage.

Doctors need to be aware of the clinical use of tumour markers, but at the same time realise their limitations and the implications of inappropriate use.

Introduction

Tumour markers have been defined as 'substances, usually proteins, that are produced by the body in response to cancer growth or by the cancer tissue itself'.[1] In fact, a tumour may not generate elevated markers, particularly in its early stages. Conversely, markers may increase due to benign conditions, as is the case with cancer antigen 125 in endometriosis, cirrhosis and diabetes.

Screening for cancer with tumour markers has only very limited applications. In patients with vague symptoms, or when the likelihood of cancer in the population is low, tumour markers should not be used in the initial diagnostic pathway. In this setting, tumour markers are rarely diagnostic due to low sensitivity and specificity.

Most established tumour markers have roles in prognosis and post-treatment monitoring. They should only be measured where knowledge of the tumour marker will benefit the patient, while bearing in mind that results can be falsely reassuring or unduly alarming.

Screening asymptomatic populations

A screening test that detects disease in an asymptomatic population has long been the goal of scientists and physicians worldwide. In reality, this goal has met with very limited success. For example, a recent European-based prostate specific antigen screening trial reported no mortality benefit,[2] while a US-based trial concluded that to prevent one death over a 10-year period, 1410 men would have to be screened and 48 treated.[3]

Bowel (colorectal) cancer screening is recommended by the Cancer Council of Australia. The National Bowel Cancer Screening Program sends an immunochemical-based faecal occult blood test to people based on their age. However there is insufficient evidence to support any other tumour-based screening program.[4]

Newly developed tumour marker tests are marketed to patients and health professionals. Physicians should realise that while their well-informed patients may actively seek a particular test, it is not likely to have been validated in prospective clinical trials and is probably not available at their local pathology laboratory.

Tumour markers in diagnosis, prognosis and monitoring

There are many different methods used to measure tumour markers, and samples analysed at different laboratories may yield different results. These discrepancies can be minimised by using the same laboratory.

The National Academy of Clinical Biochemistry (NACB) in the USA has published guidelines for the use of tumour markers in several malignancies (Table 1).[5,6] Despite the numbers of proposed tumour markers under development, only the 'traditional' markers are used in diagnosis, prognosis and monitoring. For example in bladder cancer there are at least six urine tumour marker kits available that have been approved by the US Food and Drug Administration, yet there are no prospective clinical trial data establishing increased survival time, improved quality of life or decreased cost of treatment for any of the tests. However for testicular cancer, the measurement of beta-human chorionic gonadotrophin hormone and alpha-fetoprotein has been validated and is well established for diagnosis, prognosis and monitoring. Similarly cancer antigen 15-3 in breast cancer, cancer antigen 125 in ovarian cancer and carcinoembryonic antigen in colorectal cancer are recommended for prognosis and monitoring. Prostate specific antigen is used to monitor men treated for prostate cancer (Aust Prescr 2011;34:186-8).

The patient suspected of having multiple myeloma should have serum and urine electrophoresis screening tests along with routine biochemistry and haematology tests. If paraprotein is detected, skeletal X-ray, bone marrow and other specialised tests are needed. The serum free light chain test is a fairly new

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diagnosis, monitoring, screening, tyrosine kinase inhibitors

Aust Prescr 2012;35:125–8

tumour marker which may become useful in multiple myeloma screening as an adjunct to serum and urine electrophoresis.[7] In the rare case of non-secretory multiple myeloma, testing can detect small increases in free light chains. Currently however, there are no guidelines for its use in this role, but it is accepted for monitoring previously diagnosed patients.

Less frequently requested tumour markers and their roles

Many other tumour markers exist and are used in specific clinical circumstances. However, it is doubtful if any of the following markers would be ordered outside of a specialist's office:

- beta-human chorionic gonadotrophin for diagnosing and monitoring gestational trophoblastic neoplasia
- thyroglobulin for monitoring follicular or papillary thyroid cancer
- calcitonin for monitoring medullary thyroid cancer
- cancer antigen 19-9 for monitoring pancreatic cancer
- chromogranin-A for monitoring carcinoid tumour and phaeochromocytoma
- beta-2 microglobulin for monitoring multiple myeloma
- neurone specific enolase for monitoring neuroendocrine secreting tumours
- 24-hour urinary and plasma catecholamines and metanephrine for detecting phaeochromocytoma
- 24-hour urinary 5-HIAA (5-hydroxyindoleacetic acid) for detecting carcinoid tumour
- parathyroid hormone for parathyroid adenoma.

