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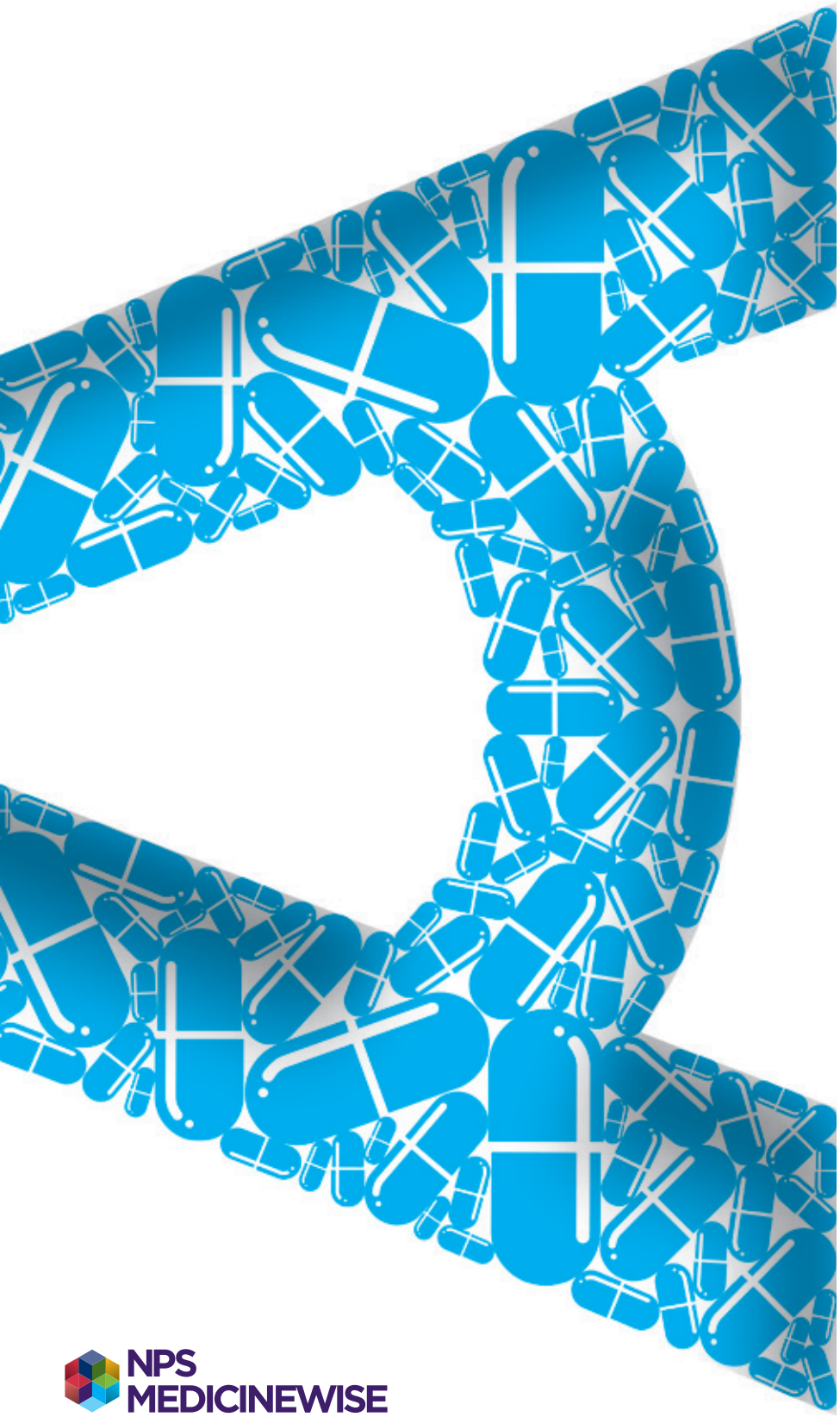

NPS MEDICINEWISE

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EDITORIAL

The hazards of rapid approval of new drugs

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drug approval, drug regulation, Therapeutic Goods Administration

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The approval of new drugs is a complicated and sometimes controversial process. Even the US Food and Drug Administration (FDA), one of the largest regulatory agencies, sometimes makes mistakes. These are often related to its 'fast-track' options, which aim to quickly approve new drugs for serious illnesses. However, approval can be made too early for drugs with limited data or data reliant on biochemical surrogate markers.[1] There is less chance of identifying adverse drug reactions before marketing for drugs that undergo fast-track approval.[2]

Canada has also developed a fast-track process and a recent analysis found that safety warnings are significantly more likely after this process than they are with drugs approved through the usual regulatory process. Between 1998 and 2013, 27 drugs were approved on limited data and 11 (41%) subsequently received a safety warning or were withdrawn because of safety concerns. In the same period there were warnings or withdrawals for 50 (19%) of the 265 drugs approved after a standard evaluation.[3]

In spite of these concerns, at the end of 2014 the Australian Government called for measures to 'cut red tape' – proposing that the Australian Therapeutic Goods Administration (TGA) accept 'trusted international standards'. 'This will remove regulatory duplication, reduce costs and delays for businesses and consumers, increase the supply of products into the Australian market and allow regulatory authorities to focus on higher priorities.' The first step will enable manufacturers of medical devices to use certification by the European Union in place of TGA certification.[4]

While this reform sounds laudable, the TGA safeguards and enhances the health of the Australian community. This consists of a population of different ethnic backgrounds and different comorbidities, which affect the pharmacokinetics and pharmacodynamics of drugs. Australian prescribing practices and treatment algorithms can also be different so the results of overseas trials may not be applicable to Australian practice. In the evaluation process, the TGA can currently request the drug's manufacturer to provide justification as to how the drug is either known to, or likely to, behave in Australian clinical practice.

The Government did not consult any clinical expert groups and seemingly ignored the overseas concerns when making its proposal. It did belatedly ask for submissions on a strategy document in December 2014 with a deadline of 5 January 2015. We were involved in preparing responses critiquing the proposal on behalf of the Royal Australasian College of Physicians and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists.

Prescribers should be aware of some of the examples where inadequate information at the time of rapid registration has been followed by significant adverse reactions, which have resulted in the drug being removed from the market.

One of the most widely known cases in Australia was rofecoxib, which was withdrawn because of serious cardiovascular adverse events. Despite a senior medical officer of the FDA noting a threefold increase in cardiovascular problems, the FDA gave rofecoxib priority status. Millions of people took the drug and worldwide sales totalled US$2.5 billion in 2003 alone. However, within months of the approval, a trial reported a doubling of heart attacks and strokes. In the USA, it was estimated that an excess of up to 139 000 people suffered a heart attack or stroke, and up to 40% of those died before rofecoxib was recalled.[5]

Ponatinib is a drug for chronic myeloid leukaemia that was assessed via the FDA's accelerated-approval pathway. This aims to expedite registration to address an 'unmet medical need', that is 'providing a therapy where none exists or providing a therapy which may be potentially better than available therapy'.[6,7] Ponatinib approval was based on data from a single

From the Editor

Gastro-oesophageal reflux disease is a common problem. Charlotte Keung and Geoffrey Hebbard review its management. At the other end of the gastrointestinal tract, Steven Schlichtemeier and Alexander Engel advise on the treatment of anal fissure.

With the increasing prevalence of kidney disease there is a greater need to be aware of drugs that are affected by renal function. Brendan Smyth, Ceridwen Jones and John Saunders discuss prescribing for patients on dialysis.

Reductions in renal function can result in toxic concentrations of digoxin. Matthew Pincus provides advice on how to manage digoxin toxicity.

Opioid toxicity is used by Sara Bird as an example of the risks of giving drugs to close acquaintances. She warns on the pitfalls of prescribing for family and friends.

There are also pitfalls in bringing new drugs to the market. Jennifer Martin and Gillian Shenfield alert us to the hazards of rapid approval of new drugs.

Australian Prescriber was one of the first medical journals in the world to provide online open access to its content. This year we celebrate 20 years of electronic publishing with the introduction of the new features that are described on page 13.

phase II study of 449 patients with a median follow-up of 10 months. This study had only historical controls and was unblinded. With such minimal data one would expect robustly demonstrated outcomes to justify approval. In fact no patient-relevant outcomes such as overall survival or quality of life were used. Efficacy was accepted on non-blinded, non-randomised comparative data about the surrogate outcome of major cytogenetic response.[8] Ponatinib was subsequently removed from the US market because nearly half the patients had adverse vascular effects, such as venous thromboembolism, at three years.[1] With more data at an earlier stage ponatinib may never have been approved. It has now been marketed in Australia with a black box warning about its potentially fatal adverse effects.

Dabigatran has been associated with severe bleeding and it has emerged that the manufacturer withheld some information about how to use the drug safely and the FDA ignored advice from a majority of its advisory committee. This resulted in the approval of doses (150 mg twice daily) that were too high for some patients.[9,10] Australians were spared some of these problems as the TGA was more cautious than the FDA and recommended a lower dose (110 mg twice daily) for patients at risk of bleeding, such as those with renal impairment.

There have been many other drugs that have come under the rapid review processes of the FDA. Examples of problems not seen when the initial marketing approval was given, usually due to small numbers of patients and short-term use, include sofosbuvir causing serious bradycardia and deaths when used with amiodarone,[11] dimethyl fumarate and the risk of progressive multifocal leukoencephalopathy,[12] and troglitazone causing acute liver failure, the need for transplants, and 94 deaths.[13] Priority review status has also been given to drugs that treat non-life-threatening diseases, for example alosetron for irritable bowel syndrome in 1999. This drug caused at least four fatalities and severe adverse effects requiring surgery. It was withdrawn in 2000, within a year of its launch, but was reintroduced in 2002 with restrictions on its use.

We conclude that, as well as the problems with safety in small and short-term studies, the use of biomarkers (as opposed to actual clinical outcomes) in the rapid review process is often insufficient for a safe assessment. A slower and more comprehensive consideration of adverse events in well-conducted trials might temporarily deny a few patients an effective treatment but save the lives of many more. The FDA is a highly respected organisation and of course makes many correct decisions that are very helpful to other countries, but it does not get everything right. The same is true of all drug regulatory agencies including the TGA. The TGA is currently interested in the fast-track option and appointed a working party of three (without a clinical pharmacologist) to review the suggestion. Their first statement recommended fast tracking as one of three parallel routes and is being discussed currently at workshops which include all interested parties.

Although small efficiencies may be possible, the Australian population has been well served by the TGA in its current form. We consider the Government's attempt to speed up drug registration approvals by reducing, or perhaps ceasing, the TGA's role could be detrimental for the appropriateness and safety of new medicines in Australia.

Jennifer Martin provides consulting advice to the TGA.

