Coprescribing and Codispensing of Cisapride and Contraindicated Drugs

Judith K. Jones, MD, PhD
Daniel Fife, MD
Suellen Curkendall, PhD
Earl Goehring, Jr, BA
Jeff Jianfei Guo, PhD
Marjorie Shannon, MS

USE OF CONTRAINDICATED drug combinations can result in serious adverse reactions. Cisapride, an oral prokinetic agent indicated for the symptomatic treatment of nocturnal heartburn due to gastroesophageal reflux disease,7 was approved for use in the United States in July 1993 and voluntarily removed from the market in July 2000 after more than 270 serious cardiac arrhythmias, including 70 fatalities, were reported among patients in the United States.3-5 Most case reports indicated that cisapride was taken concurrently with one or more drugs with which it interacts. Four label changes and physician notifications (“dear doctor” letters) were issued in February 1995, October 1995, June 1998, and June 1999 (1999 is outside of our study period).

Traditionally, physician notification letters and drug label changes are designed for and sent to physicians to alert them to potential problems with a drug, although the information is also provided to pharmacies. The letters often include a list of drugs that, taken concomitantly, could predispose the patient to an adverse reaction. Label changes have not been entirely successful and makers of health policy continue to search for more effective methods of preventing inappropriate drug use.6-9 Since a previous study of cisapride prescribing indicated that there was little change in prescribing cisapride to patients with medical or drug contraindications after the June 1998 label change,10 we studied the extent of coprescribing by the same physicians and codispensing by the same pharmacies.

METHODS

Protocare Sciences’ managed care claims database contains private health care claims and enrollment data representing health care services provided to approximately 3 million members of several preferred provider organizations and health maintenance organizations. The database covers a wide geographic area, with members residing predominantly in 22 states. Medical claims and patient

Context Cisapride, an oral prokinetic drug indicated for the symptomatic treatment of nocturnal heartburn due to gastroesophageal reflux disease, was approved by the US Food and Drug Administration in July 1993. After reports of serious cardiac arrhythmias and deaths during administration of cisapride, most involving concomitant exposure to another drug, a series of label changes and warnings were issued in February 1995, October 1995, June 1998, and June 1999. Cisapride was removed from general distribution in July 2000.

Objective To determine the frequency of contraindicated coprescribing and codispensing, in which cisapride and a contraindicated drug were prescribed or dispensed to the same patient for overlapping periods, and the proportion of contraindicated coprescribing by the same physicians and codispensing by the same pharmacies.

Design and Setting Retrospective study of prescription claims from a managed care organization database for all patients with cisapride prescriptions between July 1993 and December 1998.

Participants A total of 38,757 adult and pediatric patients who had a cisapride prescription immediately preceded by at least 60 days of insurance eligibility.

Main Outcome Measure Proportion of cisapride prescriptions or dispensing occurring during the same treatment period as a drug contraindicated at that time prescribed by the same physicians or dispensed by the same pharmacies.

Results Of 131,485 cisapride prescriptions dispensed after the warnings began, 4,414 (3.4%) overlapped with at least 1 drug contraindicated in the labeling at the time of the prescription. Of all overlapping prescription pairs, 2,190 (50%) were by the same physicians, 3,908 (89%) were by the same pharmacies, and 765 (17%) were dispensed on the same day.

Conclusion Prescriptions dispensed by the same pharmacies accounted for a far higher proportion of contraindicated medication pairs than prescriptions from the same physicians. The pharmacy may be an important and underutilized intervention point to prevent contraindicated drugs from being used together.

©2001 American Medical Association. All rights reserved.
eligibility data are linked with a unique, encrypted patient identification number (ID). During the period that a patient is eligible for drug benefits coverage, the database contains all outpatient prescription claims filed with the insurer, regardless of where the prescription is filled. Each prescription claim record includes the patient ID, the dispensing date, a national drug code (NDC), and an encrypted Drug Enforcement Administration (DEA) number identifying a unique physician. An encrypted provider ID that identifies a unique pharmacy was also provided by the data source for the subset of 10491 study prescriptions that were overlapping contraindicated prescriptions. This provider ID represents an individual pharmacy location, regardless of whether the pharmacy belongs to a chain.

All claims for patients taking cisapride between July 1993 and December 1998 were collected (49485 patients). Patients with unknown insurance eligibility, age, or sex, or with incomplete pharmacy claims, were excluded (6754 patients). Patients younger than 15 years with prescriptions for the tablet (vs liquid) form of cisapride were excluded because days of drug supply estimates are unreliable in this population (2023 patients). Patients without at least 1 cisapride prescription immediately preceded by 60 days of insurance eligibility were excluded (1951 patients). The final study population was 38757 patients.