Molecular tumour biomarkers

A number of molecular genetic markers have become available that predict a patient's response to targeted therapy. The most commonly used of these are mutations in the KRAS gene (Kirsten rat sarcoma-2 virus oncogene) which are indicative of lack of

Table 1 **Recommendations for tumour marker testing in common malignancies** [5,6]

		Tumour marker		
Malignancy*	**Sample type**	**Screening**	**Assisting diagnosis**	**Informing prognosis, monitoring and surveillance**
Liver	Serum	Alpha-fetoprotein (in high risk groups only, e.g. patients with chronic viral hepatitis)	Alpha-fetoprotein	Alpha-fetoprotein
Bladder	Serum	None	None	None
Cervical	Serum	None	None	None
Gastric	Serum	None	None	None although CEA and CA19-9 may be useful but clinical trials lacking
Testicular	Serum	Alpha-fetoprotein, B-HCG, LDH**	Alpha-fetoprotein, B-HCG, LDH	Alpha-fetoprotein, B-HCG, LDH
Prostate	Serum	None	PSA	PSA
Colorectal	Faeces	FOBT	None	CEA
Breast	Serum	None	None	CA15-3 but the clinical value is unclear
Ovarian	Serum	None***	CA125 for differential diagnosis of suspicious pelvic masses	CA125
B cell proliferative e.g. multiple myeloma	Serum and urine	Serum and urine paraprotein	Serum and urine paraprotein	Serum and urine paraprotein, sFLC

* a tumour may not raise levels, at least not in the early stages, and levels may also be raised in benign disease
** elevations in LDH can also be due to confounding factors including haemolysis and liver, muscle or cardiac disease
*** CA125 together with transvaginal ultrasonography is recommended for early detection in women with hereditary syndromes

B-HCG beta-human chorionic gonadotrophin hormone
CA cancer antigen
LDH lactate dehydrogenase
PSA prostate specific antigen
FOBT faecal occult blood test
CEA carcinoembryonic antigen
sFLC serum free light chain

response to therapy with anti-epidermal growth factor receptor (EGFR) antibodies. Similarly, mutations in the EGFR gene predict sensitivity or resistance to EGFR tyrosine kinase inhibitors, and mutations in the BRAF gene (proto-oncogene B-Raf) predict response to BRAF inhibitors.

Lung cancer

A number of international consensus groups have recommended testing for EGFR mutations in non-small cell lung cancer as a prerequisite to treatment with EGFR tyrosine kinase inhibitors, such as gefitinib or erlotinib. More than 80% of these EGFR mutations are either a single nucleotide substitution in exon 21 (p.Leu858Arg:L858R) or small deletions in exon 19.[8] These mutations are termed classical activating mutations because they both activate the receptor tyrosine kinase and respond to the EGFR inhibitors gefitinib and erlotinib.

Not all EGFR gene mutations predict sensitivity to treatment. Primary and secondary resistance has been observed in non-small cell lung carcinoma, and a single mutation in exon 20 of the EGFR gene (p.Thr790Met:T790M) accounts for approximately 50% of acquired resistance to anti-EGFR therapy.[9] Amplification of the MET oncogene is another common mechanism of acquired resistance and is associated with a poor prognosis.[10]

Importantly, high response rates to gefitinib and erlotinib can be achieved in appropriate populations of non-small cell lung cancer based on stratification by EGFR gene mutation status compared to the treatment of unselected populations with these inhibitors.

Colorectal cancer

Anti-EGFR monoclonal antibodies are increasingly being used in both first- and second-line treatment of colorectal cancer.[11] However, mutations in genes downstream of EGFR in the mitogen-activated protein kinase (MAPK) pathway can predict non-response to these therapies. Anti-EGFR therapy with cetuximab or panitumumab is generally not indicated if the tumour carries a mutation in exon 2 of the KRAS gene. These mutations commonly occur at codons 12 and 13. However, recent data suggest that not all KRAS mutations in these codons are equal in their prediction of response to cetuximab.[12]

Melanoma

Mutations in the BRAF gene have been identified in over 40% of melanomas, and specific inhibitors to a mutated form of the BRAF protein (BRAF V600E) have produced a clinical response in phase III trials (Aust Prescr 2012;35:134-5).[13] The most prevalent mutation is a single nucleotide substitution (c.1799T>A) that results in an amino acid substitution of glutamic acid for valine in the BRAF protein. Similar to KRAS, other BRAF mutations may result in varying responses to treatment.

