

Impact of a Web-Based Clinical Information System on Cisapride Drug Interactions and Patient Safety

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Background: Most commercially available drug-interaction screening systems have important limitations that fail to protect patients from dangerous drug combinations. We attempted to overcome the limitations of our commercial program by developing a Web-based clinical information system to serve as a safety net. This system identifies drug interactions with newly marketed medications not screened by our commercial program, and generates a second alert on dangerous interactions that were overridden during order processing.

Methods: The Web-based system uses patient-specific pharmacy, laboratory, and demographic data to generate detailed alerts on patients receiving potentially dangerous drug combinations. The system's impact on the use of dangerous drug combinations and related adverse events was evaluated by a retrospective analysis of patients receiving cisapride with contraindicated medications in the 2 years before and after implementation.

Results: The rate of dangerous drug combinations declined by 66% after implementing the system, from 9.0% of cisapride orders in 1994 and 1995 to 3.1% in 1996 and 1997 ($P < .001$). The mean [SD] duration of contraindicated therapy (4.1 [3.8] vs 1.6 [1.4] days, $P < .001$) and proportion of patients being discharged under treatment with a dangerous drug combination (36.2% vs 7.7%, $P < .001$) was also significantly reduced during the study period. Three patients (1.7%) during the control period experienced serious adverse events that may have been related to the targeted drug interactions. No symptomatic cardiac events were identified during the study period ($P = .21$).

Conclusions: An automated system running as a safety net can be an efficient method of detecting contraindicated drug combinations and serves an important role in the avoidance of potentially serious adverse drug events.

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THE ENORMOUS number of medications available today makes it difficult for clinicians to remember all clinically significant drug interactions. Computerized drug-interaction checking systems are capable of detecting a large number of interactions, but even these systems may not prevent patients from receiving potentially harmful drug combinations.¹⁻⁹ If these programs are not updated in a timely manner, newly discovered drug interactions or interactions with recently marketed medications may go unrecognized. This has become an increasingly important limitation, as illustrated by the growing list of agents contraindicated with cisapride and the market withdrawals of astemizole, mibefradil dihydrochloride, and terfenadine.¹⁰⁻¹⁴

Unfortunately, patients may not be protected from potentially fatal drug combinations even after these computerized systems are updated. Approximately 30% of pharmacies with a computerized drug-

interaction screening system dispensed simultaneously presented prescriptions for terfenadine and erythromycin despite the fact that ventricular arrhythmias had been described with this combination 5 years earlier.^{6,15} The most likely explanation for these performance lapses was the computerized systems' low specificity for detecting clinically meaningful interactions.¹ This is a well-described limitation of other alert-generating systems, and drug-interaction screening tools are no exception.^{1,16} In their attempt to be all-inclusive, these systems may generate so many alerts of questionable significance that busy users begin to disregard all alerts—including those with potentially fatal outcomes.

Since we could not customize our commercial drug-interaction package, we developed a Web-based clinical information system that overcomes these limitations. This system identifies drug interactions with newly marketed medications not screened by our commercial system, and generates a second alert on dangerous in-

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METHODS

DESCRIPTION OF THE SYSTEM

The Pharmacy Adverse Drug Event (PharmADE) monitoring system was developed for the pharmacy department at Barnes-Jewish Hospital by the Medical Informatics Laboratory at Washington University, St Louis, Mo. While it is designed to identify other preventable adverse drug events (eg, drug-induced hepatotoxic effects, ketorolac tromethamine orders exceeding 5 days' duration, use of metformin hydrochloride in patients with congestive heart failure), the system's primary function is to detect potentially dangerous drug combinations that were not prevented by our commercial drug-interaction package.

The commercial package consists of an integration between our pharmacy software application (Medication Control System; Productive Data Management Inc, Los Angeles, Calif) and a drug knowledge base (National Drug Data File; First DataBank Inc, San Bruno, Calif). This package generates electronic drug interaction warnings to pharmacists during the medication order entry process. Unfortunately, it alerts on many clinically insignificant interactions, allows pharmacists to easily override any of its warnings (including those considered contraindicated by the Food and Drug Administration), does not generate a second notice on potentially severe drug interactions that have been overridden, and cannot be modified by the end user to include newer drug interactions.