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LETTERS

Letters to the Editor

Iodine in breastfeeding

Aust Prescr 2016;39:4
http://dx.doi.org/10.18773/austprescr.2016.015

I refer to the breastfeeding article[1] by Neil Hotham and Elizabeth Hotham to express my concern about the inclusion of iodine as a drug contraindicated in breastfeeding. In the Table titled 'Examples of drugs contraindicated in breastfeeding' it mentions iodine with the comment 'High doses (>150 micrograms daily) lead to risk of infant hypothyroidism'. I could not find anything in the text or the references of the article that supports this view.

First, iodine is not a drug but an essential element required for normal thyroid function. Therefore including it in a table as an example of drugs contraindicated in breastfeeding is totally unacceptable.

Second, the maternal recommended daily intake for iodine during pregnancy and lactation is 250 micrograms. Given that mild iodine deficiency has been widely prevalent in Australia and continues in women of reproductive age, the National Health and Medical Research Council recommends a daily supplement of 150 micrograms for pregnant and lactating women.[2] The World Health Organization states that a maternal intake over 500 micrograms per day is excessive but not necessarily harmful.[3] It is possible to cause infant hypothyroidism by massive doses of iodine directly to the infant or via mother's milk over a prolonged period of time.

Finally, I think this article is more likely to cause harm than do good by deterring iodine supplementation during pregnancy and lactation. I would ask that a correction be published.

CJ Eastman
Consultant physician/endocrinologist
Sydney

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Neil Hotham and Elizabeth Hotham, the authors of the article, comment:

We agree with Professor Eastman that the main issue of concern is the dose of iodine supplementation. It would have been preferable had the term 'cautionary use' been adopted in relation to iodine rather than suggesting an absolute contraindication for doses over 150 micrograms.*

As Professor Eastman notes, the National Health and Medical Research Council recommends that all Australian women who are pregnant or breastfeeding take a daily supplement containing 150 micrograms,[1] to help achieve the recommended daily intake of 270 micrograms. Hale and Rowe advise limiting doses to not exceed the recommended daily intake,[2] given the risk of hypothyroidism (even if transient) in the infant.

Lactating women with thyroid disorders should be counselled to seek specialist advice.

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* *Australian Prescriber* has corrected the article by deleting iodine from the list of contraindicated drugs.

Radiopharmaceuticals in breastfeeding

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In the article on drugs in breastfeeding,[1] I was dismayed at the inclusion of 'radiopharmaceuticals' in the table of drugs contraindicated in breastfeeding. There was little elaboration within the article as to the reason for this. The other drugs listed have sufficient evidence of the potential for serious adverse effects to the infant. This evidence simply does not exist for diagnostic radiopharmaceuticals.

Breastfeeding mothers regularly refuse timely diagnostic studies (to their detriment) on the basis of this misinformation touted by clinicians with little knowledge of radiology and risks. I kindly request

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

that instead of 'referring to the obstetric information service' that you instead speak with the local nuclear medicine specialist.

Giles Craig
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1. Hotham N, Hotham E. Drugs in breastfeeding. Aust Prescr 2015;38:156-9.

Neil Hotham and Elizabeth Hotham, the authors of the article, comment:

We thank Dr Craig for his comments and recognise that inclusion in the list of contraindicated drugs without qualification could be misleading. It is important for women to discuss any concerns with a specialist. In addition, there is sound advice available from the centres and references cited in our article.

It is essential to distinguish between radiopharmaceuticals. There is universal agreement that iodide (^{131}I) is incompatible with breastfeeding, as the iodide concentrates not only in the maternal thyroid gland but also in breast tissue and breast milk. Permanent discontinuation is advised.[1,2]

For other radiopharmaceuticals, such as technetium, recommendations related to breastfeeding should be cognisant of the radioactive half-life of the pharmaceutical. For some, no interruption of breastfeeding is necessary, whereas for others, expressing breast milk for periods from 3–48 hours has been recommended (based on the individual isotope). Hale and Rowe advise that, for any radiopharmaceutical, the withdrawal period for higher doses should be a minimum of five half-lives of radioactivity and possibly up to 10.[3]

By comparison, for non-radioactive products such as gadolinium-based and iodinated contrast media, there is expert consensus that no interruption of breastfeeding is necessary.[4-6] Despite this, the Australian product information for these products has a range of suspension recommendations from 24 hours (meglumine diatrizoate and sodium diatrizoate) to complete cessation (meglumine iothalamate). These examples highlight the pitfalls of relying on the product information in clinical practice.

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ARTICLE

The management of gastro-oesophageal reflux disease

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Key words
endoscopy, gastro-oesophageal reflux disease, histamine H2 antagonists, proton pump inhibitors

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SUMMARY

If there are no features of serious disease, suspected gastro-oesophageal reflux disease can be initially managed with a trial of a proton pump inhibitor for 4–8 weeks. This should be taken 30–60 minutes before food for optimal effect.

Once symptoms are controlled, attempt to withdraw acid suppression therapy. If symptoms recur, use the minimum dose that controls symptoms. Patients who have severe erosive oesophagitis, scleroderma oesophagus or Barrett's oesophagus require long-term treatment with a proton pump inhibitor.

Lifestyle modification strategies can help gastro-oesophageal reflux disease. Weight loss has the strongest evidence for efficacy.

Further investigation and a specialist referral are required if there is no response to proton pump inhibitor therapy. Atypical symptoms or signs of serious disease also need investigation.

Introduction

Gastro-oesophageal reflux disease (GORD) is a condition in which reflux of the stomach contents into the oesophagus results in symptoms or, occasionally, complications. This is distinct from asymptomatic physiological reflux and from functional heartburn, where the symptoms resemble GORD but are unrelated to acid reflux.[1]

GORD is one of the most common gastrointestinal conditions in Australia. It is estimated to occur in 10–15% of the population, with a rising prevalence, most likely due to obesity.[1-3] In addition to obesity, risk factors include advanced age, male gender, Caucasian ethnicity, diets high in fats, sugars and salt, and smoking.

Pathophysiology

Defective function of the lower oesophageal sphincter leads to excessive acid exposure in the lower oesophagus, most commonly during transient lower oesophageal relaxations.[1] In the majority of cases, this leads to symptoms such as heartburn and regurgitation. However, in a small but important minority, complications of peptic oesophagitis may occur including oesophageal strictures, Barrett's oesophagus and rarely oesophageal adenocarcinoma, the rate of which is increased fivefold in patients with chronic GORD compared to the general population.[2]

Although hiatus hernia is statistically associated with gastro-oesophageal reflux, the presence of a hiatus hernia is neither required nor sufficient for a diagnosis of GORD. The presence of a hiatus hernia is relevant to surgical treatment, but does not affect the approach to medical therapy.

Initial assessment

A presumptive diagnosis of GORD can be made based on the typical symptoms of heartburn and regurgitation. The presence of either symptom has an overall sensitivity of 49% and specificity of 74%.[4]

Heartburn is described as a burning, retrosternal, rising sensation associated with meals, although this definition is often poorly understood by the general population.[4] Practitioners need to be aware of this and clarify the nature of the symptoms being discussed when the term is used. Regurgitation is described as the effortless appearance of gastric contents in the throat or mouth without associated nausea or retching.[4] Other non-specific symptoms include vomiting, anorexia, dysphagia, cough and other respiratory or oropharyngeal symptoms.[2,5-8]

While several validated symptom-based questionnaires exist, their use is largely limited to research studies.[4] The correlation between symptoms and the severity of oesophagitis is weak, but if typical features are present without 'red flags' (Box 1)[9] then there is no need for gastroscopy in the initial assessment and empirical treatment can commence.

A trial of a proton pump inhibitor (PPI) is frequently used. Although neither particularly sensitive nor specific, a trial is useful, cost-effective and helpful in predicting which patients will respond to therapy. Treatment should continue for 4–8 weeks. While a

negative trial does not exclude the diagnosis, it does reduce its likelihood and should prompt consideration of alternative diagnoses.[10]

Further investigations

Further investigations may be required in patients who do not respond to a trial of acid suppression, or have red flags or chronic symptoms.[9]

Endoscopy

The primary role of gastroscopy is to look for complications and to exclude other diagnoses. It is therefore only indicated in certain situations (Box 2) and should not be repeated if negative. Normal macroscopic findings are seen in almost two-thirds of patients with reflux symptoms and a normal endoscopy does not exclude GORD.[9] Gastroscopy can exclude Barrett's oesophagus and erosive GORD, which allows the patient to be informed that the focus of treatment will be on symptom control and that further endoscopy is not required.

Eosinophilic oesophagitis should be considered in patients, particularly men, in their 20s and 30s with a history of food allergy or atopy who present with dysphagia or refractory symptoms suggestive of GORD. Biopsy may be needed to exclude eosinophilic oesophagitis.[11] There is no evidence that routine screening for Barrett's oesophagus improves mortality or is cost-effective.[12] However, it may have a role in high-risk groups such as the overweight and Caucasian males over 50 years old with no previous endoscopic investigation.

Barium swallow

There is no role for the barium swallow in the routine diagnosis of GORD. Findings of gastro-oesophageal reflux induced by position or abdominal pressure are neither sensitive nor specific for GORD.[5]

Oesophageal manometry and pH studies

These studies are only required in a minority of patients who are either refractory to treatment or are being assessed for surgery.[13,14] Usually a specialist consultation is needed.

Other investigations

Helicobacter pylori infection does not cause GORD and actually appears to be slightly protective against it, Barrett's oesophagus and oesophageal adenocarcinoma. *Helicobacter pylori* eradication is not effective in reducing the symptoms of GORD.[2]

Lifestyle modification

Of the non-pharmacological approaches to the management of GORD, weight loss has been shown to have a dose-dependent association with reduction of symptoms.[3] A reduction in the body mass index of 3.5 kg/m^2 can result in nearly a 40% reduction in the risk of having frequent symptoms.[1]

Other lifestyle modifications include elevation of the head of the bed and avoidance of meals 2–3 hours before bedtime if there are nocturnal symptoms.[10] While routine global elimination of specific food groups triggering reflux is not recommended, patients should avoid foods that specifically trigger their symptoms. Cessation of tobacco and alcohol are recommended but, while this may help some patients, it has not been shown to improve symptoms overall.[10] Drugs with anticholinergic or smooth muscle-relaxing properties may exacerbate reflux symptoms, as may drugs causing a chemical oesophagitis (e.g. oral bisphosphonates).

