

Alternatives to cisapride

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SYNOPSIS

Cisapride has the potential to cause arrhythmias, particularly in susceptible patients, at higher doses and when combined with drugs or foods that inhibit its metabolism. Meta-analyses suggest that the efficacy of cisapride may have been overestimated in the past. Many currently available medications have equivalent or greater efficacy than cisapride for indications such as gastro-oesophageal reflux disease, functional dyspepsia, oesophageal dysmotility and constipation. The alternatives include acid suppressing drugs, domperidone, metoclopramide and laxatives. Several drugs currently under development, especially the new 5HT₄ agonists and GABA-B agonists, may also be of value. Cisapride still has a limited role in gastroparesis.

Index words: dyspepsia, gastroparesis, gastro-oesophageal reflux disease.

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Introduction

The recognition that cisapride may be associated with cardiotoxicity has led to a significant re-evaluation of its role in the therapy of gastrointestinal motility disorders. In addition, several recent meta-analyses have identified flaws in the literature concerning cisapride, suggesting that the benefits of cisapride may have been overestimated by publication bias.¹ The concerns about toxicity have resulted in some countries withdrawing cisapride altogether, whereas in others it has been restricted to specific indications or prescribing groups. In Australia, the Therapeutic Goods Administration now only approves cisapride for a few indications and the product information carries a boxed warning about the risk of arrhythmia. The listing of cisapride on the Pharmaceutical Benefits Scheme (PBS) is even more restricted. Cisapride is only available, with an authority prescription, for the treatment of gastroparesis diagnosed by a consultant physician.

Pharmacology

Cisapride is a prokinetic agent with actions throughout the gastrointestinal tract. It acts as an agonist at muscarinic (M₂) and some serotonergic (5HT₄) receptors, and as an antagonist at other serotonergic (5HT₃) receptors. Cisapride increases smooth muscle tone, strength and possibly the co-ordination

of contractions. This results in improved transit of gastrointestinal contents. Cisapride has therefore been widely used in disorders due, or believed to be due, to disordered gastrointestinal motility.

Toxicity

The cardiac toxicity of cisapride is attributed to its inhibition of potassium channels in the myocardium. This concentration-dependent effect leads to prolongation of the QT interval which increases the risk of torsade de pointes and sudden death. Toxicity is seen in all age groups, and is enhanced by higher doses, individual susceptibility due to disease or genetic factors, co-administration of drugs inhibiting the metabolism of cisapride via cytochrome P450 3A4 (e.g. macrolides, azole antifungals, grapefruit juice)², or other drugs which prolong the QT interval (e.g. quinidine, sotalol).

By early 2001, the Australian Adverse Drug Reactions Advisory Committee had received 58 reports of cardiac adverse events in both adults and children. These included 24 arrhythmias (one fatal) in which cisapride was the sole suspected drug.

Alternatives to cisapride

There are a number of currently available drugs which are alternatives to cisapride (Table 1), and several new drugs are under investigation.

Metoclopramide is a dopamine (D₂) antagonist, an agonist at 5HT₄ receptors and an antagonist at 5HT₃ receptors. Its peripheral effects improve gastric emptying, and its central effects on dopamine receptors are antiemetic. The central effects are also responsible for most of the therapy-limiting adverse effects including drowsiness and dystonic reactions.

Domperidone is a peripherally acting dopamine (D₂) antagonist with antiemetic effects. These are mediated through the chemoreceptor trigger zone which is situated in the area postrema, outside the blood-brain barrier. Domperidone does not cross the blood-brain barrier, and hence does not have the same range of central effects as metoclopramide, but it may still cause galactorrhoea. A difficulty with prescribing domperidone is the PBS restriction of 25 tablets with no repeats available on a standard prescription.

Two new serotonin (5HT₄) agonists – tegaserod, a partial agonist, and prucalopride, a full agonist – have recently been developed. Although they were developed for the treatment of

disorders of colonic motility, these drugs may have actions throughout the gastrointestinal tract. (At present clinical trials with prucalopride have been suspended.)

Erythromycin is the prototype drug of the motilides. These drugs act as agonists at the motilin receptors in the stomach and small intestine. In patients with diabetic gastroparesis, the administration of erythromycin results in an improvement in gastric emptying. However, this may be associated with unwanted gastrointestinal symptoms and other adverse effects. Other motilides have been developed, but have not been adequately evaluated and are not available commercially.

Gastroparesis

Gastroparesis is the sole remaining indication for prescribing cisapride on the Australian PBS. This reflects the relative lack of effective alternative treatments.