The PharmADE system was developed to serve as a safety net for our commercial drug interaction package. Pharmacy, laboratory, and patient demographic data are transferred from the hospital's mainframe computer to a UNIX system that houses an SQL-compliant database. All pharmacy orders are then electronically screened for contraindicated drug combinations. When a potentially dangerous combination is identified, an alert report is automatically sent via facsimile to the pharmacy area responsible for the patient. The system is capable of generating alerts

within minutes of an order being entered into the pharmacy computer system; however, it functioned in batch mode during the study period, providing a daily list of alerts for patients who started treatment with contraindicated drug combinations within the prior 24 hours.

Once an alert is generated, a pharmacist evaluates the appropriateness of the alert and contacts the patient's physician with a recommendation to stop treatment with one of the medications. A Web-based graphical user interface is also available that allows pharmacists to view alerts interactively and enter patient-specific outcomes from any desktop computer on the hospital intranet. A secure HyperText Transfer Protocol (http) server with a Secure Sockets Layer (SSL) and server authentication provides access to the alert data, which are stored in a clinical database. Access to the Web pages containing sensitive patient information also requires entry of a password.

Because the Web-based system has access to additional clinical data, it is able to generate more detailed alerts than commercial drug interaction packages. The PharmADE alert reports contain patient demographic data, the dosage and start date of the treatment with the interacting medications, pertinent laboratory or drug data, an educational comment with a recommendation for alternative therapy, and a customized outcome section that includes expected adverse events and treatment options for the detected interaction (**Figure 1**). Examples of pertinent laboratory or drug data that are printed on the alert reports include (1) risk factors for the development of adverse events (eg, hypokalemia, hypomagnesemia, or concomitant medications associated with QT_c prolongation in a patient with a cisapride interaction); (2) evidence that an adverse event may have occurred (eg, elevated creatine kinase values in a patient receiving the combination of mibefradil and lovastatin); (3) an order for a known antidote (eg, flumazenil in a patient with an alprazolam interaction); or (4) presence of other active medications that are known inhibitors of the object drug's metabolism but are not considered contraindicated in the manufacturer's labeling (eg,

interactions that were overridden during order processing. The impact of this safety net system was assessed by comparing the rate of cisapride drug interactions and related adverse events at our hospital before and after its implementation. This is also the first report to examine the outcomes of patients receiving cisapride with an azole antifungal agent, erythromycin, or clarithromycin.

RESULTS

The database query identified 286 patients who received cisapride with one of the targeted precipitant medications (189 during the control period and 97 during the study period). Of these, 265 medical records (93%) were available for the retrospective analysis of patient outcomes (174 [92%] and 91 [94%] in the control and study groups, respectively). The use of cisapride (127 [22%] vs 127 [12%] orders per month, $P = .94$) and the precipitant medications (375 [41%] vs 403 [56%] orders per month, $P = .15$) was similar in the 2 time periods.

The proportion of patients receiving cisapride with one of the contraindicated medications declined signifi-

cantly after the PharmADE system was implemented. Overall, the rate of dangerous drug combinations with cisapride was reduced by 66%, from 9.0% of cisapride orders in 1994 and 1995 to 3.1% in 1996 and 1997 (**Figure 2**; $P < .001$).

Fluconazole (41%), erythromycin (28%), and clarithromycin (27%) accounted for most of the interactions. These medications were prescribed on the same day as cisapride in 68 patients (36%) during the control period and 32 (33%) during the study period ($P = .62$). During the study period, the precipitant drug was almost always started after the order for cisapride had been entered in the pharmacy's computer system (86 patients [89%]). This may suggest that prospective alerting by our commercial drug interaction package is less effective (or receives less attention) when it alerts during the processing of an order for one of the precipitant drugs. A higher proportion of patients during the control period began treatment with cisapride after they were already receiving a precipitant drug (38% vs 11%; $P < .001$).