Acid suppression therapy

Many patients try over-the-counter medicines such as antacids or H_2-receptor antagonists before they

Box 1 Red flags* in gastro-oesophageal reflux

Recurrent vomiting

Dysphagia or odynophagia

Weight loss

Evidence of gastrointestinal blood loss
e.g. haematemesis, iron deficiency or anaemia

Duration of symptoms >5 years or <6 months

Epigastric mass

Age >50 years

* Red flags are warning symptoms and signs requiring further evaluation.[9]

Box 2 Indications for gastroscopy in gastro-oesophageal reflux disease[9]

Red flags (see Box 1)

Persistent symptoms despite an adequate trial of proton pump inhibitor therapy

Treatment of complications such as dilatation of oesophageal strictures

Evaluation of patients before and after anti-reflux surgical procedures

Screening for Barrett's oesophagus in high-risk patients (may be considered, e.g. in overweight men over 50 years, however evidence that screening improves outcomes is lacking)

visit a doctor. These treatments may be continued if they are effective, often with the addition of lifestyle modifications. If symptoms persist despite simple measures, and significantly interfere with quality of life, a trial of a PPI is appropriate (Fig.). This provides a degree of diagnostic confirmation and, in the case of suboptimal response, determines whether further investigation is required.

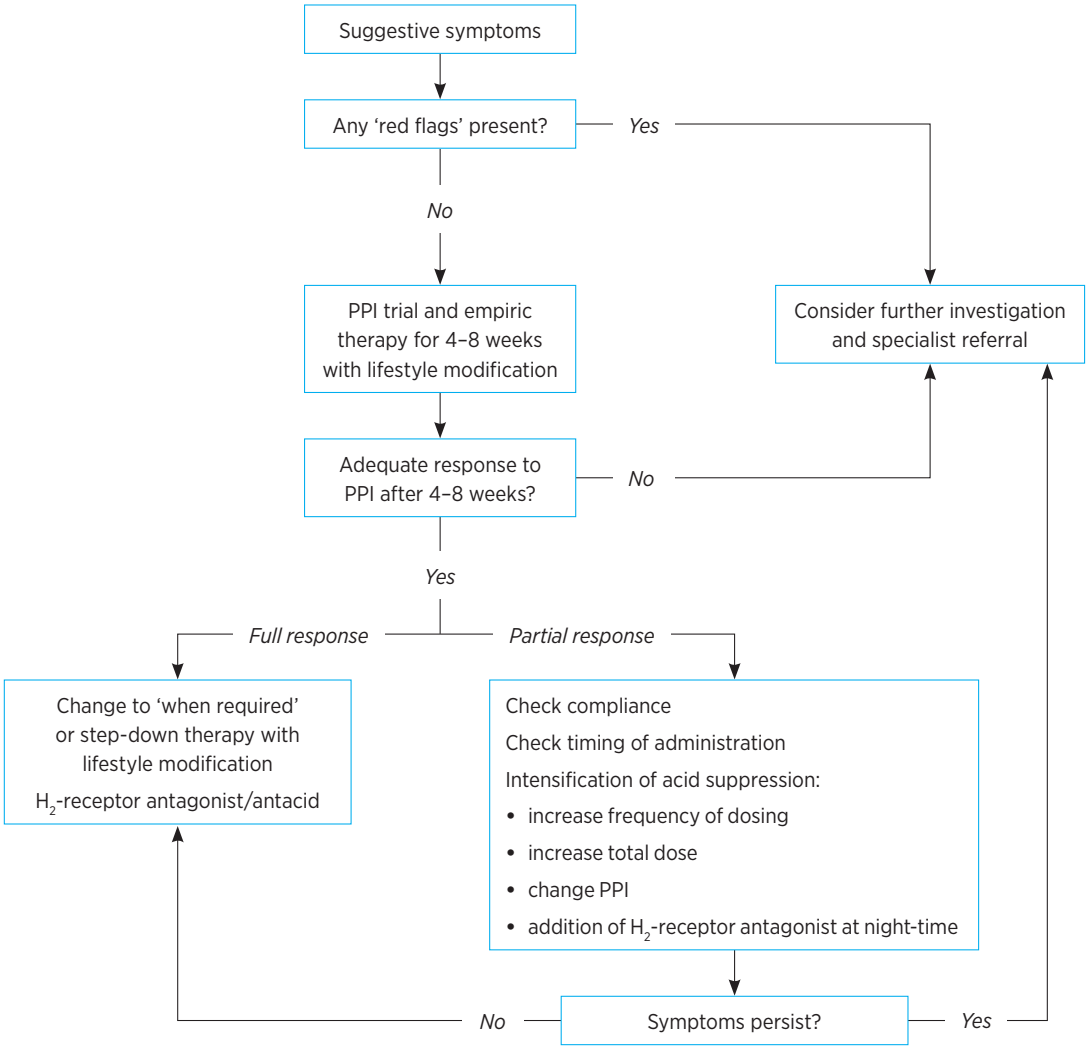
Pharmacology

PPIs are more potent at acid suppression than H_2-receptor antagonists. They block the final common pathway of acid secretion by irreversibly binding to and inactivating the proton pump (H^+/K^+-ATPase exchange). This results in a greater proportion of healed erosive oesophagitis compared with the use of H_2-receptor antagonists (84% ± 11% vs 52% ± 17%).[15]

PPIs have a short plasma half-life (mostly 1–2 hours) and are only effective when proton pumps are active (in the postprandial period). The timing of administration is therefore important, with the greatest efficacy being seen when PPI concentrations are maximal at the time of a meal. As the inactivation of the proton pump is irreversible, the biological half-life of the drug is considerably longer than its plasma half-life. Consequently, if an increase in acid suppression is required, a second dose taken later in the day (e.g. before the evening meal) is more effective than doubling the morning dose.

Start treatment with once-daily dosing 30–60 minutes before a meal. This is usually breakfast as the greatest amount of H^+/K^+-ATPase is present after a prolonged fast. Drug metabolism differs between individuals, and although some patients may respond better to

Fig. **Approach to management of gastro-oesophageal reflux disease**



PPI proton pump inhibitor

one drug than another, overall symptom relief appears to be equivalent. The most important differences between individuals are largely related to adherence and the timing of a dose, as well as the amount of PPI per unit dose.

Maintenance therapy

Patients with typical symptoms of GORD who respond to 4–8 weeks of PPI therapy can reduce their dose to 'when required' while continuing lifestyle measures, antacids and, when required, H_2-receptor antagonists as a less potent alternative to the PPI. There may be a period of acid hypersecretion following the withdrawal of PPI, but any symptoms will reduce over a period of about a month, after which recurring symptoms are most likely to be due to underlying reflux disease.[16] Using a PPI when required will be adequate for some patients, however 75–90% will relapse over six months.[5] This reflects the chronic nature of the condition rather than a failure of treatment. Surveillance gastroscopy is not required in patients with GORD.

An alternative approach is a more formal step-down of the PPI. The dose is reduced to determine the minimum needed to control symptoms. This may involve a gradual reduction in the dose or frequency with the aim of switching to 'when required' therapy. This approach allows patients to put lifestyle modifications into place and to find the lowest dose they need for adequate control of their symptoms.

Patients with evidence of significant erosive oesophagitis (Los Angeles Grades C, D), scleroderma oesophagus or Barrett's oesophagus should remain on maintenance PPI therapy even if they are asymptomatic.[17]

Adverse effects

The potential adverse effects of PPIs include headache and diarrhoea (less than 2%). Other important but rare adverse events include interstitial nephritis, hypomagnesaemia, reduced vitamin B_{12} absorption, increased *Clostridium difficile* infection and possibly community-acquired pneumonia.[7,10] An association between PPIs and osteoporotic fractures is likely to be due to shared risk factors including increased age and medical comorbidity.[18,19] A randomised trial found no evidence of an increased risk of cardiovascular events in patients taking PPIs and thienopyridines such as clopidogrel.[10,20] There was also no evidence that separating the doses of the two drugs changed cardiac risk.[21] If there are major concerns about the interaction, a PPI with less cytochrome P450 (CYP) metabolism such as rabeprazole may be used.

Persistent symptoms

Approximately 20–30% of patients do not respond completely to PPI therapy and have persistent symptoms.[22] The initial step is to review the diagnosis, particularly if there was no response to acid suppression, as delayed gastric emptying, functional dyspepsia and functional heartburn (oesophageal hypersensitivity)[23] are common conditions that may be confused with GORD. Other explanations for a suboptimal response include non-adherence or inappropriate dosing.[22] Adherence to PPIs is often poor and is reported at 46–55% in those with persistent symptoms. There is also poor understanding of the pharmacokinetics of PPIs with nearly 70% of GPs and 20% of gastroenterologists incorrectly instructing patients about when to take doses.[23]

Options for intensification of acid suppression include increasing to twice-daily doses[10] or trying a different PPI in case there are individual pharmacokinetic and pharmacogenetic differences such as in CYP2C19 metabolism.[15,24] Further intensification of treatment may include addition of a night-time H_2-receptor antagonist (although tachyphylaxis may develop within 2–6 weeks)[15] or a mucosal protectant. However, there is only limited evidence for the use of prokinetic drugs or sucralfate, a protective mucosal surface agent, in the treatment of GORD.[10]

Medical management

In patients with medically refractory GORD, ongoing non-acid or weakly acid reflux is the most common cause.[15] Although baclofen can reduce the number of reflux events by inhibiting transient relaxations of the lower oesophageal sphincter, long-term data are lacking[15] and adverse effects such as drowsiness occur in up to 63% of patients.[16] Other drugs are currently under investigation,[15,25] but there do not appear to be any 'game changers' in the pipeline.

Surgical management

Indications for anti-reflux surgery include GORD with refractory symptoms despite maximal medical management or intolerance of treatment, and symptomatic complications unresponsive to medical therapy.[26] Laparoscopic fundoplication is the most common surgical procedure and is highly effective in well-selected patients.

Fundoplication involves construction of a cuff of gastric (fundus) tissue around the lower oesophageal sphincter junction.[25] This improves function via a variety of mechanical factors and also modifies the reflexes involved in the pathophysiology. Appropriate patient selection is essential, as symptoms must be due to GORD for the procedure to be effective. The strongest predictors of success include abnormal 24-hour pH scores, classic

SELF-TEST QUESTIONS

True or false?

1. Gastroscopy should be repeated after a course of proton pump inhibitor to confirm that gastro-oesophageal reflux disease has healed.

2. If a patient with gastro-oesophageal reflux disease does not improve with a course of proton pump inhibitor, the likely cause is persistent infection with *Helicobacter pylori*.

Answers on page 27

symptoms of GORD and a positive PPI trial.[26] Factors that predict failure include a lack of response to PPI therapy and atypical features. Surgery does not lead to significant regression of Barrett's oesophagus or reduce the risk of oesophageal adenocarcinoma.

There is evidence that gastric bypass surgery, in particular the Roux-en-Y procedure or laparoscopic gastric banding, decreases GORD symptoms. This is at least in part because of the resulting substantial weight loss.[3] In contrast, sleeve gastrectomy often increases or precipitates the symptoms of reflux.

