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

S. Troy McMullin, PharmD; Richard M. Reichley, BSPharm; Lesley A. Watson, BSPharm; Sherry A. Steib, MS; Mark E. Frisse, MD, MS, MBA; Thomas C. Bailey, MD

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. 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.

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. The most likely explanation for these performance lapses was the computerized systems’ low specificity for detecting clinically meaningful interactions. This is a well-described limitation of other alert-generating systems, and drug-interaction screening tools are no exception.

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-
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 commerical 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 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 significantly 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 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 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 metfradol 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,
Serious drug interactions are now identified within 24 hours, (eg, treatment with a selective serotonin reuptake inhibitor within 2 weeks of discontinuing treatment with a monoamine oxidase inhibitor).

**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 combination). 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 them during drug 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 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 χ² 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 QTc 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 interval after a precipitant medication was added to cisapride therapy (the mean [SD] QT 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 QTc 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...
was readmitted to our hospital in either period as a re-
ous drug combination could not be assessed. No patient
tient was discharged while being treated with a danger-
drug event. These cases illustrate the importance of hav-
ting the medications was discontinued following the alert by
spite this, they both received prescriptions for erythro-
liseconds) on admission during the study period. De-
flucytosine) were available and we could document the
nos, or clarithromycin despite the use of a comput-
erized drug-interaction system that alerts on these com-
ations at the time of order entry. This rate of con-
ained drug use is similar to that observed in the com-
ity, and is likely the result of similar system failures (eg, faulty drug-interaction checking systems, in-
adequate drug knowledge, and performance lapses by medical personnel).9 Without a safety net function in
place, these drug combinations might continue indefi-
ently or until an adverse event prompts the discontinu-
ation of one of the medications.

Since adding a Web-based safety net function to our
comuterized drug interaction screening system, we have
observed a 66% reduction in the use of potentially dan-
gerous drug combinations, a 61% reduction in the du-
ration of overlapping drug orders, and a 79% reduction in the number of patients being discharged under treat-
ment 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 con-
trol 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, eryth-
romycin, and fluconazole were not specifically added as con-
traindications to the use of cisapride until October 1995.18 Nevertheless, a noticeable decline in the con-
comitant 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 Pharm-
ADE alerts more than 2 years later is disappointing, and
further highlights the limitations of commercially avail-
able 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 ex-
posed to the dangerous drug combination and the num-
ber of days those orders overlapped. This indicator was
unchanged in the months following the addition of these
interactions to our commercial system, but declined im-
mediately 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

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

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**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.
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 overriden 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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