While cutaneous melanomas commonly harbour mutations in the BRAF gene, melanomas arising from acral and mucosal surfaces tend to harbour KIT gene mutations (8% of tumours) that predict response to another tyrosine kinase inhibitor, imatinib.

A role for BRAF mutations in the pathogenesis, diagnosis and targeted therapy of diseases beyond melanoma is also possible. In a recent report, all of 40 patients with hairy cell leukaemia carried the BRAF p.Val600Glu(V600E) mutation.[14]

Conclusion

Despite considerable scientific research into developing and validating tumour markers for screening asymptomatic patients, this goal is largely not met. However, a number of tumour markers are recommended in diagnostic, prognostic and monitoring roles. Tests for tumour markers should only be done if the result will benefit the patient. It is important to be aware that benign conditions can cause false elevations. To ensure continuity with results, the same pathology laboratory should be used each time.

Molecular biomarkers are increasingly being used to predict sensitivity to a specific therapy and can help identify patients who are more likely to respond. <

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

7. Cancer antigen 125 is recommended for monitoring testicular cancer.

8. Mutations in the KRAS gene can help to predict a patient's response to cetuximab therapy for colorectal cancer.

Answers on page 135

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New drugs

Abiraterone acetate

Approved indication: metastatic prostate cancer
Zytiga (Janssen-Cilag)
250 mg tablets
Australian Medicines Handbook section 14.3.1

Androgens have an important role in the progression of prostate cancer. While castration can reduce progression, the cancer eventually becomes castration resistant and requires chemotherapy with drugs such as docetaxel. As androgen activity is increased at this late stage of the disease, anti-androgen treatments have been researched.

Abiraterone is an inhibitor of cytochrome P450 (CYP) C17. This enzyme is involved in androgen synthesis, so inhibiting it decreases the concentrations of testosterone and other androgens. When given alone abiraterone can cause secondary hyperaldosteronism. To reduce this problem it should be given with prednisone or prednisolone.

This combination was used in a phase II trial to treat 58 men with metastatic prostate cancer which had failed to respond to docetaxel. The response to therapy was assessed by changes in the men's concentrations of prostate specific antigen (PSA). This declined by at least half in 36% of the men. The median time to PSA progression was 169 days.[1]

The same daily dose of abiraterone (1 g orally) was then used in a placebo-controlled phase III trial in 1195 men who had been previously treated with docetaxel. These patients also took prednisone 5 mg twice daily. The median follow-up was 12.8 months. There was a decrease of 50% or more in the PSA concentration in 29% of the men who took abiraterone and in 6% of the placebo group. The time to PSA progression was 10.2 months with abiraterone and 6.6 months with placebo. In the abiraterone group, 42% of the patients died compared with 55% of the placebo group. Overall survival was 14.8 months with abiraterone and 10.9 months with placebo.[2]

In the phase III trial the most common adverse events were fatigue, nausea and back pain, but they occurred at a similar frequency in the placebo group. Hypokalaemia, oedema and fluid retention were more frequent with abiraterone. Less frequent adverse events which occurred more often with abiraterone than placebo included urinary tract infections, hypertension and cardiac disorders, such as arrhythmias and heart failure. Patients with clinically significant heart disease or uncontrolled hypertension were excluded from the trial.[2]

Abiraterone can increase liver enzymes, so liver function must be monitored frequently. Treatment may need to be reduced or stopped depending on liver function. If prednisolone is stopped abruptly there is a risk of adrenocortical insufficiency. Abiraterone is metabolised by CYP3A4, but interactions with strong inducers and inhibitors of the enzyme have not been evaluated. CYP1A2 and CYP2D6 are inhibited by abiraterone so there is a potential for interactions with drugs which are metabolised by these enzymes. These include codeine, oxycodone and tramadol. Only 5% of the dose is excreted in the urine and there is no recommendation for a reduced dose in renal disease. Abiraterone must not be taken with meals because food alters absorption.

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

The options for treating metastatic prostate cancer have increased, but the prognosis is still poor. Patients may prefer oral abiraterone to intravenous cabazitaxel, with its cytotoxic adverse effects, but the drugs' effectiveness has not yet been compared. The use of abiraterone in earlier stages of prostate cancer is being investigated. A trial involving men with metastatic castration-resistant prostate cancer was recently unblinded so patients in the placebo group could be switched to active treatment because of the emerging benefit of abiraterone.

T manufacturer provided the product information

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First published online 16 May 2012

Cabazitaxel

Approved indication: metastatic prostate cancer
Jevtana (Sanofi-Aventis)
concentrate containing 60 mg/1.5 mL for dilution
Australian Medicines Handbook section 14.1.6

Androgen ablation is the usual treatment for metastatic prostate cancer, but the disease becomes refractory to hormone treatment. The patient is then offered chemotherapy with drugs such as mitoxantrone or docetaxel.