Endoscopic management

There are several endoscopic procedures for GORD but they are limited by the durability of symptomatic relief and the lack of correction of pathological reflux.[26] Other novel therapies currently include implantable electrical stimulators and placement of an expandable ring of magnetic beads around the lower oesophageal sphincter. However, experience with these is limited and they are yet to find their place in therapy.

Conclusion

GORD is one of the most common gastrointestinal conditions and may result in significant morbidity. In patients with typical symptoms, treatment can be based on symptoms alone with a trial of PPI therapy. Reduce treatment after a response is established. Further investigation is required if there are 'red flags', a lack of response to the trial or complications of GORD.

Geoffrey Hebbard has received research support, travel assistance or eaten food provided by most of the Australian manufacturers and/or distributors of acid suppressing medication (from cimetidine onwards). He has recently been paid to appear in a video presentation by NPS MedicineWise, and is involved in the (unpaid) writing of guidelines for the use of acid suppression in Therapeutic Guidelines.

Charlotte Keung has eaten food provided by the manufacturers and distributors of PPIs.

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ARTICLE

The pitfalls of prescribing for family and friends

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SUMMARY

In most of Australia there is no legislation prohibiting medical practitioners from prescribing for family and friends. In South Australia it is prohibited to prescribe Schedule 8 drugs for family members unless it is a verifiable emergency.

The Medical Board of Australia states medical practitioners should avoid providing medical care to anyone with whom they have a close personal relationship. Medical defence organisations may exclude treatment of family members from doctors' insurance cover.

Think very carefully before you prescribe for family and friends. It is only considered ethically and professionally appropriate to prescribe in exceptional circumstances, and there are potential risks to you and your family member or friend if you do.

Introduction

Prescribing for family and friends can be hazardous. Although such prescribing is not prohibited by legislation, it is not recommended by the Medical Board of Australia.

Recent cases

A doctor was found guilty of professional misconduct for providing prescriptions to her defacto partner.[1] Over a period of two years, she had prescribed morphine, pethidine, psychotropic and various other drugs for her partner. The medical tribunal found that she prescribed the Schedule 8 drugs without having the proper authority, when she knew or should have known that her partner was a drug-dependent person, and that she did not maintain adequate medical records. She was disqualified from being registered as a medical practitioner for a period of 18 months.

Another case involved the death of a family friend. The 22-year-old man died four days after he had three wisdom teeth removed.[2] Two days after the extraction, he was suffering from increasing pain which was not relieved by ibuprofen, or paracetamol with codeine. His mother contacted a long-standing family friend who was a GP. The GP agreed to see the man and gave him a prescription for a combination of paracetamol, codeine and doxylamine. She also gave him a box containing seven methadone tablets. These tablets were past their expiry date and had been prescribed for the GP a few years earlier after a surgical procedure. The GP wrote instructions on the box saying '1 tab every 6–8 hours'. Two days later, the man was found dead in his bed.

Toxicology revealed the presence of morphine, codeine, methadone, doxylamine, norfluoxetine and paracetamol. An expert opinion concluded that the death was a result of excessive exposure to methadone, most likely due to its respiratory depressant effect, or due to sudden cardiac death from fatal QT prolongation, or both. According to the expert, the major contributory factor to the toxicity of the methadone was a drug interaction with fluoxetine. The coroner found that the primary drugs contributing to the death were methadone, and its interaction with fluoxetine, and a very high dose of codeine. The coroner noted that the man's parents and the GP were not aware that he had recently taken fluoxetine. The coroner determined that the death was preventable and referred the GP for disciplinary action.[2]

Legislation

Each state and territory has specific legislation that regulates the prescription of drugs.[3-10] There are no legal restrictions on medical practitioners prescribing Schedule 4 drugs for their family and friends. Similarly, medical practitioners are not legally restricted from prescribing Schedule 8 drugs for family and friends, except in South Australia. There the legislation prohibits the prescription of Schedule 8 drugs for a practitioner's spouse, domestic partner, parent, grandparent, child, grandchild, brother or sister, unless it is a 'verifiable emergency'.[11]

There are also restrictions on self-prescribing. For example, in Victoria doctors cannot prescribe drugs for their own use.

Professional conduct

The Medical Board of Australia discourages all medical practitioners from providing medical care to family and friends and there is the possibility of disciplinary action. Section 3.14 of the Medical Board of Australia's 'Good medical practice: a code of conduct for doctors in Australia' states:

> Whenever possible, avoid providing medical care to anyone with whom you have a close personal relationship. In most cases, providing care to close friends, those you work with and family members is inappropriate because of the lack of objectivity, possible discontinuity of care, and risks to the doctor and patient. In some cases, providing care to those close to you is unavoidable. Whenever this is the case, good medical practice requires recognition and careful management of these issues.[12]

The Medical Council of NSW's 'Guideline for self-treatment and treating family members' states:

> Whenever possible, medical practitioners should not treat themselves and members of their family, because in these circumstances:
>
> - professional objectivity may be compromised and their judgment may be influenced by the nature of their relationship with the patient
> - medical practitioners may fail to explore sensitive areas when taking a medical history or may fail to perform an appropriate physical examination
> - the patient may feel uncomfortable disclosing sensitive information or undergoing a physical examination when the medical practitioner is a family member
> - patient autonomy may be compromised when a medical practitioner treats a member of their family
> - the principles of informed consent may not be adhered to when a medical practitioner treats a member of their family.[13]

Specifically in relation to prescribing for family members, the guideline states:

- medical practitioners should not initiate treatment (including prescribing) for members of their family
- in emergency situations or isolated settings where there is no help available, medical practitioners may treat members of their family until another medical practitioner becomes available
- medical practitioners should not serve as primary or regular care providers for members of their family, although there are circumstances in which they may work together with an independent medical practitioner to maintain established treatment.[13]

It is also important to be aware that medical defence organisations may exclude cover for claims or investigations arising from elective medical treatment of a medical practitioner's immediate family. This would include situations where a medical practitioner had electively prescribed for their family.

Prescribing for family and friends: to do or not to do?

There is limited published research on the prevalence of prescribing for family and friends. A survey of US paediatricians found that 76% had been asked to provide a prescription for a first-degree relative.[14] Interestingly, 86% of the respondents reported that they had refused to write a prescription for a family member or a friend on at least one occasion. The following reasons 'strongly influenced' their decision to refuse a request:

- outside the practitioner's field of expertise (88%)
- opinion that the person needed their own physician (70%)
- request not medically indicated (69%)
- need for a physical examination (65%).

If you are asked to provide a prescription for a family member or friend, it is important to ask yourself:

- Am I able to provide appropriate medical care to my family member or friend in this situation?
- Am I following my usual practice in providing a prescription or repeat prescription in this situation?
- Would my peers agree that prescribing in this situation was consistent with good medical practice?
- If I prescribe, does this mean that my family member or friend is my patient?
- Would our personal relationship survive an adverse outcome of treatment?

It is useful to consider in advance how you might refuse to provide a prescription, for example 'professional guidelines and regulations prevent me from prescribing for you'.

Conclusion

The starting point for a request to prescribe for family or close friends should be 'no', unless there are exceptional circumstances. Exceptional circumstances may include an emergency where no other medical practitioner is available to assist, or providing a repeat prescription at the request of the treating practitioner. Remember you can still assist a family member or friend without getting out your prescription pad by

acting as a knowledgeable guide to help them obtain the required care from their treating practitioner or another medical practitioner. ◁

This article is provided by MDA National. It recommends that you contact your indemnity provider if you need specific advice in relation to your insurance policy.

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Exciting things happening in the digital space

Australian Prescriber is confirming its place as a trusted source of independent information by meeting the new standards of scholarly publication.[1]

We are pleased to announce that *Australian Prescriber* has been accepted for inclusion in PubMed Central – a free archive of full-text biomedical and life sciences journal articles, hosted by the US National Library of Medicine.

Starting from this issue (Volume 39, Number 1), all articles will be available through PubMed Central within a month. Back issues of *Australian Prescriber* will also be added over time.

Inclusion in PubMed Central is a significant milestone for *Australian Prescriber*. Readers will now be able to search for and access *Australian Prescriber* articles through PubMed – the database of choice for researching medical literature.

Other developments include the assignment of digital object identifiers (DOIs) to all articles in *Australian Prescriber* through CrossRef. DOIs are links that preserve the scholarly citation record. In addition to displaying our own DOIs, we will include the DOI of each of the cited references if they have one. This will make it easier for our readers to link directly to other relevant articles.

Australian Prescriber will soon start using Altmetrics as an alternative to traditional impact factors. Altmetrics is an online tool that will monitor the impact of our articles across traditional and social media, online reference managers, post-publication peer-review sites, and public policy documents. Watch out for the Altmetrics badge or 'doughnut' displayed next to *Australian Prescriber*'s most popular articles. It will give a score indicating the quantity and quality of attention the article has received. Readers can click on the badge and get direct access to the online conversations about the article.

Australian Prescriber has been freely available online since 1996, and has been listed in the Directory of Open Access Journals since 2003. With the rise in online 'predatory' journals,[1] however, the requirements for inclusion in the directory have increased. We are now in the process of meeting these new standards.

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ARTICLE

Anal fissure

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SUMMARY

An anal fissure is a common, mostly benign, condition that can be acute or chronic. The diagnosis is usually made on history and physical examination, but further investigations are sometimes necessary.

Primary fissures are usually benign and located in the posterior or anterior position. Secondary fissures are lateral or multiple and often indicate a more serious underlying pathology.

The management of primary anal fissures is generally non-operative and includes increased dietary fibre, sitz baths, topical ointments and botulinum toxin injections. If these treatments are ineffective the patient will need a surgical referral.

Secondary anal fissures require further investigation. Multidisciplinary management is preferable and is essential in the case of malignancy.

Introduction

An anal fissure is a longitudinal tear or defect in the skin of the anal canal distal to the dentate line (Fig. 1). The classification of anal fissures is based on causative factors.

Primary fissures are typically benign and are likely to be related to local trauma such as hard stools, prolonged diarrhoea, vaginal delivery, repetitive injury or penetration. Secondary fissures are found in patients with previous anal surgical procedures, inflammatory bowel disease (e.g. Crohn's disease), granulomatous diseases (e.g. tuberculosis, sarcoidosis), infections (e.g. HIV/AIDS, syphilis) or malignancy.[1]

An acute anal fissure commonly heals with 4–8 weeks of conservative therapy. If this therapy fails and the fissure becomes chronic, surgery is usually required.[2-4]

Pathophysiology and histology

The pathophysiology of anal fissures is not entirely clear. It is probable that an acute injury leads to local pain and spasm of the internal anal sphincter. This spasm and the resulting high resting anal sphincter pressure[5] leads to reduced blood flow and ischaemia,[6,7] and poor healing. Unless this cycle is broken the fissure will persist (Fig. 2).