Diabetes mellitus and idiopathic gastroparesis account for the majority of cases. If simple dietary modification with small, frequent, low fat meals is unsuccessful, prokinetic drugs can be considered. There are few comparative trials of prokinetics in gastroparesis, and the trials that do exist are of relatively poor quality. The endpoints of the majority of trials assessed acceleration in gastric emptying alone, and few have assessed improvement in symptoms and/or quality of life scores.

A recent systematic analysis found that erythromycin appears to accelerate gastric emptying more than other prokinetic drugs (44% improvement in gastric emptying time compared to domperidone 28%, cisapride 27% and metoclopramide 21%). In terms of improving the symptoms of gastroparesis in this systematic analysis, erythromycin, domperidone, metoclopramide and cisapride (in descending order of apparent efficacy) were all found to be of value.³ However, their clinical usefulness is limited by their modest efficacy, poor tolerability and toxicity.

Any patient prescribed cisapride should have an ECG to check for pre-existing QT prolongation, and at least one ECG while on therapy. The use of cisapride in patients with diabetic gastroparesis requires consideration of specific problems. Diabetic autonomic neuropathy may be associated with prolongation of the QT interval, and care must be taken to ensure that patients do not become hypokalaemic (for example because of hypoglycaemia or vomiting) as this could predispose to ventricular arrhythmias. Patients with diabetic nephropathy and renal impairment have a reduced clearance of cisapride, and will require lower doses.

If any of the motilides become available they may play an important role in the management of gastroparesis. Although the newer 5HT₄ agonists (tegaserod and prucalopride) will not initially be marketed for treatment of upper gastrointestinal motility disorders they may have beneficial effects on the upper gastrointestinal tract. The efficacy of tegaserod in the treatment of diabetic gastroparesis will be examined in clinical trials in the near future.

Two small uncontrolled trials have suggested that there is some benefit from injecting botulinum toxin into the pyloric

sphincter in idiopathic and diabetic gastroparesis. Controlled studies are required before this treatment can be recommended.

If drug therapies are unsuccessful, gastric electrical stimulation (a therapy which is commercially available, but still undergoing clinical evaluation) or alternative methods of feeding such as a surgically or endoscopically placed jejunostomy may be required.

Gastro-oesophageal reflux disease

Cisapride is effective in the treatment of mild gastro-oesophageal reflux disease because of its effects on oesophageal motility. However, its potential risks, lack of PBS listing and the availability of acid suppressing drugs mean that cisapride is unlikely to have a significant role in future. Most cases of gastro-oesophageal reflux disease can be managed adequately with lifestyle changes and acid suppression, using H₂ receptor antagonists or proton pump inhibitors, according to severity.

Cisapride has sometimes been used in reflux disease as an adjunct when the clinical response to acid suppression is inadequate. If inadequate suppression of gastric acidity is the problem (demonstrated for example by measuring ambulatory pH), increasing acid suppression (by either dose escalation or changing to an alternative drug) is likely to be more effective than cisapride. Continuing regurgitation of non-acid gastric contents will not be improved by further acid suppression and, although this has not been examined formally, it is arguable whether cisapride has any role to play in this group of patients. Surgery is likely to be their best option.

There is a sub-group of patients with symptoms of reflux that respond to cisapride. Their symptoms recur when it is ceased and cannot be adequately controlled using other medications. In this group, continued therapy with cisapride is reasonable, provided low doses are used, with appropriate care and patient education. An ECG should be recorded during treatment with cisapride to check for QT prolongation. This treatment is outside the PBS authority prescribing restrictions unless the patient also has concurrent gastroparesis (delayed gastric emptying is common in patients with gastro-oesophageal reflux disease).

Table 1
Alternatives to cisapride

<i>Indication</i>	<i>Current alternatives</i>
<i>Adult</i>	
Gastroparesis	Erythromycin Metoclopramide Domperidone
Gastro-oesophageal reflux disease	Acid suppression with H ₂ receptor antagonist or proton pump inhibitor
Functional dyspepsia/gas/bloat	Acid suppression Domperidone Metoclopramide <i>H. pylori</i> eradication (limited value)
<i>Paediatric</i>	
Gastro-oesophageal reflux disease	Acid suppression

Another class of drugs, GABA-B agonists (prototype drug baclofen), is under investigation for the treatment of reflux disease. These drugs reduce the number of transient lower oesophageal sphincter relaxations (the major mechanism of gastro-oesophageal reflux) in healthy subjects, and trials are being conducted in patients with reflux disease. The use of baclofen itself is not appropriate for reflux disease because of its adverse effects. Efforts are under way to develop new GABA-B agonists with a more favourable adverse effect profile.