The first taxanes were derived from the Pacific yew tree. Cabazitaxel is derived from the needles of the European yew tree. It was found to have antitumour activity which included an effect in cells which were poorly responsive to docetaxel.

After dilution, cabazitaxel is given intravenously over one hour. PVC containers and polyurethane infusion sets should not be used. The recommended regimen is an infusion every three weeks, adjusted according to toxicity. As cabazitaxel is extensively metabolised by the liver, it is not recommended for patients with liver impairment. The metabolism involves cytochrome P450 3A4. While there is a potential for interactions with inducers and inhibitors of this enzyme, drug interaction studies are yet to be reported.

The main study of cabazitaxel was an open-label trial of 755 patients with metastatic prostate cancer that had progressed despite treatment with docetaxel. These men were randomised to receive cycles of treatment with cabazitaxel or mitoxantrone, in addition to daily doses of 10 mg prednisone or prednisolone. The median number of treatment cycles was six with cabazitaxel and four with mitoxantrone. Median progression-free survival was 2.8 months with cabazitaxel and 1.4 months with mitoxantrone. Approximately 61% of the cabazitaxel group and 74% of the mitoxantrone group died during the study. Median overall survival was 15.1 months with cabazitaxel and 12.7 months with mitoxantrone.[1]

More than 80% of the patients treated with cabazitaxel developed severe or life-threatening neutropenia, compared with 58% of the mitoxantrone group. While 1% of the men given mitoxantrone developed febrile neutropenia, it occurred in 8% of the cabazitaxel group. Anaemia and thrombocytopenia were also more frequent with cabazitaxel.[1]

Frequent non-haematological adverse effects of cabazitaxel included diarrhoea (47%), fatigue (37%), nausea (34%), vomiting (23%), haematuria (17%) and peripheral neuropathy (14%). Adverse effects were more frequent with cabazitaxel and resulted in 18.3% of patients stopping treatment compared with 8.4% of the mitoxantrone group.[1] As hypersensitivity reactions can occur, patients need intravenous antihistamines and corticosteroids before each infusion. It is important that patients are kept well hydrated as there is a risk of renal failure. Arrhythmias have also been reported.

While the 30% reduction in the risk of death is statistically significant, the absolute gain in survival is a few weeks. This comes with the increased risk of dying from adverse effects. Cabazitaxel also had no advantage over mitoxantrone in its effect on the patients' pain.[1] Further research is needed to investigate the patients' quality of life and whether lower doses of cabazitaxel would produce the same benefits with less toxicity.

T T manufacturer provided additional useful information

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Rasagiline mesilate

Approved indication: Parkinson's disease
Azilect (Lundbeck)
1 mg tablets
Australian Medicines Handbook section 16.2.3

When Parkinson's disease requires drug treatment, the patient is usually prescribed a drug containing levodopa or a dopamine agonist. Another treatment

option is an inhibitor of monoamine oxidase type B. Blocking this enzyme increases the concentration of dopamine in the brain. Selegiline is a monoamine oxidase type B inhibitor which has been available for several years. It is now joined by rasagiline which can be used as monotherapy or with levodopa.

Rasagiline is a once-daily treatment. The tablet can be taken with or without food. Although the drug appears to be selective for monoamine oxidase type B at recommended doses, there is a potential for interactions with foods, such as aged cheeses, which contain high concentrations of tyramine. Rasagiline is metabolised by the liver and liver impairment is a contraindication. The metabolites of rasagiline are mainly excreted in the urine. Unlike selegiline, rasagiline is not converted into amphetamine metabolites.

The metabolism of rasagiline involves cytochrome P450 1A2. Rasagiline should not be given with ciprofloxacin or other inhibitors of this enzyme. Fluvoxamine should be avoided as it is also metabolised by cytochrome P450 1A2. A serotonin syndrome may also result if rasagiline is used with antidepressant drugs. Monoamine oxidase inhibitors and St John's wort are contraindicated. Other contraindicated medicines include pethidine, tramadol and methadone.