In approximately 90% of patients the anal fissure is located in the posterior midline. It is hypothesised that this predilection for the posterior midline may occur because this portion of the anal canal is poorly perfused.[7,8] Anterior anal fissures affect approximately 10% of patients and may have a different pathophysiology. They are associated with younger, mostly female, patients often with injury to or dysfunction of the external anal sphincter. In less than 1% of patients the fissures are lateral or multiple.[2] Irrespective of these differences posterior and anterior anal fissures are thought to be of primary aetiology, whereas lateral or multiple fissures are more likely to be secondary in nature.[2]

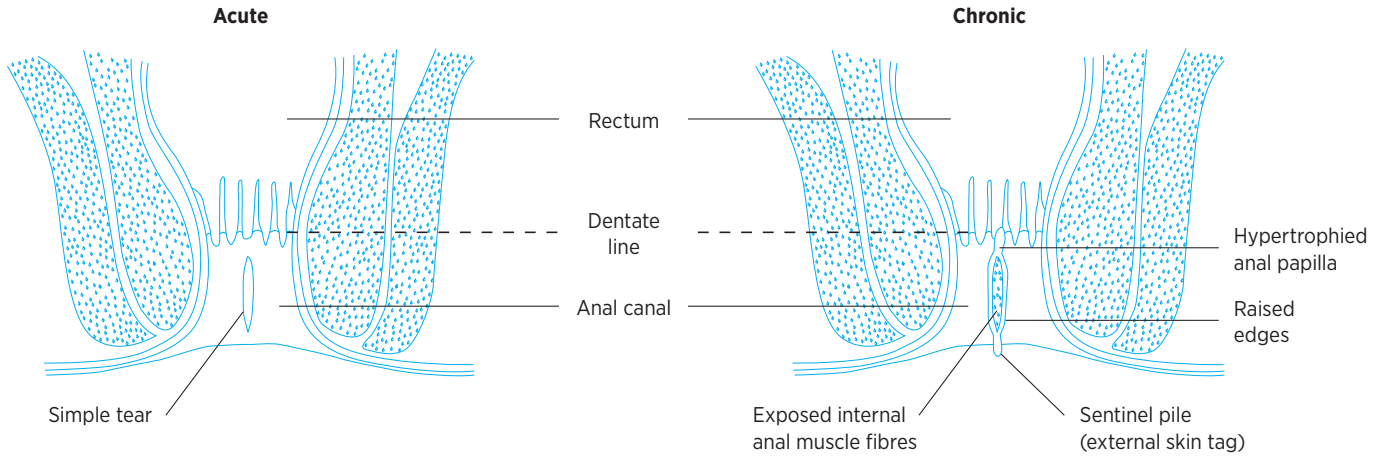
A small study of completely excised anal fissures found no underlying microscopic features of inflammation in most of the patients. Further, these fissures or defects showed little in the way of ulcer characteristics and appeared to be more consistent with unstable anodermal scar tissue.[9] Additional research is needed to understand the temporal relationship between poor perfusion and lack of inflammation, as well as to identify the best terminology to describe these lesions.

Assessment

History and physical examination will allow the diagnosis of an anal fissure without further investigations in most patients. The clinical features are severe tearing pain with the passage of faeces often with a small amount of bright red blood on the stool or toilet paper. The ideal way of examining is to have the patient lie comfortably in a lateral position and then gently part the buttocks to look first at the posterior midline.

An acute anal fissure appears as a fresh laceration, while a chronic anal fissure has raised edges exposing the internal anal sphincter muscle fibres underneath. Chronic anal fissures are also often accompanied by an external skin tag (sentinel pile) at the distal end of the fissure and a hypertrophied anal papilla at the proximal end (difficult to see on physical examination) (Fig. 1).

Fig. 1 **Diagram of anal fissures**



A digital rectal examination is usually not needed to make the diagnosis and is contraindicated in many cases given the associated pain. However, examination under anaesthesia with anoscopy, endoscopy, biopsy and imaging (i.e. CT scan, MRI or endoanal ultrasound) may all be required if:

- the fissure cannot be seen
- the diagnosis is unclear
- there is significant bright red bleeding in a patient with an increased risk for colorectal cancer
- there are features suggesting a secondary anal fissure.

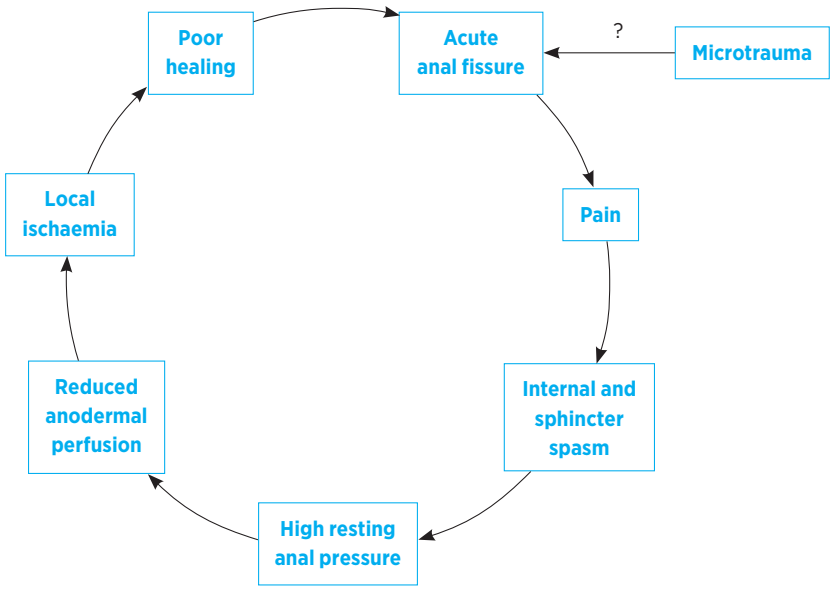
The differential diagnosis of a primary anal fissure is limited but includes a haemorrhoid, anal fistula or solitary rectal ulcer. These conditions can be excluded by careful clinical assessment.

Secondary anal fissures may have characteristic features in the patient's history such as risk factors for anal cancer, or medical conditions such as Crohn's disease, tuberculosis, sarcoidosis, HIV/AIDS and syphilis. These fissures often lie laterally or are multiple in number. Further investigations must be performed as the underlying cause will determine subsequent management.

Conservative management

There are no clear guidelines on anal fissure management. The goals of management are to break the cycle of anal sphincter spasm allowing improved blood flow to the fissured area so that healing can occur. Almost 50% of patients with acute anal fissures will heal with conservative measures alone involving only increased fibre intake (e.g. psyllium) and warm bathing of the perineum (sitz baths).[4,10] It is hypothesised that warm baths lead to relaxation of the internal anal sphincter via a somatoanal reflex.[11]

Fig. 2 **Pathophysiology of anal fissure** [3]



Topical ointments and creams

First-line therapy often includes the conservative measures plus a topical drug. The preparations used in clinical practice contain glyceryl trinitrate or a calcium channel blocker.

A recent Cochrane review reported that topical glyceryl trinitrate is better than placebo in healing anal fissures (healing rates 49% vs 36%). However, late recurrence occurred in around 50% of those initially cured. It also reported that calcium channel blockers (pooling results from studies using topical or oral preparations) had comparable efficacy to topical glyceryl trinitrate.[12] One study from this review reported that topical diltiazem has superior

healing rates to oral diltiazem (65% vs 38%).[13] While topical diltiazem is the most predominantly studied and clinically used calcium channel blocker, topical nifedipine has also shown some encouraging results.[14]

The typical dosing of either 0.2% nitroglycerin ointment or 2% diltiazem cream is twice daily for 6–8 weeks.[4] Topical glyceryl trinitrate is believed to work through its metabolites. It breaks the cycle of spasm by relaxing the internal anal sphincter and reducing resting anal pressure. Topical calcium channel blockers also relax the internal anal sphincter by blocking the influx of calcium into smooth muscle cells.

The main limitation to using topical glyceryl trinitrate is headaches and lightheadedness. This results in up to 20–30% of patients ceasing therapy prematurely.[2,12] Headaches also occur in a similar proportion of patients using topical calcium channel blockers, however they occur less frequently so may be more tolerable.[3]

Patients using topical glyceryl trinitrate should not take sildenafil, tadalafil or vardenafil due to the risk of hypotension. For patients with angina or heart failure taking nitrates, topical glyceryl trinitrate may cause nitrate tolerance if used during the nitrate-free interval.[15]

Other topical medications commonly used in clinical practice are lignocaine and hydrocortisone. However, they have inferior healing rates to bran plus warm sitz baths.[16] There are also several other topical medications under investigation including bethanechol, indoramine, minoxidil, clove oil and sildenifil, but current evidence does not support their use.[4] Current evidence also does not support the use of oral rather than topical calcium channel blockers in the management of anal fissures.[12]

Botulinum toxin injection

The reported healing rates of anal fissure following botulinum toxin injection are 60–80% (superior to placebo). Although recurrence can occur in up to 42% of patients, repeated injection has similar healing rates. Common adverse effects include temporary incontinence of flatus (in up to 18%) and stool (in up to 5%).[4] The available evidence suggests that these injections probably have at least similar efficacy (certainly not worse) to both topical glyceryl trinitrate and calcium channel blockers.[12,17]

In clinical practice, given the invasiveness of these injections and the adverse-effect profile, some clinicians use botulinum toxin as second-line therapy, particularly in high-risk patients (young multiparous females with reduced sphincter mass), before referring them for a surgical opinion. However, other than the common adverse effects, the main disadvantage with botulinum toxin is that there is no consensus on the number of units to inject or the preferred location for these injections. This makes it difficult to interpret the variable healing rates published in the literature.

Surgical management

Surgery is considered for patients not responding to conservative measures. Although the timing of surgery is individual and variable, the literature often suggests between 4 and 12 weeks (6–8 weeks may be the ideal timing) after starting conservative treatment given the recommended duration of some of the topical dosing regimens.

The gold standard surgical operation for anal fissure is lateral internal sphincterotomy. This procedure commonly involves division of the internal anal sphincter from its distal end to either the proximal end of the fissure or the dentate line (whichever comes first). Lateral internal sphincterotomy has an excellent healing rate of approximately 95%. Common complications include recurrence in up to 6% and incontinence of flatus or stool (usually transient) in up to 17% of patients.[12]

When comparing lateral internal sphincterotomy to the historical four-finger anal stretch, lateral internal sphincterotomy is superior both in terms of recurrence and minor incontinence. However, a more standardised approach using pneumatic balloon dilation has shown healing rates of 83%, approaching those of lateral internal sphincterotomy, but with a lower incidence of long-term incontinence.[1]

When comparing lateral internal sphincterotomy to topical glyceryl trinitrate, calcium channel blockers and botulinum toxin injection, lateral internal sphincterotomy is clearly superior in terms of healing rates. However, it has more complications in some but not all studies.[18-20]

In recent years there has been growing interest in spinchter-sparring surgical techniques, predominantly that of fissurectomy either alone or in combination with other techniques (e.g. botulinum toxin injection or advancement flap). One observational study with good long-term follow-up reported that simple fissurectomy had a healing rate of 88%, a recurrence rate of 11.6% and an incontinence rate of 2.3%.[21] Although not as successful or durable as lateral internal sphincterotomy, some would argue this to be more than a fair trade-off given the preservation of the sphincter complex and hence much lower incontinence rate.