Functional dyspepsia

The use of cisapride in functional dyspepsia or for non-specific upper gastrointestinal symptoms is difficult to justify because of its potential toxicity, even though the absolute risks are low if appropriate care is taken. Alternative drugs such as domperidone, metoclopramide or acid suppressing drugs (especially in reflux-type functional dyspepsia) should be used if simple dietary advice is ineffective and more serious disorders have been excluded. In patients infected with *Helicobacter pylori*, eradication therapy can be tried, but is unlikely to be of benefit in the majority of patients with functional dyspepsia.⁴

Patients with upper gastrointestinal symptoms (e.g. gas/bloating) which are currently controlled on cisapride, and which recur on cessation of cisapride, should probably be re-evaluated for the presence of gastroparesis.

Oesophageal motility disorders

Cisapride has been used to treat disordered oesophageal motility, after disorders such as achalasia have been excluded by oesophageal manometry. Given the lack of convincing evidence of clinical benefit, this use of cisapride is now difficult to justify. The new 5HT₄ agonists may have a role to play, but this requires considerable further research.

Paediatric conditions

In children cisapride has been most widely used for gastro-oesophageal reflux disease. However, clinical trials have failed to show that cisapride has a clinical benefit.^{5,6} Some children's hospitals have introduced significant

restrictions on the prescription of cisapride, including the requirement for neonatology and/or gastroenterology review, and for ECGs to monitor the QT interval.

Simple alternatives such as thickening of feeds and posturing have usually been tried and proven ineffective by the time a drug is required, and acid suppression may be an alternative in this situation.

REFERENCES

1. Soo S, Moayyedi P, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia (Cochrane Review). In: The Cochrane Library, 3, 2001. Oxford: Update Software.
2. Martin J, Fay M. Cytochrome P450 drug interactions: are they clinically relevant? *Aust Prescr* 2001;24:10-2.
3. Sturm A, Holtmann G, Goebell H, Gerken G. Prokinetics in patients with gastroparesis: a systematic analysis. *Digestion* 1999;60:422-7.
4. Talley NJ, Lam SK, Goh KL, Fock KM. Management guidelines for uninvestigated and functional dyspepsia in the Asia-Pacific region: First Asian Pacific working party on functional dyspepsia. *J Gastroenterol Hepatol* 1998;13:335-53.
5. Cohen RC, O'Loughlin EV, Davidson GP, Moore DJ, Lawrence DM. Cisapride in the control of symptoms in infants with gastroesophageal reflux: A randomized, double-blind, placebo-controlled trial. *J Pediatr* 1999;134:287-92.
6. Gilbert RE, Augood C, MacLennan S, Logan S. Cisapride treatment for gastro-oesophageal reflux in children: a systematic review of randomized controlled trials. *J Paediatr Child Health* 2000;36:524-9.

Dr Hebbard has been sponsored to attend scientific meetings by Novartis (tegaserod) and AstraZeneca (omeprazole, esomeprazole). He is a member of an expert advisory team on esomeprazole and has met with Pharmacia regarding pantoprazole.

Professor Young and Ms Gailer: no conflict of interest declared.

Self-test questions

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

1. Erythromycin should not be prescribed for a patient who is taking cisapride.
2. Erythromycin may improve gastric emptying in patients with diabetic gastroparesis.

Anaphylaxis Wall Chart

Included in this issue is an updated version of the *Australian Prescriber* Wall Chart 'Medical management of severe anaphylactoid and anaphylactic reactions'. This version replaces the previous wall chart which was published in 1994, but which can be still found in many clinics and treatment rooms across Australia.

The new wall chart has been produced with the assistance of the postgraduate organisations which contributed to previous versions (the Australasian College for Emergency Medicine, the Australasian Society of Clinical Immunology and Allergy, the Australian and New Zealand College of Anaesthetists, the Royal Australasian College of

Physicians and the Royal Australian College of General Practitioners). In addition, the Executive Editorial Board of *Australian Prescriber* welcomes the contribution of the Royal Australian and New Zealand College of Radiologists.

The main change in the wall chart is an increase in the paediatric dose of adrenaline. Our consensus was that the first dose should be 10 microgram/kg. The doses for adults are unchanged.

The Executive Editorial Board believes that the wall chart will be useful in an emergency, but hopes that it does not have to be used too often.