Rasagiline was compared to placebo in 404 patients with early Parkinson's disease. The main outcome of the study was the change in the 176-point Unified Parkinson's Disease Rating Scale. At the start of the study the patients had mean scores of 24–25. After 26 weeks, impairment had increased by 0.1 with rasagiline 1 mg, 0.7 with rasagiline 2 mg, and 3.9 with placebo.[1] The patients in the placebo group were then switched to rasagiline 2 mg. One year after the trial began, the increases in the scores were 3.01 with 1 mg rasagiline, 1.97 with 2 mg rasagiline, and 4.17 in the patients who switched to rasagiline from placebo.[2]

The possible advantages of starting rasagiline early in the course of the disease were studied in a trial of 1176 previously untreated patients. These patients were randomised to start rasagiline at once or after 36 weeks. A total of 588 patients were given the 1 mg daily dose recommended in Australia. From mean baselines of 20–21 points, the rate of change in their scores on the Unified Parkinson's Disease Rating Scale showed a slower rate of deterioration when treatment was started sooner. After 72 weeks the score had changed by 2.82 points with early treatment and by 4.5 points with delayed treatment. However, early or delayed treatment did not have a significantly different effect on the total scores of the other patients who were given 2 mg.[3]

Patients who have been treated with levodopa eventually develop motor complications. These fluctuations adversely affect the patient's quality of life and can be difficult to control. Rasagiline has therefore been studied as an adjunct to levodopa.

Patients (n=472) with at least 2.5 hours of 'off time' each day were randomised to add rasagiline or a placebo to their levodopa treatment. After 26 weeks, off time was reduced by 1.85 hours with rasagiline 1 mg and by 1.41 hours with 0.5 mg. Off time was reduced by 0.91 hours in the placebo group.[4]

Entacapone was included in another placebo-controlled trial of rasagiline involving 687 patients who were having motor fluctuations for at least one hour every day while taking levodopa. After 18 weeks the average reduction in off time was 1.18 hours with rasagiline 1 mg, 1.2 hours with entacapone and 0.4 hours with placebo.[5]

The dopaminergic actions of rasagiline are associated with adverse reactions such as hallucinations and postural hypotension. Common adverse effects include headache, arthralgia, dyspepsia and dizziness. In one of the adjunctive studies, anorexia, vomiting and weight loss were more frequent with rasagiline 1 mg than with placebo. Although 'on time' increased, 32% of the increase included troublesome dyskinesias.[4]

The Therapeutic Goods Administration originally rejected the application to register rasagiline in Australia because of an apparent increase in the risk of melanoma. However, it is uncertain that the drug was responsible. As a precaution, patients should have periodic checks for skin cancer.

Although rasagiline has statistically significant effects as monotherapy its clinical effectiveness seems uncertain. The Unified Parkinson's Disease Rating Scale has a range of 176 points, so small changes may not be clinically significant. Any benefit of early treatment was lost if a higher dose of rasagiline was used.[3] Early treatment may not significantly delay the need for levodopa.[1]

While rasagiline can be added to treatment with levodopa, it is unclear if it is more effective than selegiline or other adjunctive therapies. The trial which studied rasagiline and entacapone did not have the statistical power to detect any differences between them.[5]

T manufacturer provided the AusPAR

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First published online 16 May 2012

Rilpivirine

Approved indication: HIV

Endurent (Janssen-Cilag)

25 mg film-coated tablets

Australian Medicines Handbook section 5.4.2

Rilpivirine is a new antiretroviral for HIV. Like other non-nucleoside reverse transcriptase inhibitors – efavirenz (Aust Prescr 1999;22:147-51), etravirine (Aust Prescr 2009;32:51-5) and nevirapine – rilpivirine reduces viral DNA synthesis by inhibiting HIV-1 reverse transcriptase. It is indicated in combination with other antiretroviral drugs for treatment-naïve patients with a viral load less than 100 000 copies/mL.

Following a dose-finding study,[1] two phase III trials compared the efficacy of once-daily rilpivirine (25 mg) and efavirenz (600 mg) added to different antiretroviral regimens.[2,3] At enrolment, patients had to have a viral load of at least 5000 copies/mL and be sensitive to the background drug regimen. There were three background regimens in the THRIVE trial[2] (tenofovir disoproxil fumarate/emtricitabine, zidovudine/lamivudine or abacavir/lamivudine) and one regimen in the ECHO trial[3] (tenofovir disoproxil fumarate/emtricitabine). Rilpivirine was non-inferior to efavirenz in both trials. Overall, 84% of patients who added rilpivirine had a viral load of 50 copies/mL or less after 48 weeks compared to 82% of those who added efavirenz. Increases in CD4 T cell counts were noted with both treatments.[4]

Not all patients responded to treatment in the trials, and virological failure was more common with rilpivirine than with efavirenz – 10% (72 of 686 patients) vs 6% (39 of 682 patients). The majority of treatment failures with rilpivirine (53 cases) occurred in patients with a high baseline viral load (>100 000 copies/mL).[5] Cross-resistance to other non-nucleoside reverse transcriptase inhibitors is likely when the virus has become resistant to rilpivirine.

