Contraindicated Use of Cisapride
Impact of Food and Drug Administration Regulatory Action

Walter Smalley, MD, MPH
Deborah Shatin, PhD
Diane K. Wysowski, PhD
Jerry Gurwitz, MD
Susan E. Andrade, DSc
Michael Goodman, PhD
K. Arnold Chan, MD, DSc
Richard Platt, MD, MS
Stephanie D. Schech, MPH
Wayne A. Ray, PhD

Context Cisapride, a gastrointestinal tract promotility agent, can cause life-threatening cardiac arrhythmias in patients susceptible either because of concurrent use of medications that interfere with cisapride metabolism or prolong the QT interval or because of the presence of other diseases that predispose to such arrhythmias. In June 1998, the US Food and Drug Administration (FDA) determined that use of cisapride was contraindicated in such patients and informed practitioners through additions to the boxed warning in the label and a “Dear Health Care Professional” letter sent by the drug’s manufacturer.

Objective To evaluate the impact of the FDA’s 1998 regulatory action regarding contraindicated use of cisapride.

Design and Setting Analysis of data for the 1-year periods before (July 1997-June 1998) and after (July 1998-June 1999) the regulatory action from the population-based, pharmacoepidemiology research databases of 2 managed care organizations (sites A and B) and a state Medicaid program (site C).

Participants Patients with at least 180 days of prior enrollment in 1 of the 3 sites who were prescribed cisapride at least once in the period before (n=24840) or after (n=22459) regulatory action. Patients could be included in both cohorts.

Main Outcome Measures Proportion of cisapride users in each period for whom cisapride use was contraindicated by the product label, based on computerized patient medical encounter records.

Results In the year prior to regulatory action, cisapride use was contraindicated for 26%, 30%, and 60% of users in study sites A, B, and C, respectively. In the year after regulatory action, use was contraindicated for 24%, 28%, and 58% of users, a reduction in contraindicated use of approximately 2 per 100 cisapride users at each site. When the analysis was restricted to new users of cisapride after regulatory action, only minor reductions in contraindicated use were found.

Conclusion The FDA’s 1998 regulatory action regarding cisapride use had no material effect on contraindicated cisapride use. More effective ways to communicate new information about drug safety are needed.

Author Affiliations: Departments of Medicine and Preventive Medicine, Vanderbilt University School of Medicine and Geriatric Research, Education and Clinical Center, and VA Medical Center, Nashville, Tenn (Drs Smalley and Ray); Center for Health Care Policy and Evaluation, UnitedHealth Group, Minnetonka, Minn (Dr Shatin and Ms Schech); Office of Postmarketing Drug Risk Assessment, Food and Drug Administration, Rockville, Md (Dr Wysowski); Fallon Healthcare System and Meyers Primary Care Institute, University of Massachusetts Medical School, Worcester (Dr Gurwitz); College of Pharmacy, University of Rhode Island, Kingston (Dr Andrade); HealthPartners Research Foundation, Bloomington, Minn (Dr Goodman); Channing Laboratory, Brigham and Women’s Hospital (Drs Chan and Platt), Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care (Dr Platt), and Harvard Medical School, (Drs Chan and Platt) Boston, Mass. Corresponding Author and Reprints: Wayne A. Ray, PhD, Department of Preventive Medicine, Medical Center North, A-1124, Vanderbilt University Medical Center, Nashville, TN 37232.
cisapride prolonged the QT interval in healthy volunteers,\(^7\) which suggested a mechanism underlying the reported cases of torsade de pointes.\(^5\) Further cases of serious arrhythmias were reported.\(^4,6\) The FDA thus expanded the black-box warning in June 1998 to note that cisapride use also was contraindicated in patients taking medications that could prolong the QT interval or in patients with baseline heart disease or other conditions that could predispose to cardiac arrhythmias. The FDA also drew attention to this change through circulation of a press release and the manufacturer of cisapride distributed a Dear Health Care Professional letter informing practitioners of the revised label.\(^7\) This letter was distributed to 800,000 health care professionals in the United States including physicians (both primary care and specialists), pharmacists (retail and hospital), and vendors of drug-alert databases, such as Medispan and First Data Bank.

However, the effect of the 1998 and previous FDA regulatory actions is unknown. This study was conducted to quantify the prevalence of contraindicated use of cisapride before and after the June 1998 warning, using data from 3 large populations with computerized records of medical encounters.

**METHODS**

**Study Periods**

The amended cisapride labeling and Dear Health Care Professional letter were dated June 26, 1998. Thus, the study periods included the years before (July 1997-June 1998) and after (July 1998-June 1999) this regulatory action.