Prescriptions for cisapride and contraindicated drugs were identified and the number of cisapride prescriptions that were overlapped with a contraindicated drug was computed. Refills were counted as separate prescriptions. A drug was only counted as contraindicated beginning in the month that the physician notification letter was sent to inform professionals that the cisapride label was changed to include that drug. The overlap of cisapride and a contraindicated drug was defined to exist when cisapride and the contraindicated drug were dispensed either on the same day or on overlapping therapy days. If a single prescription for a contraindicated drug overlapped during more than 1 cisapride prescription, each overlapping prescription was counted as a separate overlap.

Beginning in February 1995, the month of the first warning, we examined the proportion of the overlapping contraindicated prescriptions prescribed by the same physician and the proportion dispensed by the same pharmacy.

**RESULTS**

Sixty-one percent of the study population were women, 3% were younger...
than 15 years (received the liquid form), 17% were aged 15-39 years, 41% aged 40-64 years, and 39% 65 years or older.

There were 141,119 cisapride prescriptions dispensed during the study period. Of these, 131,485 were dispensed from February 1995 through December 1998, after the warnings began, and 4414 (3.4%) overlapped with at least 1 contraindicated drug. The proportion overlapped was 1.9% in 1995, 4.3% in 1996, 3.5% in 1997, and 3.2% in 1998. The overlaps involved 2657 patients, 3301 physicians, and 1715 pharmacies. Of the patients, 1716 (65%) were women, 58 (2%) were younger than 15 years old, 376 (14%) were aged 15-39 years, 1339 (50%) were aged 40-64 years, and 881 (33%) were 65 years or older.

The most frequent overlapping contraindicated drugs were clarithromycin (43% of all overlapping prescriptions), erythromycin (26%), and fluconazole (22%). The average days of supply were 26 for cisapride, 10 for clarithromycin, 10 for erythromycin, 9 for fluconazole, 18 for ketoconazole, 19 for itraconazole, 29 for nefazodone, 30 for troleandomycin, 21 for indinavir, and 27 for ritonavir. Thus, concurrent use was reported with clarithromycin, erythromycin, and fluconazole.

The average days of supply for the same patient were 5 days, and 1134 (3% of all overlapping prescriptions) were from the same pharmacy each month. In nearly every month, more than 85% of the contraindicated medications were dispensed by the same pharmacy that had dispensed the same prescription for cisapride.

Throughout the study period, most patients with overlapping contraindicated dispensations had obtained both drugs from the same pharmacy. This suggests that a pharmacy-based intervention to prevent co-prescribing of contraindicated medication pairs could be accomplished without involving complicated communications among different pharmacies.

Because the present study was based on dispensings, we were unable to determine how many contraindicated medication pairs were successfully identified by pharmacists and not dispensed or how often the pharmacists called physicians to question the prescriptions. We also could not determine how often pharmacists dispensed overlapping prescriptions for cisapride and a contraindicated medication but instructed the patient to discontinue one of the medications while taking the other. Other evidence suggests that while most pharmacists have computer-based warning systems, these systems do not consistently prevent the dispensing of contraindicated drugs. Possible reasons for such inconsistent prevention include label design that embeds contraindications in a large volume of other material, warning systems that do not present current information in a rationally prioritized layout, and pharmacists’ concerns about questioning the prescribing physician’s decision.

The 3% of cisapride prescriptions that overlapped with contraindicated medications represent a substantial and preventable risk to patients. If pharmacists and physicians had better methods to use the information available to them, they might be able to reduce this risk for other contraindicated drug combinations. We found that 89% of the contraindicated co-prescriptions were associated with the same pharmacies that also dispensed the prescriptions for cisapride, vs 50% that occurred when the same physician wrote both prescriptions. This suggests that the pharmacist, who is focused solely on the therapy, more often has the opportunity to apply critical information necessary to prevent contraindicated codispensing.

Author Contributions: Dr Curkendall, as principal investigator of the study herein, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Study concept and design: Jones, Guo, Fife, Curkendall. Analysis and interpretation of data: Jones, Guo, Curkendall, Goehring, Shannon. Drafting of the manuscript: Fife, Curkendall, Guo. Critical revision of the manuscript for important intellectual content: Jones, Guo, Fife, Curkendall, Goehring, Shannon. Statistical expertise: Curkendall, Goehring, Guo. Obtained funding: Jones, Curkendall. Administrative, technical, or material support: Guo, Fife, Curkendall, Goehring, Shannon. Study supervision: Jones, Curkendall.

Funding/Support: The Janssen Pharmaceutical Research Foundation provided financial support to The Degge Group for data analysis. Dr Fife, a Janssen Pharmaceutical employee, participated in the study design and reviewed the manuscript. The Degge Group leased the prescription data for patients with cisapride prescriptions from Protocare Sciences. The Degge Group coauthors analyzed the data, interpreted the results, and drafted the manuscript.

Acknowledgment: We thank Dewei She, MS, Amishi Gandhi, MPH, and Ann Marie Rezelman, BA, for programming and editing assistance, and to Amy Solis, BS, and Ben Sotelo of Protocare Sciences for providing the data.

REFERENCES

©2001 American Medical Association. All rights reserved.