Rilpivirine seemed to be better tolerated than efavirenz with fewer adverse events leading to discontinuation (1.6% vs 4%). In the trials, the most common adverse effects (grade 2 or more) with rilpivirine were depression (3.5%), insomnia (2.9%), headache (2.6%), rash (2.2%), abnormal dreams (1.5%), nausea (1.2%) and dizziness (0.7%).[4] There have been two attempted suicides and one suicide ideation with rilpivirine.

Rilpivirine should be taken with a meal as absorption is increased. Maximum plasma concentrations are reached after 4–5 hours. The elimination half-life is 50 hours with most of the drug and its metabolites being excreted in faeces.

Rilpivirine is metabolised by the cytochrome P450 3A system so drugs that induce this may reduce concentrations of rilpivirine and lead to treatment failure. Drugs that are contraindicated include carbamazepine, phenobarbitone, phenytoin, rifampicin, other non-nucleoside reverse transcriptase inhibitors, systemic dexamethasone (multiple doses) and St John's wort. Drugs that increase gastric pH such as proton pump inhibitors may also reduce plasma concentrations and are contraindicated.

Rilpivirine is a pregnancy category B1 drug. It should only be used in pregnancy if the maternal benefit outweighs the risk to the fetus.

Most patients in the trials responded to rilpivirine. However, response rates in the real world may be lower as patients with resistance to the background antiretrovirals were excluded from the trials. Although rilpivirine appears to be better tolerated than efavirenz, viral resistance is more common.

T manufacturer provided the AusPAR

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First published online 14 May 2012

NEW DRUGS

Telaprevir

Approved indication: hepatitis C
Incivo (Janssen-Cilag)
375 mg film-coated tablets
Australian Medicines Handbook section 5.4.3

Like boceprevir (Aust Prescr 2012;35:102), telaprevir is a protease inhibitor that can be added to standard treatment (peginterferon and ribavirin) for patients with hepatitis C genotype 1. It works by binding to the NS3 (non-structural 3) protease which is essential for viral replication.

The approval of telaprevir is based on safety and efficacy data from three phase III trials. Two trials were in previously untreated patients – ADVANCE[1] and ILLUMINATE[2] – and one in patients who had relapsed or failed to respond to previous treatment – REALIZE[3]. In each trial, telaprevir 750 mg (orally every eight hours) was added to peginterferon alfa 2a and ribavirin for 12 weeks. This was then followed by standard treatment alone for varying durations. The ADVANCE and REALIZE trials also included a control arm of placebo added to standard treatment.

Adding telaprevir compared to adding placebo significantly increased the rate of sustained virological responses in previously untreated and treated patients (ADVANCE and REALIZE trials).[1,3] Similar responses to telaprevir were observed in the open-label ILLUMINATE trial (Table 1).[2]

In the trial of previously treated patients (REALIZE), sustained responses to telaprevir were more likely in people who had relapsed after previous treatment compared to those who had not responded or only partially responded to previous treatment (particularly those with cirrhosis) (Table 2).[3] In many cases, distinct mutations in the viral protease were associated with treatment failure.

The most common adverse reactions (at least grade 2 in severity) to telaprevir were anaemia, pruritus, rash, nausea and diarrhoea in a cohort of 1346 people.

Severe rash occurred in 4.8% of patients who added telaprevir compared to only 0.4% receiving standard treatment. Rashes can take several weeks to resolve and discontinuation of treatment and referral may be needed in severe cases. Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms have also been reported with telaprevir. Patients should be warned to report skin reactions.

Telaprevir increased the incidence of anaemia (haemoglobin <10 g/100 mL) compared to standard treatment alone (34% vs 14% of patients). Haemoglobin should therefore be measured at baseline and at least every four weeks. Reducing the dose of ribavirin may be needed to manage the anaemia.

Hyperbilirubinaemia, hyperuricaemia, hypokalaemia, decreased lymphocytes and platelet counts, and increased low-density lipoprotein and total cholesterol were more common with telaprevir than with standard treatment alone. With the exception of platelet counts, these had normalised by the end of treatment.

Following oral administration of telaprevir 750 mg, maximum plasma concentrations are reached after 4–5 hours. It is metabolised in the liver and is not recommended for patients with moderate to severe liver impairment or decompensated liver disease. Telaprevir and its metabolites are excreted mainly in faeces. Its elimination half-life is 4–4.7 hours.