Prior to implementing PharmADE, there was no systematic mechanism in place to detect a dangerous drug combination after the medications had been dispensed.

diltiazem hydrochloride in a patient receiving the combination of nefazodone hydrochloride and triazolam).

DETECTABLE DRUG COMBINATIONS

Active drug orders are screened for approximately 130 dangerous drug interactions. Most drug combinations detected by the PharmADE system are considered contraindicated in manufacturers' labeling, and many have resulted in serious adverse events including cardiac arrhythmias, respiratory failure, hypertensive crises, rhabdomyolysis, acute renal failure, and death. The system is also capable of detecting potentially severe drug interactions between recently begun and recently discontinued drug regimens (eg, treatment with a selective serotonin reuptake inhibitor within 2 weeks of discontinuing treatment with a monoamine oxidase inhibitor).

STUDY OBJECTIVES

The primary objective of the study was to assess the rate of concomitant orders for contraindicated medications in the 2 years before and after implementing the Web-based system. The new system was implemented in January 1996 and detected 151 contraindicated drug combinations in the first 2 years of operation. Most (97%) of these potentially dangerous drug combinations were dispensed despite our commercial drug interaction package alerting on them during order entry. Since cisapride accounted for the greatest number of alerts ($n = 107$ [71%]), we limited our retrospective analysis to patients receiving this agent with an azole antifungal agent, erythromycin, or clarithromycin. In addition to being the most common offenders, these medications were considered to carry the greatest risk for patient harm and were available throughout the 4-year study period (other medications could not provide an adequate baseline period for comparison because they were marketed after 1994).

A retrospective database query was used to identify all patients who had received cisapride with one of the

precipitant medications between 1994 and 1997. Because our Web-based system was batch driven during the study period (ie, data transfers only occurred once daily), we limited the query to patients who received one of these combinations for longer than 24 hours. This should also have excluded those interactions that would have been addressed as a result of other checks that were in place, such as the commercial drug interaction system, physician monitoring, and nursing or pharmacy review. Additional study outcomes included the duration of overlapping drug therapy, the likelihood of being discharged under treatment with a dangerous drug combination, readmissions related to the targeted drug interactions, and the incidence of serious adverse events.

Serious adverse drug events were identified by retrospectively reviewing physicians' progress notes, nurses' notes, and electrocardiograms for all patients receiving the dangerous drug combinations between 1994 and 1997. Only symptomatic events that occurred while the patient was receiving both interacting medications were included; however, a cause-effect relationship still cannot be confirmed. Asymptomatic prolongation of the QT_c interval beyond 480 milliseconds was noted but not considered a serious adverse event owing to the retrospective nature of the review and because electrocardiograms were not available on all patients.

STATISTICAL ANALYSIS

A χ^2 test was used to compare the proportion of cisapride orders that overlapped with a precipitant medication, patients still receiving a dangerous drug combination at the time of discharge, readmissions, and adverse events possibly related to the targeted drug interactions. The duration of overlapping drug therapy, patient days, and orders for targeted medications were compared using the Wilcoxon rank sum test. Statistical calculations were performed with SAS for Windows, version 6.11 (SAS Institute Inc, Cary, NC).

Serious drug interactions are now identified within 24 hours, and the mean (SD) duration of overlapping orders with cisapride has declined from 4.1 (3.8) days in 1994 and 1995 to 1.6 (1.4) days in 1996 and 1997 ($P < .001$). The mean (SD) number of patient-days when a cisapride order overlapped with one of the precipitant medications decreased from 32.6 (18.2) to 6.3 (4.7) patient-days per month (**Figure 3**, $P < .001$). Perhaps most importantly, patients who received a potentially dangerous drug combination during the study period were less likely to be discharged from the hospital still receiving that combination (36.2% vs 7.7%; $P < .001$).