**Study Sites**

The study was conducted at 3 pharmacoepidemiology research sites, each of which included a defined population enrolled in a health plan for which there are automated records of medical care encounters, including prescriptions dispensed, hospital admissions, and outpatient visits.\(^6,8\) Each of the 3 study sites conducts postmarketing surveillance studies in collaboration with the FDA, but this activity is not linked to clinical practice or guidelines at any of the sites. The 3 sites included a large managed care organization (site A) with geographically dispersed health plans (primarily independent practice associations); a consortium (site B) of 3 health maintenance organizations (2 on the Eastern seaboard and 1 in the Midwest) that included independent practice associations and staff and group practice models; and a state Medicaid program (site C). During the study period, there were no changes in membership or coverage in any of the 3 sites that were material to this study.

**Study Data**

Each of the sites used computerized plan files to provide study data. Enrollment files identified persons who qualified for the study and provided demographic information. Pharmacy files identified prescription drug use and included information on the date a drug was dispensed and the prescribed days of supply. The latter defined medication use days, or those days on which a medication was likely to be taken. Inpatient and outpatient files were used to identify previous encounters for medical conditions identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)\(^9\) or Current Procedural Terminology, Fourth Edition (CPT-4)\(^10\) codes. Confidentiality was preserved because the files used for the study analysis did not have linkable individual identifiers. The study was approved by each site’s committee for the protection of human subjects.

**Study Cohorts**

The cohorts for the primary analysis consisted of persons who had at least 1 prescription for cisapride dispensed during either year and, prior to the dispensing of the first such prescription, had at least 180 days of continuous enrollment (required to identify contraindicated medical conditions). Two cisapride cohorts thus were identified, 1 for each of the years before and after the regulatory intervention. A person was included in both cohorts if cisapride was dispensed in both years and enrollment criteria were met. In a secondary analysis, we identified the patients in each cohort with a new episode of cisapride use, as these patients should provide a better test of the effect of the regulatory intervention. New use was defined as dispensing of a cisapride prescription with no cisapride use in the preceding 180 days; if in a given year there was more than 1 episode of new use, only the first was included in the study.

**Contraindicated Cisapride Use: Medications and Conditions**

Cisapride use was defined as contraindicated if there was at least 1 day that dispensed prescriptions indicated was both a day of cisapride use and a concurrent day of use for a medication listed in the label as contraindicated. These were drugs that interfere with P450-3A4 metabolism (clarithromycin, erythromycin, troleandomycin, nefazodone hydrochloride, fluconazole, itraconazole, ketoconazole, indinavir, ritonavir) or those that can prolong QT intervals (class IA or III antiarrhythmics, cyclic antidepressants, and antipsychotics). Use was also defined as contraindicated if either an inpatient or outpatient encounter record indicated a medical condition listed as contraindicated in the cisapride label in the 180 days preceding dispensing of any cisapride prescription in that year. The listed conditions were ventricular arrhythmia, heart failure, other ischemic heart disease, electrolyte disorders, renal failure, or respiratory failure. If the use days of a cisapride prescription encompassed both study years, we classified all days for the prescription according to the year in which it was dispensed. Detailed lists of medications and other study codes are available on request.

**Analysis**

For each of the study years, we calculated the proportion of cisapride users for whom such use was contraindicated according to the revised label. We calculated the difference between the proportions for the before and after
CONTRAINDICATED USE OF CISAPRIDE

RESULTS

During the study period, the 3 study sites included approximately 6.8 million insured lives. During the year preceding the regulatory intervention, there were 24,840 qualifying cisapride users at sites A (n = 13,613), B (n = 6,848), and C (n = 4,379) (Table). The proportions of cisapride users that were female were 60%, 61%, and 68%, respectively. The respective proportions for ages 0 to 2 years were 12%, 13%, and 8% and the respective proportions for age 60 years and older were 14%, 23%, and 45%. In the year following the regulatory intervention, there were 22,459 qualifying cisapride users, reflecting a slight drop in numbers from each of the sites. There were only minor changes in the demographic characteristics of cisapride users in the postintervention year.

In each of the sites in the year before the regulatory intervention, the proportion of cisapride users whose use was contraindicated because of concomitant medication was high, with respective proportions of 14% (1,946/13,613), 19% (1,280/6,848), and 34% (1,481/4,379) for sites A, B, and C (Table). The most common contraindicated medications were amitriptyline, erythromycin, and clarithromycin. Similarly, the proportion of users with use contraindicated because of concomitant conditions was also high, with respective proportions of 15% (2,029/13,613), 15% (1,047/6,848), and 41% (1,809/4,379) for sites A, B, and C, respectively. The most common conditions were heart failure and other ischemic heart disease. In the year before the regulatory action, the proportions of cisapride users with use contraindicated because of either a concomitant medication or condition were 26% (3,506/13,613), 30% (2,025/6,848), and 60% (2,614/4,379), respectively, for the 3 study sites.

There was little change in contraindicated use of cisapride in the year after the FDA regulatory action (Table). During this year, the proportions of study cisapride users with use contraindicated because of either a concomitant medication or condition were 24% (2,963/12,418), 28% (1,598/5,812), and 58% (2,432/4,229), respectively, for sites A, B, and C; a reduction in contraindicated use of approximately 2 patients per 100 cisapride users at each site.