ARTICLE

Secondary fissures

A high index of suspicion is warranted for fissures in lateral or multiple locations and those not healing despite conservative therapies. Once investigated and diagnosed, management of secondary fissures will involve an extensive multidisciplinary approach involving gastroenterologists, infectious disease specialists, oncologists, pathologists and colorectal surgeons. Although surgery may ultimately benefit some patients with inflammatory bowel disease or HIV/AIDS, it may be contraindicated if there is malignancy.

Conclusion

The management of primary anal fissures usually follows a step-wise approach with first-line medical therapy for up to 6–8 weeks. Botulinum toxin injections may be reserved for second-line therapy although they may be used in combination with the conservative therapies. Patients not responding to these measures should be referred for surgery. In the case of a suspected secondary anal fissure, surgical therapies should be postponed or avoided depending on the results of further investigations and multidisciplinary management. ◁

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. Topical administration of a calcium channel blocker for anal fissure is more effective than oral administration.

4. Applying topical glyceryl trinitrate to an anal fissure can cause headaches.

Answers on page 27

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ARTICLE

Management of digoxin toxicity

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Key words
arrhythmia, digoxin, digoxin-specific antibody fragments

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SUMMARY

Digoxin toxicity can emerge during long-term therapy as well as after an overdose. It can occur even when the serum digoxin concentration is within the therapeutic range.

Toxicity causes anorexia, nausea, vomiting and neurological symptoms. It can also trigger fatal arrhythmias. There is a range of indications for using digoxin-specific antibody fragments. The amount ingested and serum digoxin concentration help to determine the dose required, but are not essential.

Digoxin-specific antibody fragments are safe and effective in severe toxicity. Monitoring should continue after treatment because of the small risk of rebound toxicity.

Restarting therapy should take into account the indication for digoxin and any reasons why the concentration became toxic.

Introduction

Digoxin can be used to treat heart failure when symptoms remain despite the use of other drugs. It is also used for atrial fibrillation to reduce the ventricular rate.[1] For heart failure, the recommended range for the serum digoxin concentration has been reduced over the past decade from 0.8–2.0 nanogram/mL to 0.5–0.9 nanogram/mL.[2] This is because of evidence of better outcomes at lower concentrations.[3] Whether this range should also apply to patients with atrial fibrillation without heart failure is unknown.

Incidence of toxicity

Digoxin use has declined since the 1990s.[4] While the overall incidence of toxicity per population has also declined, the incidence per treated patient may have remained unchanged.[4,5] The Australian Institute of Health and Welfare records cardiac glycoside toxicity as the diagnosis on hospital discharge in 280, 233 and 139 patients in 1993–94, 2003–04 and 2011–12 respectively.[6] Chronic toxicity is far more common than acute intoxication.[7]

Digoxin pharmacology

Digoxin increases intracellular calcium in myocardial cells indirectly, by inhibiting the sodium–potassium pump in the cell membrane. Increased intracellular calcium increases cardiac contractility, but also the risk of tachyarrhythmias.[8] Inhibition of this pump causes the hyperkalaemia commonly seen in toxicity. Digoxin also causes an increase in vagal activity, reducing activity in the sinus node and prolonging conduction in the atrioventricular node.

After a dose of digoxin, distribution to the tissues takes several hours. This means that the serum digoxin concentration is inaccurate unless taken at least six hours after the last dose. Only a post-distribution measurement reflects the severity of intoxication and this is the measurement that can help when calculating the dose of digoxin-specific antibody.[9] This applies in both acute and chronic poisoning.

The elimination of digoxin is mainly by renal clearance and is prolonged in patients with renal impairment. Transport by P-glycoprotein also contributes to elimination.[8] Consequently, a higher serum digoxin concentration for a given dose occurs in patients with renal impairment, lower body weight and in those taking amiodarone, verapamil, macrolides, azole antifungals and cyclosporin, which inhibit P-glycoprotein transport.[10]

Although the serum digoxin concentration does predict the likelihood of toxicity,[8,11] several conditions increase sensitivity to digoxin. They at least partly account for patients who develop toxicity when their serum digoxin concentration is within the therapeutic range.[11] These conditions include hypokalaemia, hypomagnesaemia, hypercalcaemia, myocardial ischaemia, hypoxaemia and acid–base disturbances.[10]

Clinical features

The clinical features of toxicity are often non-specific. They commonly include lethargy, confusion and gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhoea and abdominal pain).[10] Visual effects (blurred vision, colour disturbances, haloes and scotomas) are rarer in contemporary practice.[8] Cardiac arrhythmias account for most deaths.[9]

Arrhythmias can occur even if the patient has no symptoms. Almost any arrhythmia can occur, with the exception of atrial tachyarrhythmias with a rapid ventricular response,[8] because these usually require intact conduction in the atrioventricular node. Characteristic arrhythmias are those in which a tachyarrhythmia occurs simultaneously with sinus or atrioventricular node suppression, such as atrial and junctional tachycardia with atrioventricular block. However, sinus bradycardia, atrioventricular block and ventricular ectopy are more common.[12] With severe toxicity, ventricular tachycardia (which may be bidirectional) and ventricular fibrillation can occur. 'Reverse tick' T-wave inversion is not a sign of toxicity.

Treatment

There are no evidence-based guidelines for the management of mild to moderate toxicity so there is a wide variation in treatment.[13] Severe toxicity requires hospital admission and consideration of the need for digoxin-specific antibody fragments. Although digoxin-specific antibody fragments are safe and effective, randomised trials have not been performed.

The antibody fragments form complexes with the digoxin molecules. These complexes are then excreted in the urine.

Indications for digoxin-specific antibody fragments

The indications for digoxin-specific antibody fragments are inconsistent. Four contemporary sources[1,9,14,15] recommend administration for strongly suspected or known digoxin toxicity with:

- life-threatening arrhythmia
- cardiac arrest
- potassium >5.0 mmol/L (significant hyperkalaemia is a strong indication for treatment because of its association with a poor prognosis if digoxin-specific antibody fragments are not given[16]).

However, the same sources vary in their recommendations for administration when there is:

- acute ingestion of >10 mg in adults or >4 mg in children
- evidence of end-organ dysfunction
- moderate to severe gastrointestinal symptoms
- serum digoxin concentration >12 nanogram/mL
- significant clinical features of digoxin toxicity with serum digoxin concentration >1.6 nanogram/mL.

Such disagreements over when to use digoxin-specific antibody fragments arise from cost–benefit, not harm–benefit, considerations. The cost is roughly $1000 per ampoule and several ampoules may be used. However, economic arguments have been made for their use in non-life-threatening toxicity, as the duration of hospitalisation may be reduced.[17]

Dose and administration

Only one formulation is available in Australia. Each ampoule contains 40 mg of powdered digoxin-specific antibody and is reconstituted with 4 mL of water. This can be given as a slow push in cardiac arrest, but otherwise the total dose is diluted further with normal saline and infused over 30 minutes.

The response begins about 20 minutes (range 0–60 min) after administration. A complete response occurs in 90 minutes (range 30–360 min).[14]

Conventional dosing protocols aim to neutralise total body digoxin completely. The total dose is usually expressed in vials. It depends on whether the post-distribution serum digoxin concentration is known, the amount ingested is known, or neither is known.[15]

Known digoxin concentration

If the post-distribution concentration is known (in either acute or chronic ingestion), knowing the amount ingested is unnecessary. The dose is:

> number of vials = post-distribution serum digoxin concentration (nanogram/mL) x weight (kg)/100 (multiply by 0.78 if SI units are used for post-distribution serum digoxin concentration).

Known amount ingested

If the quantity of digoxin ingested is known, but the post-distribution serum digoxin concentration is unknown, the dose is:

> number of vials = amount ingested (mg) x 2 x 0.7 (0.7 is the bioavailability of digoxin tablets supplied in Australia).

Unknown data

When neither the post-distribution serum digoxin concentration nor the amount ingested is known, use empiric dosing. Repeat in 30 minutes if the response is inadequate. The dose is:

> for adults and children greater than 20 kg
>
> - five vials if haemodynamically stable
> - 10 vials if unstable
>
> for children less than 20 kg
>
> - one vial.

Other regimens

Some authors have argued for modification of the calculated doses to be given as an initial half dose followed by either further doses as required[18] or an infusion.[19] These suggestions follow from the view that full dosing is unnecessary to achieve tolerable

concentrations of digoxin and may be undesirable in patients who need digoxin.[18,20] There are also concerns that significant amounts of digoxin-specific antibody fragments may be eliminated before full removal of digoxin from tissue stores.[19] Furthermore, in practice many hospitals will not stock sufficient ampoules for the full calculated dose. In this case specialist toxicological advice should be sought on the adequacy of modified dosing.

Precautions and adverse effects

Hypomagnesaemia and, more importantly, hypokalaemia (common with diuretic use) should be corrected before or during administration because digoxin-specific antibody fragments will further lower potassium.[14] Hypokalaemia occurs as a result of treatment in about 4% of patients.[21] Serum potassium should be frequently monitored.[14]

'Rebound' toxicity[14] is the reappearance of toxicity after an initial response to digoxin-specific antibody fragments. This occurs in about 2% of patients given a full neutralising dose.[21] It can develop 12–24 hours after treatment, but up to 10 days later in patients with renal failure.[14] Serum digoxin concentration is of no use in diagnosis, because it measures the digoxin in the complexes with antibody fragments as well as unbound digoxin. The concentration therefore rises many fold after digoxin-specific antibody fragments are given even in the absence of rebound toxicity.[22]

Heart failure or atrial fibrillation with rapid ventricular response (presumed re-emergent due to removal of digoxin effect) occurs in up to 3% of patients.[14] Allergic reactions occur in about 1% of infusions.[21]

Other treatments

Other treatments for severe toxicity should be seen as temporising or adjunct measures, rather than alternatives to digoxin-specific antibody fragments. Activated charcoal[23] can be used in patients who present within two hours of acute ingestion.

Hyperkalaemia will improve with giving digoxin-specific antibody fragments, and conventional treatments such as calcium will generally be unnecessary or harmful.[15] If the patient has severe hypokalaemia and digoxin toxicity, it is important to correct the serum potassium.