Adverse events possibly related to the targeted drug interactions were identified in 3 patients (1.7%) prior to implementing the PharmADE system. These included a patient who suffered anoxic brain injury after a cardiac arrest (torsades de pointes and ventricular fibrillation) on the third day of combined therapy, and 2 cases of sudden, unexpected death (on days 4 and 14 of combined therapy). In both cases of unexpected death, the patients were found unresponsive and pulseless by their nurses. While the actual cause of death is unknown, one

of these patients did have a prolonged QT_c interval (506 milliseconds) while receiving the combination of cisapride and erythromycin. Four additional patients during the control period were noted to have asymptomatic prolongation of the QT_c interval after a precipitant medication was added to cisapride therapy (the mean [SD] QT_c interval increased from 439 [11] to 512 [11] milliseconds). Another patient during the control period experienced an episode of torsades de pointes and ventricular fibrillation while receiving cisapride, but *after* treatment with the interacting medication had been discontinued.

No symptomatic cardiac events were identified during the study period ($P = .21$). One patient had asymptomatic QT_c prolongation (increased from 430 to 556 milliseconds) while receiving a dangerous drug combination, and another experienced a 7-beat run of asymptomatic ventricular tachycardia. This arrhythmia occurred 8 hours after the first dose of clarithromycin, spontaneously corrected without treatment, and was only detected because the patient was being monitored by telemetry at the time of the event. The patient also had a potassium level of 3.1 mmol/L. He received potassium

| Barnes-Jewish Hospital Contraindicated Drug Combination | | | | | |
|---------------------------------------------------------|-------------|------------------|-----------|----------------|------------|
| Patient Name | Age | Sex | Room | Discharge date | Alert date |
| Jane Doe | 77 | F | 6300 | | 07/22/1997 |
| Drug interaction | Dose | Start date | Stop date | | |
| Cisapride | 10 mg QID | 07/20/1997 09:00 | | | |
| Clarithromycin | 500 mg BID | 07/21/1997 21:00 | | | |
| Pertinent drug data | Dose | Start date | Stop date | | |
| Procainamide | 1000 mg BID | 07/21/1997 09:00 | | | |
| Pertinent lab data | Result | Collection date | | | |
| Potassium, plasma | 2.4 mEq/L | 0/21/1997 22:20 | | | |

Comment: Fatal cardiac arrhythmias have occurred in patients taking cisapride with other drugs that inhibit the cytochrome P450 3A4 enzyme. Cisapride is contraindicated in this patient. Metoclopramide may be considered if the patient requires a promotility agent.

Please enter outcomes for this alert

| | |
|------------------------------------------------------------------------|-------------------------------------------|
| Adverse events? (please check) | Treatment required? (please check) |
| <input type="checkbox"/> Patient was asymptomatic | <input type="checkbox"/> None |
| <input type="checkbox"/> Arrhythmia (please describe below) | <input type="checkbox"/> Cardioversion |
| <input type="checkbox"/> No arrhythmia, but QT _c > 480 msec | <input type="checkbox"/> Overdrive pacing |
| <input type="checkbox"/> Hypotension | <input type="checkbox"/> Magnesium |
| <input type="checkbox"/> Dizziness | <input type="checkbox"/> Lidocaine |
| <input type="checkbox"/> Other _____ | <input type="checkbox"/> Other _____ |

| | |
|---------------------------------------------------------------|--------------------------------------------------------------------|
| Pharmacist's assessment (please check) | Physician's assessment (please check) |
| Agree with intervention: | <input type="checkbox"/> Agree with pharmacist's recommendation |
| <input type="checkbox"/> Discontinue one or more drug orders | <input type="checkbox"/> Decision pending |
| Disagree with intervention: | <input type="checkbox"/> Disagree with pharmacist's recommendation |
| <input type="checkbox"/> Patient was already discharged | Reason _____ |
| <input type="checkbox"/> MD already changed drug order(s) | |
| <input type="checkbox"/> Other reason (please describe below) | |
| Reason _____ | |

| | |
|---------------------------------------------------------------|----------------------------|
| Outcomes attributed to adverse event | Physician contacted |
| <input type="checkbox"/> None | Name _____ |
| <input type="checkbox"/> Transfer to ICU | Date _____ |
| <input type="checkbox"/> Disability | Time _____ |
| <input type="checkbox"/> Hospitalization—initial or prolonged | |
| <input type="checkbox"/> Life threatening | |
| <input type="checkbox"/> Death | |

Figure 1. Representative alert generated by the Pharmacy Adverse Drug Event (PharmADE) monitoring system. QID indicates 4 times daily; BID, twice daily; and ICU, intensive care unit.

repletion, and the cisapride treatment was discontinued the next morning after the physician was notified about the drug interaction. The patient's QT_c interval was 443 milliseconds on the day prior to the event, but no subsequent electrocardiograms were available for comparison.