Telaprevir is metabolised by cytochrome P450 (CYP) 3A4 and is a substrate for P-glycoprotein so there is a potential for many drug interactions. Contraindicated drugs include amiodarone, ergot alkaloids, simvastatin and atorvastatin, sildenafil (for pulmonary arterial hypertension), rifampicin, carbamazepine, phenytoin and phenobarbitone. As telaprevir increases the QT interval, care should be taken when it is co-prescribed with other drugs that have a similar effect, such as methadone.

Telaprevir should be taken every eight hours with food. It should be started in combination with peginterferon and ribavirin and given for 12 weeks.

Table 1 **Patient responses to 12 weeks of telaprevir (added to standard treatment) for hepatitis C**

Trial	Participants	Sustained virological response *	
		telaprevir	placebo
ADVANCE[1]	1088 previously untreated patients	75%	44%
ILLUMINATE[2]	540 previously untreated patients	72%	–
REALIZE[3]	662 previously treated patients	64–66%	17%

* proportion of patients who had undetectable viral RNA for six months after treatment

Table 2 **The efficacy of telaprevir in previously treated patients[3]**

Patients	Sustained virological response *	
	telaprevir	placebo
Previous relapse	83–88%	24%
Previous partial responders	54–59%	15%
Previous non-responders	29–33%	5%

* proportion of patients who had undetectable viral RNA for six months after treatment

If, however, viral RNA counts are above 1000 IU/mL after four weeks, telaprevir should be discontinued.

This drug is not recommended for patients who are co-infected with hepatitis B, and there are limited data in patients with HIV. Telaprevir with peginterferon and ribavirin is contraindicated in pregnancy, as ribavirin is teratogenic. Two forms of contraception are recommended for women, including partners of men taking telaprevir, during treatment and for four months after.

In patients with hepatitis C genotype 1, telaprevir significantly improves the rates of sustained virological responses when added to standard treatment. It is uncertain how telaprevir will compare to boceprevir. However, a meta-analysis comparing the two found that efficacy was comparable, but rash and pruritus were more common with telaprevir.[4] Longer-term studies are needed to investigate telaprevir's effect on morbidity and mortality.

T manufacturer provided the product information

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Terlipressin

Approved indication: hepatorenal syndrome type 1
Lucassin (Ikaria)
vials containing 0.85 mg powder for reconstitution
Australian Medicines Handbook section 10.6.3

Hepatorenal syndrome occurs when hepatic failure is complicated by renal failure. It often develops in patients with decompensated cirrhosis and severe ascites. Type 1 hepatorenal syndrome develops over a couple of weeks and the mean survival time is also about two weeks.

The kidneys are thought to fail because of the changes in vascular resistance induced by liver failure. There is severe vasoconstriction of the renal arteries. The best treatment is liver transplant, but there is a need to manage the hepatorenal syndrome while a transplant is being considered.

One strategy for improving renal blood flow is to reduce blood flow in the splanchnic circulation. This effect can be achieved with vasopressin (antidiuretic hormone), but this risks mesenteric ischaemia.

Terlipressin is a long-acting analogue of vasopressin, given by slow intravenous injection. Its vasoconstrictor effect comes on more slowly and it has a pharmacological half-life of about six hours. As the vasoconstrictor effect is mainly in the splanchnic circulation, terlipressin has been used in the treatment of variceal bleeding.

A systematic review included three randomised trials of terlipressin in patients with hepatorenal syndrome. Terlipressin increased creatinine clearance and urine output. Only five of the 25 patients given terlipressin died compared with 15 of the 23 patients in the control group.[1]

A later pooled analysis aimed to find out if increases in blood pressure improved renal function. The 21 trials of vasoconstrictors for hepatorenal syndrome included 15 studies of terlipressin. An increase in mean arterial pressure was associated with a decrease in serum creatinine, but had no significant effect on urine output.[2]

A decrease in serum creatinine was used to assess the reversal of hepatorenal syndrome in some of the eight randomised controlled trials included in another systematic review. Terlipressin was significantly more efficacious than placebo. The syndrome was reversed in 55 of 117 patients given terlipressin and 14 of 117 patients given placebo. Blood pressure increased and urine output was significantly higher.[3]

Giving an intravenous vasoconstrictor can cause hypertension, and arrythmias may occur. Terlipressin should not be used in patients with unstable angina. Other adverse effects include myocardial ischaemia, necrosis at the injection site, vomiting, diarrhoea and abdominal pain.