Lignocaine[8] can be used for ventricular tachyarrhythmias and atropine[15] for bradyarrhythmias. Cardioversion, which can result in ventricular fibrillation, should be avoided.

In cardiac arrest, resuscitation efforts should be continued for at least 30 minutes after giving digoxin-specific antibody fragments.

Restarting digoxin

When considering restarting digoxin, first determine whether the patient's indication for use and target serum digoxin concentration were consistent with current guidelines, as these have changed markedly over the past couple of decades. Digoxin can be resumed after adjusting the dose for changes in target serum digoxin concentration, renal function and weight if necessary. This should be delayed until all the digoxin-specific antibody fragments have been cleared, which will take up to a week, but far longer in the presence of renal dysfunction.[18,22]

Conclusion

Digoxin toxicity has declined, possibly as a result of a decreasing use and a reduced recommended therapeutic range. It can occur when serum digoxin concentration is within the therapeutic range and, as the presenting features are usually non-specific, the diagnosis can be difficult.

Digoxin-specific antibody fragments are used when there is a risk of a life-threatening arrhythmia. The decision to use digoxin-specific antibody fragments is not dependent on knowledge of the serum digoxin concentration or the amount of digoxin ingested, but when either of these is known they should be used to calculate the dose. Further research is needed into optimal dosing protocols and whether digoxin-specific antibody fragments can be cost-effectively used for non-life-threatening toxicity.

Dr Pincus has been an investigator in trials sponsored by Bristol-Myers Squibb, GlaxoSmithKline, AstraZeneca, Sanofi, Servier, Amgen and Janssen. He received financial assistance for conference attendance from Eli Lilly, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb and Pfizer. Digoxin and the only available digoxin-specific Fab (DigiFab) are not supplied by these companies.

Q:

SELF-TEST QUESTIONS

True or false?

5. Digoxin toxicity can occur when the serum digoxin concentration is within the reference range.

6. Concentrations of serum digoxin should be measured within six hours of a dose.

Answers on page 27

REFERENCES

The full list of references is available online at http://dx.doi.org/10.18773/austprescr.2016.006

ARTICLE

Prescribing for patients on dialysis

SUMMARY

The pharmacokinetics of a drug may be altered in patients with renal impairment who require dialysis. Some drugs are contraindicated.

The drug's clearance and therapeutic index determine if a dose adjustment is needed. A lower dose or less frequent dosing may be required.

Consult a reference source or the patient's nephrologist before prescribing. Start at a low dose and increase gradually. If possible give once-daily drugs after dialysis.

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Key words
haemodialysis, kidney, pharmacokinetics, renal disease

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Introduction

The prevalence of kidney disease is rising and there are now over 11 400 Australians receiving dialysis.[1] These patients may rely on their GPs for much of their medical care. Prescribing for patients who are on dialysis can be challenging, however a few basic principles and the use of easily available reference materials (Box) can ensure that these patients are managed safely. A study in the USA found up to one-third of haemodialysis patients are prescribed a drug at a dose that differs from the recommended dose and adverse reactions occur in one-fifth.[2] Polypharmacy, multiple comorbid illnesses and drug clearance by dialysis all complicate prescribing.[3]

Dialysis

Dialysis is the transfer of uraemic solutes from blood to an extracorporeal fluid (dialysate) by diffusion across a semi-permeable membrane. This may be done by pumping blood through a dialyser containing a membrane and dialysate (haemodialysis), or by instilling dialysate into the peritoneal cavity and using the peritoneum itself as a membrane (peritoneal dialysis). Solute removal via haemodialysis is relatively efficient and so can be done intermittently – typically three times per week – whereas peritoneal dialysis is less efficient and so is usually required for 12–24 hours every day.

Principles of prescribing

Renal impairment reduces the clearance of some drugs.[4] When prescribing for patients on dialysis, it is essential to consult a reference guide (Box) to determine if the drug is subject to renal clearance and requires a dose adjustment. Given the paucity of large pharmacokinetic studies, dosing recommendations often differ and it may be difficult to favour one source over another. If no 'dialysis' dose is available, one should assume that the patient's glomerular filtration rate is less than 10 mL/min/1.73m^2. Although many patients have some residual renal function, their serum creatinine may fluctuate markedly and it should not be used to estimate glomerular filtration rate.

Dose adjustments can be made by reducing the dose, increasing the interval between doses or a combination of the two. The approach to take is determined by the relative importance of stable serum drug concentrations (for instance to maintain the antimicrobial effect of penicillins), the adverse effects of peak concentrations after intermittent doses, and patient convenience.

Multiple practitioners often share the care of patients on dialysis (e.g. GPs, specialist physicians, vascular surgeons and dialysis nurses). Information about the adjusted dosing regimen should be included in correspondence and, where appropriate, explain why the dose has been adjusted, to avoid confusion.

Pharmacokinetics

The two main considerations that determine if a particular drug requires dose reduction in dialysis patients are renal clearance and therapeutic index. Other factors that may affect dosing include clearance by dialysis, increased availability of highly protein-bound drugs due to hypoalbuminaemia,[5] altered volume of distribution and the presence of comorbid hepatic dysfunction.

Box **Suggested resources for drug dosing in dialysis**

Australian Medicines Handbook (https://amhonline.amh.net.au)

Therapeutic Guidelines: Antibiotic. Version 15 (www.tg.org.au)

MIMS Australia (http://mims.com.au)

Bailie and Mason's 2014 Dialysis of Drugs (http://renalpharmacyconsultants.com/publications)

Oxford Handbook of Dialysis. 3rd ed. Oxford: Oxford University Press; 2009.

The Renal Drug Handbook. 4th ed. London: Radcliffe Publishing; 2014.

Clearance

Consider the magnitude of the renal component of total clearance of the drug and any active metabolites. For drugs subject to significant renal clearance, the marked decrease in glomerular filtration rate seen in patients on dialysis results in an increase in half-life[6] and drug accumulation with repeated dosing in the absence of dose adjustment. These changes also apply to renally cleared drug metabolites which may be active or toxic.

The increased half-life also prolongs the time to achieve a steady-state which, in clinical practice, means a longer period is required before judging that the maximum effect of a particular dose has been achieved.[7] The starting dose should be low and caution is required before increasing drug doses. Given the longer time to steady state, a loading dose can be considered if giving a renally adjusted dose could lead to a delay in reaching a therapeutic serum concentration (for instance, if treating a severe infection). In practice, loading doses are rarely used.

Therapeutic index

A drug with a wide therapeutic index may be safely given without a dose reduction knowing that, although the drug concentration will be higher, this is unlikely to result in harm. However, drugs with narrow therapeutic indices may require substantial dose reductions.[7]

Dialysis and drug clearance

Patients on dialysis are subject to extracorporeal clearance of small molecules, including many drugs. The extent to which dialysis removes a particular drug from plasma is dependent on its water solubility, molecular weight, protein binding and volume of distribution.[3] Many reference sources contain lists of drugs cleared by dialysis (Box).

Haemodialysis can pose a challenge as it is intermittent and has the potential for relatively rapid drug clearance. In practice this is most important when prescribing once-daily drugs, especially antibiotics. It may be best to give them after dialysis. Dose timing is typically left unchanged for drugs dosed more frequently, as complex dosing regimens may reduce adherence to therapy. In peritoneal dialysis, timing is not important as the clearance of small molecules is slower and more even than in haemodialysis.[7]

Commonly prescribed drugs

Many drugs are not renally cleared. Specific examples of commonly used drugs include proton pump inhibitors, statins, corticosteroids and calcium channel blockers. They are unlikely to need a dose adjustment in patients on dialysis.

Analgesics

Patients on dialysis may have comorbid pain, but its treatment is often suboptimal.[8,9] Paracetamol is the preferred simple analgesic. It is safe and can be used without dose modification.[10]

Although nephrotoxicity might be considered of little importance, non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided as they may cause sodium retention, hypertension and gastrointestinal toxicity. Due to the increased risk of myocardial infarction seen in the general population, we do not recommend cyclo-oxygenase-2 inhibitors in dialysis patients as they are already at markedly higher baseline cardiovascular risk.[11,12] Topical NSAIDs appear to be safe as systemic absorption is minimal.[7]

Many opioids, or their active metabolites, are renally cleared (Table).[7,10,13,14] Codeine and morphine have active, renally excreted metabolites so they are not recommended because of the increased risk of toxicity. Hydromorphone is our preferred oral opioid for treating severe pain. It is five to seven times more potent than morphine so starting doses are correspondingly low (0.5–1 mg orally 6-hourly).[10] Its active metabolite hydromorphone-3-glucuronide can accumulate, but is substantially cleared by haemodialysis and is less likely to cause adverse effects than morphine metabolites.[15] Oxycodone may be used, although the sustained-release formulations should be used only with caution due to the risk of accumulation and toxicity. Fentanyl and buprenorphine both undergo hepatic clearance and can be used when the oral route is not suitable.[13] Whichever opioid is chosen, it is important to use small starting doses and closely monitor up-titration to avoid toxicity.

Neuropathic pain is common in patients on dialysis.[16] Amitriptyline is hepatically metabolised and does not accumulate. However, it has numerous adverse effects including anticholinergic effects and postural hypotension which may limit its use in patients with multiple comorbidities.[10] Gabapentin and pregabalin are effective and may also treat uraemic pruritis. However, they are extensively renally cleared and marked dose reductions are necessary to avoid sedation, ataxia and dizziness. Doses should be taken after dialysis.[10,17]

Opioid-induced constipation

In surveys, over half of the patients on dialysis report constipation.[9] Prevention of opioid-induced constipation is particularly important in patients on peritoneal dialysis as constipation may markedly reduce its effectiveness. Lactulose, docusate, senna and bisacodyl are all suitable treatments. Preparations containing polyethylene glycol (macrogol) are also generally safe as laxatives or bowel preparation. Patients should be advised that the co-administered

Table **Analgesic use in dialysis** [6,9-11]