Two additional patients receiving long-term cisapride therapy had prolonged QT_c intervals (492 and 541 milliseconds) on admission during the study period. Despite this, they both received prescriptions for erythromycin while hospitalized. Fortunately, treatment with the medications was discontinued following the alert by PharmADE, and neither patient experienced an adverse drug event. These cases illustrate the importance of having a safety net system such as PharmADE.

Adverse events that may have occurred after a patient was discharged while being treated with a dangerous drug combination could not be assessed. No patient was readmitted to our hospital in either period as a result of the targeted drug interactions.

COMMENT

Although computerized drug-interaction checking systems are an efficient method for detecting drug interac-

tions, they may not protect patients from receiving even well-known potentially fatal drug combinations. In our institution, approximately 3% of patients receiving cisapride will also receive an azole antifungal agent, erythromycin, or clarithromycin despite the use of a computerized drug-interaction system that alerts on these combinations at the time of order entry. This rate of contraindicated drug use is similar to that observed in the community, and is likely the result of similar system failures (eg, faulty drug-interaction checking systems, inadequate drug knowledge, and performance lapses by medical personnel).⁹ Without a safety net function in place, these drug combinations might continue indefinitely or until an adverse event prompts the discontinuation of one of the medications.

Since adding a Web-based safety net function to our computerized drug-interaction screening system, we have observed a 66% reduction in the use of potentially dangerous drug combinations, a 61% reduction in the duration of overlapping drug orders, and a 79% reduction in the number of patients being discharged under treatment with a dangerous drug combination. In addition, we have not had any further patient injuries as a result of the targeted drug interactions. Despite heightened awareness of its risks, the amount of cisapride used at our institution has not changed.

Because our patients were hospitalized, we were able to assess several significant outcomes during the control period. It is important to note that most clinicians were unaware of cisapride's drug interactions in 1994 and 1995. This time frame was chosen because the principal drugs (eg, cisapride, clarithromycin, erythromycin, and fluconazole) were available and we could document the clinical course when these agents were used together. The risk for serious arrhythmias in patients receiving cisapride with an azole antifungal agent or macrolide antibiotic was first described in February 1995.¹⁷ Clarithromycin, erythromycin, and fluconazole were not specifically added as contraindications to the use of cisapride until October 1995.¹⁸ Nevertheless, a noticeable decline in the concomitant use of these agents did not occur until several months later, when PharmADE was implemented. The fact that cisapride still accounts for most of the PharmADE alerts more than 2 years later is disappointing, and further highlights the limitations of commercially available drug interaction screening systems.

Since our data were gathered retrospectively, we cannot confirm that the reduced rate of contraindicated drug use was due solely to the addition of our safety net system. These drug interactions were added to our front-end screening system in October 1995, which is likely to have had some impact on the concomitant use of these agents. Perhaps the most accurate estimate of PharmADE's impact is shown in Figure 3, in which *patient-days* is used to reflect both the number of patients exposed to the dangerous drug combination and the number of days those orders overlapped. This indicator was unchanged in the months following the addition of these interactions to our commercial system, but declined immediately following the implementation of PharmADE. It is unlikely that the front-end commercial system (which only alerts at the time of order processing) would have