The effectiveness of terlipressin is not completely clear. Many patients will not respond. Although terlipressin may improve survival, the larger systematic review did not have enough data for a meta-analysis of survival.[3] Assessment of the trials is further complicated by the use of different doses of terlipressin and the role of other treatments such as albumin. Two small studies found no difference between terlipressin and noradrenaline.[3] Few patients survive without a liver transplant.

T manufacturer provided the product information

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NEW DRUGS

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First published online 2 May 2012

Vemurafenib

Approved indication: metastatic melanoma

Zelboraf (Roche)

240 mg film-coated tablets

Australian Medicines Handbook section 14.2

The prognosis for patients with metastatic melanoma is poor. Apart from the recently approved ipilimumab (Aust Prescr 2011;34:153-9), treatment options are limited. Vemurafenib offers another alternative for patients whose melanoma carries a specific mutation called BRAF V600. This is found in 40–60% of melanomas. The abnormal BRAF protein kinase stimulates cell proliferation and cell survival. Vemurafenib blocks BRAF and slows tumour growth.

The approval of vemurafenib for patients with unresectable or metastatic BRAF V600-positive melanoma is based on results from two trials (Table). These were a phase III trial comparing vemurafenib with dacarbazine in 672 previously untreated patients[1] and a single-arm phase II trial in 132 previously treated patients[2]. Overall, 92% of people in the trials had the BRAF V600E mutation. The remaining 8% mainly had the BRAF V600K mutation. Patients with untreated brain metastases were excluded from both trials.

In the phase III trial, more patients responded to vemurafenib than to dacarbazine and progression-free survival was longer (Table). After an interim analysis, it was recommended that patients receiving dacarbazine cross over to vemurafenib.[1] Outcomes with vemurafenib were similar in the phase II trial.[2] Median overall survival was calculated to be 13.2–15.9 months.[1,2] It is unclear if vemurafenib is effective against melanomas which have BRAF V600 non-E mutations.

Adverse events in the trials were common. In the comparative trial, 38% of patients taking vemurafenib had their dose modified or stopped because of an adverse event compared with only 16% of those receiving dacarbazine.[1] Arthralgia, rash, alopecia, fatigue, nausea, pruritus and skin papilloma were frequently reported with vemurafenib. Photosensitivity reactions were also common and patients should be advised to avoid the sun and cover up or wear sunscreen outdoors. The dose may need to be reduced for severe cases. Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis and uveitis have also been reported.

Between 18% and 26% of patients in the trials developed cutaneous squamous cell carcinoma or keratoacanthoma.[1,2] These occurred after a median of 7–8 weeks and some patients had more than one lesion. New primary melanomas were also reported. Both of these malignancies are not a contraindication to treatment and can usually be excised. Rare cases of non-cutaneous squamous cell carcinoma of the head and neck also occurred in the trials. It is important that patients are examined for new malignancies at baseline and during treatment.

Vemurafenib can prolong the QT interval so it is not recommended for patients with uncorrected electrolyte abnormalities, long QT syndrome or who are taking other drugs that prolong the QT interval. ECG and electrolytes should be measured at baseline and after a dose change.

Liver abnormalities have occurred with vemurafenib so liver enzymes and bilirubin should be monitored before and during treatment. Dose reduction or interruption may be necessary to manage elevations.

Following oral administration of vemurafenib, maximum plasma concentrations are reached after four hours. Most of the metabolites are recovered in the faeces and the elimination half-life is 57 hours. Vemurafenib is an inhibitor of P-glycoprotein and the cytochrome P450 (CYP) enzymes 1A2 and 2C9. It is also a substrate of CYP3A4 so there is a potential for many drug interactions.

Up to half of patients carrying the BRAF V600 mutation are expected to respond to vemurafenib with a median overall survival of up to 16 months. However, adverse reactions may limit treatment and monitoring for new malignancies is important.

T manufacturer provided the product information

Table **Efficacy of vemurafenib in patients with BRAF V600-positive metastatic melanoma**

Clinical outcome	Phase III trial[1] (672 patients)		Phase II trial[2] (132 patients)
	vemurafenib	dacarbazine	vemurafenib
Response rate *	48% (2 complete responses, 104 partial responses)	5% (12 partial responses)	53% (8 complete responses, 62 partial responses)
Median progression-free survival	5.3 months	1.6 months	6.8 months
Survival rate at 6 months	84%	64%	77%
Median overall survival	13.2 months	9.6 months	15.9 months

* complete response – disappearance of all target lesions
partial response – at least 30% decrease in the sum of the diameters of target lesions

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

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

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

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

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