JOEL E. RICHTER, MD*
Chairman, Department of Gastroenterology,
Cleveland Clinic

Cisapride: Limited access and alternatives

ABSTRACT

The withdrawal of cisapride from the market will present challenges for physicians treating patients with nocturnal heartburn, gastroparesis, and dyspepsia. However, alternatives to the drug exist, and it will continue to be available under a limited-access program for patients for whom other drug treatments fail.

CISAPRIDE (Propulsid), used by millions of patients worldwide, is being withdrawn from the market by its manufacturer Janssen Pharmaceutica, because of cases of toxicity leading to arrhythmia and death.[1] However, cisapride will continue to be available under a limited-access program for patients for whom alternative medications have failed.[2] Alternatives to cisapride exist, but the drug will be missed, especially for the treatment of patients with gastroparesis and dyspepsia.

HOW CISAPRIDE WORKS

Cisapride is a prokinetic drug that stimulates the release of acetylcholine, thereby increasing lower esophageal sphincter pressure and improving motility of the upper digestive tract including the esophagus, stomach, and proximal small bowel.[3] The US Food and Drug Administration (FDA) approved it for treating nocturnal heartburn caused by gastroesophageal reflux disease (GERD). It was also used to treat gastroparesis, chronic intestinal pseudo-obstruction, and dyspepsia. Since its approval in 1993, it has been used by millions of patients with good clinical efficacy and few adverse side effects, primarily diarrhea and headaches.

*The author discusses off-label use of medications.

DECREASED METABOLISM LEADS TO ARRHYTHMIAS

Cisapride is metabolized by the cytochrome P450 3A4 enzyme.[4] Decreased metabolism and resulting high cisapride blood levels can cause serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. From July 1993 through May 1999, more than 341 cases of cisapride-associated arrhythmias were spontaneously reported to the FDA, including 80 deaths.[1] In approximately 85% of these cases, the events occurred when cisapride was used in patients with known risk factors.

Risk factors for cisapride toxicity include:

- A history of prolonged QT intervals on electrocardiography or known family history of congenital long QT syndrome
- A history of serious cardiac disease, respiratory failure, or renal failure
- Conditions that predispose to severe dehydration, vomiting, or malnutrition with electrolyte imbalance
- Potential drug interactions.

Drugs that can increase blood levels of cisapride include a number of commonly used medications, such as:

- Macrolide antibiotics (eg, clarithromycin, erythromycin)
- Certain antifungals (eg, fluconazole, itraconazole, ketoconazole)
- Protease inhibitors (indinavir, ritonavir)
- Class I and class III antiarrhythmics (eg, quinidine, procainamide, sotalol)
- Phenothiazines (eg, chlorpromazine)
- Certain tricyclic antidepressants (eg, amitriptyline)
- Other antidepressants (eg, nefazodone, maprotiline)
- Other agents such as bepridil, sparfloxacin, and grapefruit juice.[5]

Comment. The recent adverse events

Cisapride is effective, but can cause fatal arrhythmias

with cisapride are not totally surprising to me. Interestingly, seizures and possibly cardiac arrhythmias were noted during experimental studies with an intravenous preparation of cisapride in the late 1980s, precluding this form of drug development. On the other hand, I have used cisapride in oral and liquid preparation in research and clinical patients since 1988 without any known cardiac side effects.

HOW THE LIMITED-ACCESS PROGRAM WILL WORK

Over the past few years, Janssen has implemented labeling changes and sponsored educational programs to help ensure the safe and appropriate use of cisapride. However, the level of adverse event reporting and risk associated with the drug did not sufficiently decrease.

Consequently, Janssen decided to stop marketing the drug and make it available only through an investigational limited-access program. Janssen will market cisapride until July 14, 2000, and the product will remain available through pharmacies until mid-August 2000.

On May 1, 2000, enrollment began in the Janssen investigational limited-access program for patients who require cisapride when all other therapies have failed. All patients must be under the care of a gastroenterologist by consultation if the prescribing physician is not a gastroenterologist. Institutional review board approval, signed informed consent, baseline and serial laboratory tests, and electrocardiograms will be required.

For more information on the program or to enroll patients, physicians can call Janssen's hotline at 877-795-4247.

For more information on the limited-access program, call 877-795-4247

ALTERNATIVES TO CISAPRIDE

The loss of cisapride will certainly affect the treatment of many of our patients.

Gastroesophageal reflux disease

Most cases of GERD can easily be controlled with H_2 blockers or proton pump inhibitors.

Gastroparesis and dyspepsia

I will miss cisapride most in the treatment of my patients with gastroparesis and dyspepsia. Alternative drugs include metoclopramide, erythromycin, and domperidone.

Metoclopramide unfortunately has unpredictable effectiveness in many of these disorders and has a poor side-effect profile, with 10% to 30% of patients developing anxiety, restlessness, depression, headaches, and (rarely) tardive dyskinesia.[6] The recommended dosage is 10 to 20 mg three times a day before meals.

Erythromycin may be a better alternative, although it is not FDA-approved for this indication.[7] It needs to be given in low doses three times a day before meals for its best prokinetic effects.[8] Some suggest starting doses as low as 50 mg, while others recommend 125 to 250 mg.

Domperidone is similar to metoclopramide but with a better side-effect profile because it does not cross the blood-brain barrier.[9] It is not available in the United States but can be obtained in Canada. The dose is similar to that of cisapride: 10 mg to 20 mg three times a day before meals.

ADDRESS: *Joel E. Richter, MD, Department of Gastroenterology, S40, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail richtej@ccf.org.*

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See "Diabetic gastropathy: A practical approach to a vexing problem" in the August issue