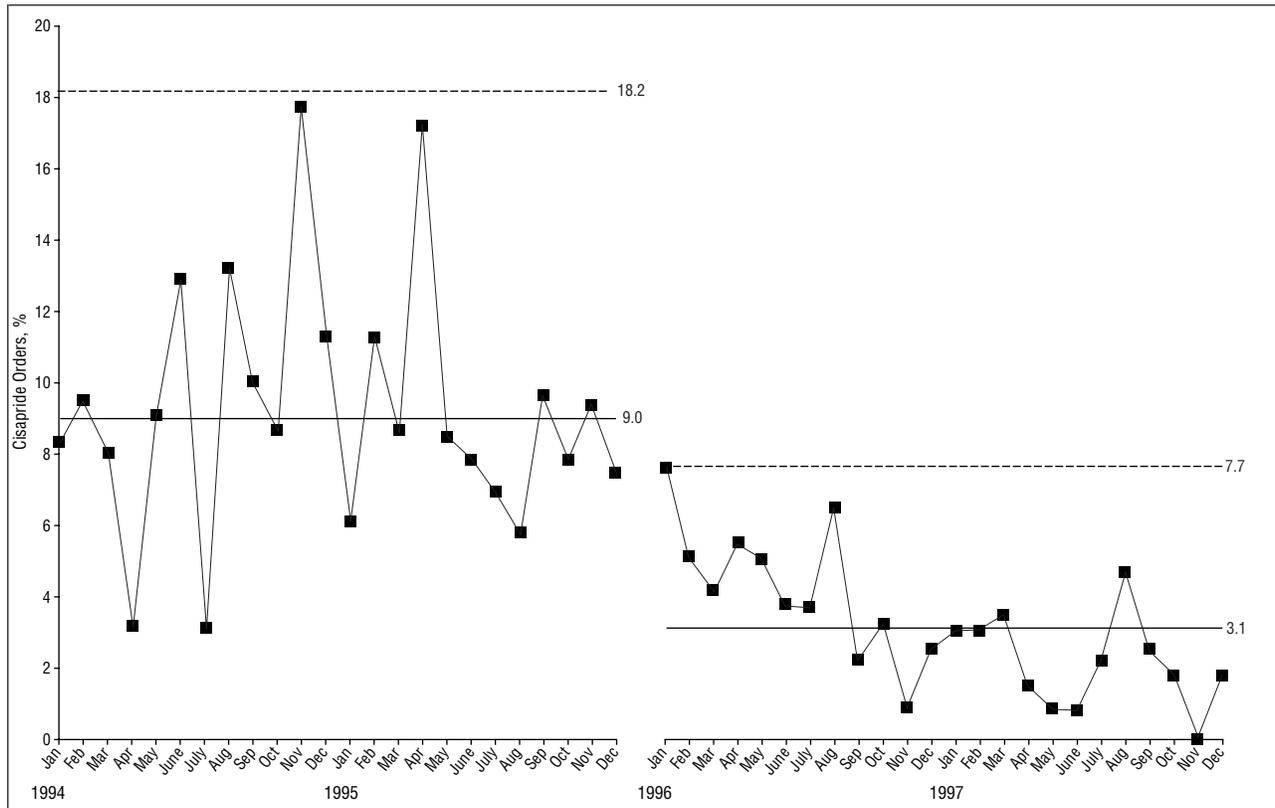


Figure 2. Cisapride orders overlapping with an order for an azole antifungal agent, erythromycin, or clarithromycin before and after the implementation of the Pharmacy Adverse Drug Event (PharmADE) monitoring system.