Drug	Clearance	Suggested starting dose	Comments
Hydromorphone	Its major renally excreted metabolite hydromorphone-3-glucuronide is inactive	0.5–1 mg orally 4 times a day	Preferred oral opioid in dialysis patients
Oxycodone	Both oxycodone and its active metabolite oxymorphone are renally excreted	2.5–5 mg orally 3 times a day	Use controlled-release preparations with caution
Tramadol	Active renally excreted metabolite O-desmethyltramadol	50 mg orally twice a day	Maximum 100 mg twice a day Avoid controlled-release preparations
Buprenorphine	Hepatic metabolism with no accumulation of metabolites	5 microgram/hour transdermally	Not dialysed
Fentanyl	Hepatic metabolism with no active metabolites	12 microgram/hour transdermally	Not dialysed Use with caution in opioid-naïve patients
Gabapentin	Renal excretion	100 mg orally at night on dialysis days	Large dose reductions required Can treat uraemic pruritis and restless legs syndrome
Pregabalin	Renal excretion	25 mg orally at night on dialysis days	Large dose reductions required Can treat uraemic pruritis and restless legs syndrome
Morphine	Metabolised to renally excreted glucuronide metabolites (M-6-G and M-3-G) M-6-G is active and accumulates within the central nervous system, M-3-G lacks analgesic activity but may cause hyperalgesia and allodynia	2.5 mg orally 3 times a day	Avoid if possible Could be used for emergency analgesia if hydromorphone or fentanyl not immediately available
Codeine	Renally excreted active metabolites	–	Avoid
Dextro-propoxyphene	Cardiotoxic metabolite norpropoxyphene accumulates	–	Avoid
Paracetamol	Hepatic clearance	1 g orally 3–4 times a day	Preferred simple analgesic

fluid is not significantly absorbed and so does not count towards a fluid restriction. Saline laxatives (containing magnesium or phosphate salts) are contraindicated in patients on dialysis due to the possibility of severe electrolyte disturbances.[18] In particular, sodium phosphate-containing bowel preparations (Fleet) can cause severe hyperphosphataemia and calcium phosphate deposition.[19]

Antimicrobials

Many antibiotics require dose adjustment in patients receiving dialysis. Therapeutic Guidelines: Antibiotic provides a comprehensive and user-friendly reference.[20] Quinolones, sulfamethoxazole with trimethoprim, glycopeptides and aminoglycosides all require significant dose reductions. Trimethoprim should be avoided in patients due to the risk of hyperkalaemia and bone marrow suppression.[20,21] Nitrofurantoin is primarily renally excreted, and relies on urinary concentration to achieve its effect. It is rarely associated with neurotoxicity and life-threatening pulmonary toxicity.[22] Despite recent support for extending its use in chronic kidney disease, it should be avoided in patients on dialysis.[23] Cephalosporins and penicillins have wider therapeutic indices and vary in the need for dose adjustment.[7] Once-daily doses should be prescribed after haemodialysis.

The antiviral drug aciclovir and its prodrugs, famciclovir and valaciclovir, are extensively renally excreted. These drugs accumulate rapidly in patients on dialysis and may cause severe neurological toxicity.[24] They should only be prescribed after discussion with the treating nephrologist and with appropriate dose reduction and close clinical follow-up.

Anticoagulants

Despite controversy surrounding its use for stroke prevention in dialysis patients with atrial fibrillation, warfarin remains the anticoagulant of choice for those with venous thromboembolism or other indications for anticoagulation. The dose is adjusted according to the INR in the usual manner. Close monitoring and avoidance of supratherapeutic INRs is particularly

important as patients on dialysis have increased rates of bleeding with warfarin.[25] Low-molecular-weight heparins are renally excreted and they are rarely used for anticoagulation as their effect is difficult to predict.[7] Unfractionated heparin is preferred for acute treatment of venous thromboembolism in patients on dialysis.

The newer oral anticoagulants (such as dabigatran and rivaroxaban) are contraindicated. They all undergo a degree of renal clearance which makes them unsuitable for patients on dialysis.[26]

Drugs for diabetes

Patients with diabetes who need dialysis have reduced insulin clearance, so they may be more liable to hypoglycaemia with both insulin and insulin secretagogues (sulfonylureas). These patients may also be at increased risk of hypoglycaemia unawareness due to comorbid illnesses and co-prescribed drugs.[7]

Gliclazide and glipizide are the preferred sulfonylureas as they have short half-lives and no active metabolites. All sulfonylureas should be started at low doses and up-titrated carefully. The dipeptidyl peptidase-4 inhibitors vary in their suitability for use in dialysis so the product information should be reviewed before prescribing.[27] Metformin is contraindicated due to the risk of lactic acidosis. Although not renally excreted, thiazolidinediones are associated with fluid retention and are not recommended.[7] The sodium-glucose co-transporter inhibitors are contraindicated in dialysis patients as they depend on the glomerular filtration of glucose for their effect.[28]

Conclusion

Recognising that patients on dialysis are more prone to drug toxicity is the first step in avoiding harm. There are many easily accessible reference sources to guide dose adjustments in renal failure. Clinical judgement is always required to balance the required treatment intensity against the risk of toxicity in an individual patient. If in doubt, contact the treating nephrologist or renal unit pharmacist for advice. In general, commence with a low dose, observe closely for adverse effects and increase the dose only after a timely interval. Put simply: 'start low and go slow'.

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

7. Trimethoprim is not recommended in patients who require dialysis.

8. The usual dose of paracetamol should be reduced by half in patients receiving dialysis.

Answers on page 27

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New drugs

Lurasidone

Aust Prescr 2016;39:25–6
http://dx.doi.org/10.18773/austprescr.2016.001
First published online 6 November 2015

Approved indication: schizophrenia

Latuda (Dainippon Sumitomo Pharma)
20 mg, 40 mg and 80 mg tablets
Australian Medicines Handbook section 18.2

There are over 15 antipsychotics approved for schizophrenia in Australia. Lurasidone is the most recent addition to this drug class. As with other antipsychotics, lurasidone blocks dopaminergic transmission in the brain via the dopamine D_2 receptor. It also antagonises serotonin $5HT_7$ and $5HT_{2A}$ receptors and is a partial agonist of $5HT_{1A}$. Lurasidone does not appear to affect muscarinic and histamine receptors.

The efficacy of lurasidone for acute schizophrenia has been assessed in several short-term, placebo-controlled trials.[1-5] After six weeks of treatment, once-daily doses of 40 mg, 80 mg, 120 mg and 160 mg significantly lowered signs and symptoms of schizophrenia, measured on psychiatric rating scales (see Table).[1-5] However, efficacy was not consistently shown for each dose and a dose–response relationship was not evident in the trials. For example, in a study of lurasidone 40 mg, 80 mg and 120 mg, only the 80 mg dose had a statistically significant effect over placebo.[4] Discontinuation rates were very high in some of the trials (28–65%).[1-5] Lack of efficacy and withdrawal of consent were the most common reasons for stopping treatment.

One of the placebo-controlled trials[1] was extended to assess the long-term efficacy of lurasidone (40–160 mg/day) compared to quetiapine (200–800 mg/day) in 292 people.[6] Flexible dosing was allowed. At 12 months, the estimated probability of relapse was 23.7% in people receiving lurasidone compared with 33.6% in those receiving quetiapine. Discontinuation rates were high (48% for lurasidone, 61% for quetiapine).[6]

Another longer term comparative study enrolled patients with stable schizophrenia. After 12 months, 20% of people (82/410) receiving lurasidone had relapsed compared with 16% (32/198) receiving risperidone.[7]

Table **Efficacy of lurasidone in acute schizophrenia in short-term, placebo-controlled trials**

Trial	Number of patients	Daily treatments	Outcome‡ after 6 weeks of treatment
Loebel[1]	488	lurasidone 80, 160 mg placebo (quetiapine 600 mg) §	lurasidone 80 mg and 160 mg (p<0.001) and quetiapine (p<0.001) significantly better than placebo on PANSS
Meltzer[2]	478	lurasidone 40, 120 mg placebo (olanzapine 15 mg) §	lurasidone 40 mg (p<0.001) and 120 mg (p=0.011) and olanzapine (p<0.001) significantly better than placebo on PANSS
Nakamura[3]	180	lurasidone 80 mg placebo	lurasidone 80 mg significantly better than placebo on BPRSd (p=0.012)
Nasrallah[4]	500	lurasidone 40, 80, 120 mg placebo	only lurasidone 80 mg significantly better than placebo on PANSS (p<0.05)
Ogasa[5]	149	lurasidone 40, 120 mg placebo	lurasidone 40 mg (p=0.018) and 120 mg (p=0.004) significantly better than placebo on BPRSd

PANSS Positive and Negative Syndrome Scale
BPRSd Brief Psychiatric Rating Scale derived from PANSS scale
‡ Mean change from baseline score on schizophrenia rating scale
§ Olanzapine and quetiapine were included as active reference treatments which were compared to placebo but not to lurasidone.

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, 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. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

The most common adverse events in the short-term trials were somnolence (17% of patients), extrapyramidal symptoms (14%), akathisia (13%), insomnia (10%) and nausea (10%). Tachycardia, blurred vision, abdominal pain, diarrhoea, decreased appetite, rash, pruritus, hypertension and elevated creatine kinase also occurred in 1–10% of people. Prolactin elevations were more frequent with lurasidone than with placebo (2.8% vs 1%). QT prolongation did not seem to be a problem in the trials.

In the six-week trials, weight gain was modest with lurasidone compared with placebo (mean change of 0.43 kg vs –0.02 kg). In the longer term comparative studies, people taking lurasidone were less likely to have gained weight than those taking quetiapine[6] and risperidone.[7]

As with other antipsychotics, lurasidone can cause neuroleptic malignant syndrome, tardive dyskinesia and orthostatic hypotension. It should be used with care in patients at risk of hypotension or seizures. Lurasidone should not be used in elderly patients with dementia-related psychosis because of an increased risk of death with antipsychotics.

Lurasidone should be started at 40 mg once daily, taken with food. In the trials no additional benefit was seen with the 120 mg dose. The recommended starting dose in moderate to severe renal impairment is 20 mg. Lurasidone should not be used in people with severe hepatic impairment and the recommended starting dose is 20 mg in those with moderate impairment.

Peak concentrations are reached 1–3 hours after taking an oral dose and steady-state concentrations are reached within seven days. The drug's elimination half-life is 18 hours and most of the dose is excreted in the faeces.

Concomitant use of strong cytochrome P450 (CYP) 3A4 inhibitors (ketoconazole, clarithromycin, ritonavir) and inducers (rifampicin, St John's wort, phenytoin) is contraindicated as lurasidone is metabolised by CYP3A4. The lurasidone dose should be halved in people taking moderate inhibitors (diltiazem). Patients should avoid grapefruit juice as it may increase lurasidone exposure.

Lurasidone is a category B1 drug in pregnancy. In animal studies, no fetal toxicities were observed. However, exposure during the third trimester in pregnant women increased the risk of extrapyramidal and withdrawal symptoms in newborns. Some babies had to be managed in the intensive care unit.

Breastfeeding is not recommended with lurasidone as it has been found to be excreted in the milk of lactating rats.

In general, lurasidone was better than placebo in patients with acute schizophrenia. However, efficacy was not consistent at all doses and a dose–response relationship could not be shown. It is unclear how lurasidone will compare to other drugs in the class.

Transparency score not allocated

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The Transparency score (T) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

* 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).

Correction

Drugs in breastfeeding

Aust Prescr 2015;38:156-9

Iodine has been deleted from the Summary and the Table as it is not contraindicated during breastfeeding.

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A:

ANSWERS TO SELF-TEST QUESTIONS

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

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