We conducted a separate analysis of patients with a new episode of cisapride use because they had the greatest likelihood of benefitting from the regulatory intervention (Figure). At each of the 3 sites, there were only minor reductions in the proportions of new users of cisapride for whom such use was contraindicated.

COMMENT

The findings of this population-based study show that a substantial proportion of patients dispensed cisapride at each of the study sites also had concurrent medications or concomitant medical conditions thought to increase the risk of potentially lethal cardiac arrhythmias in these patients. There was no material reduction in such use at any of the study sites following FDA regulatory action, which included a black-box warning in the cisapride label indicating such use was contraindicated and a Dear Health Care Professional letter. Thus, despite this and previous modifications to the cisapride label, in the year ending in June 1999, cisapride use was contraindicated for between 24% and 58% of patients dispensed this drug. Even the group most likely to be affected by the regulatory action—patients begin-

Table. Contraindicated Use of Cisapride in the Years Before and After FDA Regulatory Action*

<table>
<thead>
<tr>
<th>Site</th>
<th>Contraindicated use</th>
<th>Before Regulation</th>
<th>After Regulation</th>
<th>Absolute Reduction in Users, % (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site A (3.2m)</td>
<td>Contraindicated drug</td>
<td>1946 (14.3%)</td>
<td>1567 (12.6%)</td>
<td>1.7 (0.7 to 2.7)</td>
</tr>
<tr>
<td></td>
<td>Contraindicated condition</td>
<td>2029 (14.9%)</td>
<td>1743 (14.6%)</td>
<td>0.9 (−0.1 to 1.9)</td>
</tr>
<tr>
<td></td>
<td>Either</td>
<td>3506 (28.5%)</td>
<td>2963 (23.9%)</td>
<td>1.9 (0.6 to 3.2)</td>
</tr>
<tr>
<td>Site B (2.2m)</td>
<td>Contraindicated drug</td>
<td>1280 (18.7%)</td>
<td>969 (16.7%)</td>
<td>2.0 (0.3 to 3.7)</td>
</tr>
<tr>
<td></td>
<td>Contraindicated condition</td>
<td>1047 (15.3%)</td>
<td>840 (15.5%)</td>
<td>−0.2 (−1.8 to 1.4)</td>
</tr>
<tr>
<td></td>
<td>Either</td>
<td>2025 (29.6%)</td>
<td>1598 (27.5%)</td>
<td>2.1 (0.0 to 4.2)</td>
</tr>
<tr>
<td>Site C (1.4m)</td>
<td>Contraindicated drug</td>
<td>1481 (33.8%)</td>
<td>1421 (33.6%)</td>
<td>0.2 (−2.8 to 3.2)</td>
</tr>
<tr>
<td></td>
<td>Contraindicated condition</td>
<td>1809 (41.3%)</td>
<td>1641 (38.8%)</td>
<td>2.5 (−0.6 to 5.6)</td>
</tr>
<tr>
<td></td>
<td>Either</td>
<td>2614 (59.7%)</td>
<td>2432 (57.5%)</td>
<td>2.2 (−0.9 to 5.3)</td>
</tr>
</tbody>
</table>

*FDA indicates Food and Drug Administration.
n a new episode of cisapride use—had no material change in contraindicated use.

Some of the variation among the 3 sites with regard to absolute proportion of cisapride use that was contraindicated is probably explained by differences in the populations served at each site. The study included a Medicaid population, known to overrepresent patients of advanced age and with chronic illnesses. This population thus was likely to include more persons with medication use or chronic illnesses that would contraindicate cisapride use. Conversely, the study included plans with employment-based insurance, in which the prevalence of contraindications to cisapride use may be lower. Despite these baseline differences, data from the 3 sites were consistent in that the proportion of cisapride use that was contraindicated was high in absolute terms and did not change materially following the regulatory intervention.

In March 2000, prior to when an FDA advisory committee was scheduled to review cisapride’s benefits and risks for the approved indication, the manufacturer terminated marketing of cisapride in the United States effective as of July 2000. Thus, the public health problem of contraindicated use of cisapride has been resolved in the United States, although cisapride continues to be marketed in other countries. However, 4 years prior to this action, case reports received by the FDA and published in the scientific literature had identified the vulnerability of cisapride users taking contraindicated drugs or having contraindicated conditions to also be at an increased risk of serious arrhythmias. During this period, millions of patients received cisapride; our data suggest these would have included hundreds of thousands in whom such use was deemed contraindicated as of June 1998. Our data also indicate that in the 12 months following this regulatory action, hundreds of thousands of patients in whom cisapride use was contraindicated were likely to have received this drug. The exposure of these patients to inappropriate cisapride use, despite the prominent publication of case reports, label changes, and Dear Health Care Professional letters, highlights the need to develop more effective methods for modifying practice to reflect new information about a drug’s risks and benefits.

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REFERENCES