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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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, allowing 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 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 ($P<.001$).

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.
Serious drug interactions are now identified within 24 hours, from 32.6 (18.2) to 6.3 (4.7) patient-days per month (SD number of patient-days when a cisapride order overlapped with one of the precipitant medications decreased). In both cases of unexpected death, the patient who suffered anoxic brain injury after a cardiac arrest (torsades de pointes and ventricular fibrillation) occurred 8 hours after the first dose of clarithromycin, spontaneously corrected without treatment, and was only asymptomatic 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 

patient was discharged while being treated with a danger-

ing a safety net system such as PharmADE. 

drug event. These cases illustrate the importance of hav-

the medications was discontinued following the alert by 

liseconds) on admission during the study period. De-

Figure 1. 

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 

next morning after the physician was notified about the 

drug interaction. The patient’s QTc interval was 443 mil-

seconds 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 QTc intervals (492 and 541 mil-

seconds) on admission during the study period. De-

spite 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 hav-

ing a safety net system such as PharmADE. 

Adverse events that may have occurred after a pa-

ient was discharged while being treated with a danger-

ous drug combination could not be assessed. No patient 

was readmitted to our hospital in either period as a re-

sult of the targeted drug interactions.

Although computerized drug-interaction checking sys-

tems 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, eryth-

romycin, or clarithromycin despite the use of a comput-

erized drug-interaction system that alerts on these com-

binations 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, in-

adequate drug knowledge, and performance lapses by 

medical personnel). Without a safety net function in 

place, these drug combinations might continue indefi-

nitely or until an adverse event prompts the discontinu-

ation 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 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. Clarithromycin, eryth-

romycin, and fluconazole were not specifically added as 

contraindications to the use of cisapride until October 

1995. 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 

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 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 

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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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References