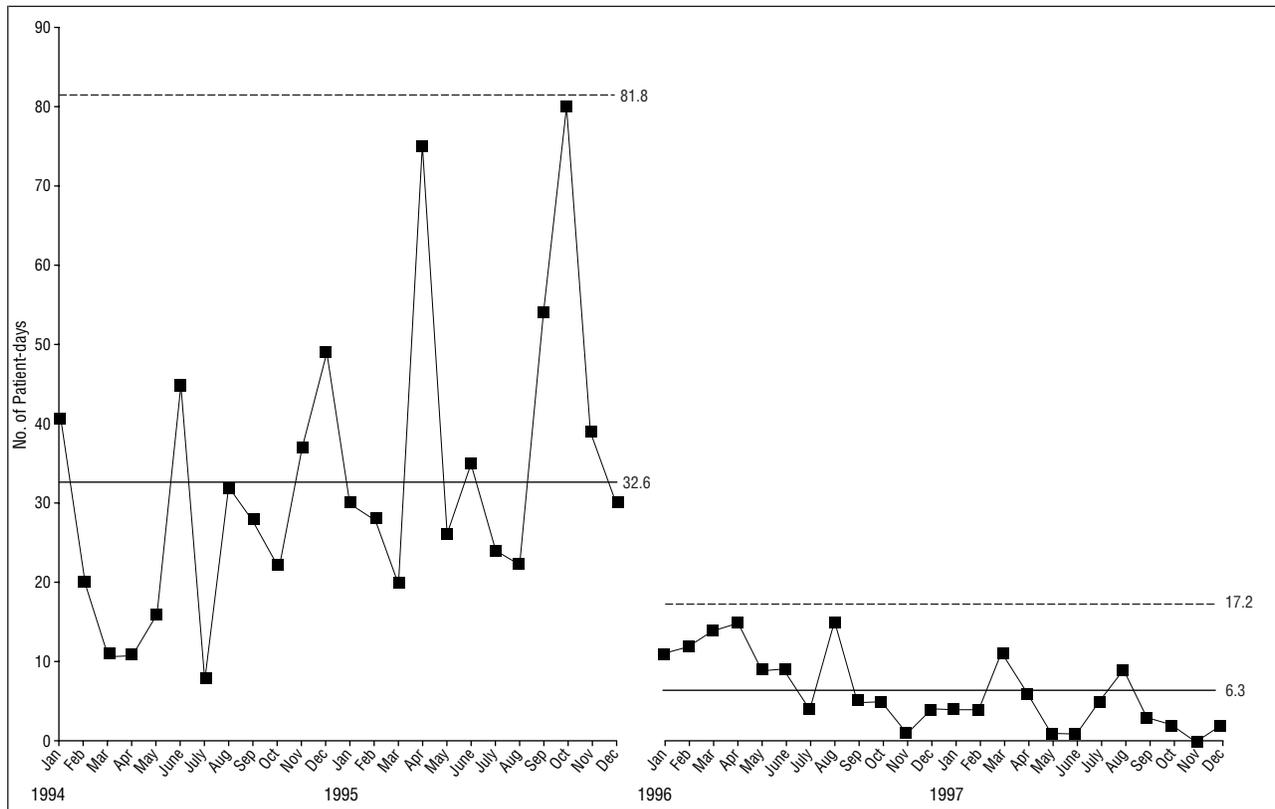


Figure 3. Patient-days in which an order for cisapride overlapped with an order for an azole antifungal agent, erythromycin, or clarithromycin before and after the implementation of the Pharmacy Adverse Drug Event (PharmADE) monitoring system.

affected the other outcome measures such as duration of overlapping drug orders and number of patients being discharged under treatment with the combination since we limited our review to patients receiving the combination for longer than 24 hours.

Another interesting finding was that the effectiveness of alerts provided by our commercial screening system depended on the drug being entered at the time of the alert. To our knowledge, we are the first to describe this phenomenon, which may be another important limitation of commercially available drug-interaction screening systems. When looking at which medication was ordered last (and therefore should have generated a prospective alert preventing the combination from being dispensed), we found that only 11% of patients during the study period received cisapride after they were already prescribed a precipitant medication. This was significantly lower than that observed during the control period (during which most of these drug interactions were not detected by either our front-end system or PharmADE). This may be the result of pharmacists perceiving prospective alerts on cisapride orders as more severe than the same alert encountered while entering one of the precipitant medications (eg, clarithromycin, erythromycin, or fluconazole). With a safety net system such as PharmADE, alerts are given equal importance regardless of the order in which medications were prescribed.

In conclusion, we believe drug-interaction screening software should allow end users to customize its rules when necessary, and should provide a mechanism for timely feedback on life-threatening drug interactions that have slipped through the system or been overridden during order entry. At our institution, an automated clinical information system that uses World Wide Web technology has proven to be an efficient method of detecting contraindicated drug combinations. Although we have had considerable success with our batch-driven model, we anticipate further improvements through the use of real-time notification methods.

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