Cleveland Clinic Center for Continuing Education

Cisapride Withdrawal Requires Alternative Therapy

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Introduction

Janssen Pharmaceutica, in consultation with the FDA, has decided to stop marketing the prokinetic agent cisapride (Propulsid®) on July 14, 2000 due to the risk of serious cardiac arrhythmias and death associated with this agent. It is well recognized that cisapride can prolong the QT interval and lead to a lethal arrhythmia (torsade de pointes), especially when administered to patients at high risk for such an arrhythmia. High risk patients include those with underlying QT prolongation (e.g., congenital or drug-induced) and those with electrolyte disturbances.

Availability

Cisapride will be available only by an investigational limited access program for patients meeting strict inclusion criteria. Only certified physicians will be able to enroll patients into such protocols. Adult patients eligible for the program include those receiving cisapride for the management of gastroesophageal reflux disease (GERD), gastroparesis, intestinal pseudo-obstruction, or severe chronic constipation. Other protocols exist for pediatric patients and neonates.

Alternative Agents

The withdrawal of cisapride leaves medical professionals with the task of prescribing a ppropriate alternative therapy for patients. Treatment must be individualized to each patient's condition. Agents other than prokinetic agents (e.g., proton pump inhibitors) may be appropriate in certain situations. **Table 1** summarizes alternative prokinetic agents.

Table 1: Alternative Prokinetic Agents

Drug and Usual Adult Dose	Mechanism of Action	Adverse Effects	Comments
Metoclopramide (Reglan®) 10 mg IV or PO QID, before meals & at bedtime	• Dopamine receptor antagonist & cholinergic stimulant • Stimulates motility of upper GI tract • Increases gastric contractions • Increases gastric emptying and intestinal transit time • Enhances LES pressure • Blocks stimulation of CTZ	EPS Depression Anxiety Drowsiness Galactorrhea Amenorrhea Gynecomastia	• Crosses the BBB, increasing risk of CNS side effects. • Higher risk of side effects in elderly due to reduced drug clearance. • Primarily renally eliminated; adjust dose in renal insufficiency (if CrCl < 50 ml/min, recommend half of usual dose). • May exacerbate Parkinson's disease symptoms and diminish effectiveness of dopamine agonists such as levodopa.
Bethanechol (Urecholine®) 25 mg PO QID	• Cholinergic agent • Stimulants GI smooth muscle contraction • Does not improve peristalsis • Does not enhance GI transit	Abdominal cramps Diarrhea Urinary frequency Nausea Vomiting Headache Hypertension Blurred vision	• Motor stimulant rather than prokinetic agent. • Use is limited by side effects. • May be added to metoclopramide (when side effects limit metoclopramide dose).
Erythromycin **Ethylsuccinate:** 250 mg PO TID, before meals **Lactobionate:** 200 mg IV TID, before meals	• Mimics the effects of motilin on GI smooth muscle • Stimulates gastric emtying • May enhance esophageal contractions • May increase LES pressure	Nausea GI upset	• Clinically ineffective for GERD. • Used for treatment of diabetic gastroparesis. • Monitor for drug interactions. • May increase risk of antibiotic resistance development. • Only macrolide currently used for its prokinetic properties.

BBB Blood brain barrier; CrCl Creatinine clearances; CNS Central nervous system; CTZ Chemo-receptor trigger zone; EPS Extrapyramidal symptoms; GERD Gastroesophageal reflux disease; GI Gastrointestinal; LES Lower esophageal sphincter

Effectiveness of Alternative Agents

Of the alternative prokinetic agents, metoclopramide is used most often due to its proven efficacy. However, metoclopramide must be used with caution in patients with decreased renal function, including the elderly, because of increased central nervous system side effects. The use of bethanechol is limited by cholinergic side effects. Erythromycin has been used for diabetic gastroparesis, but it is not clinically effective in the management of GERD. While the intravenous preparation of domperidone was withdrawn from the market due to reports of adverse cardiovascular effects, oral domperidone (not available in the United States) may be a future option based on efficacy data and safety profile.

Conclusion

When choosing an agent to replace cisapride, therapy must be patient specific. Health care professionals must weigh risks (e.g., side effects, drug interactions) versus benefits when initiating alternative therapy.

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