A NEW KNOWLEDGE STRUCTURE FOR DRUG-DRUG INTERACTIONS

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ABSTRACT

We developed a program to automatically screen patients' medication profiles for pairs of interacting drugs. Since some drug-drug interactions are indicated by changes in physiological parameters (e.g., ciprofloxacin and theophylline leading to an elevation of theophylline levels), the program considered the patients' relevant laboratory parameters prior to generating the alerts. We developed an editor to facilitate maintenance of the knowledge base. We evaluated the program for 3 weeks in two satellite pharmacies. The program reported 160 alerts of which 5 resulted in a change in the patients' therapies (one per 500 patient-days of care). These five interactions were potentially very serious. An additional 3 alerts led to changes in medication administration times. Subjectively, the program is well received and continues to be in routine clinical use.

INTRODUCTION

Although drugs are an essential part of medical treatment, the use of medications often leads to undesired adverse events. Leape, et al.[1] noted that 3.7% of hospitalized patients had disabling injuries caused by medical treatments and the most commonly implicated treatment was medication use accounting for 19% of all injuries. Steel, et al.[2] noted that 9% of hospitalized patients incurred iatrogenic complications that were life-threatening or produced disability and medications accounted for 37% of the complications. Drug-related injuries are known as adverse drug events (ADEs). Examples of ADEs include allergic reactions, gastrointestinal bleeding, neurologic side effects, and metabolic abnormalities. The costs of ADEs are high: one study estimated the incremental costs associated with an ADE to be about $2000.[3]

Distinct from ADEs, several types of medication-related errors may occur during a hospital stay. A medication error is an error in the process of ordering or delivering a medication regardless of whether an injury occurred or whether the potential for injury was present.[4] Examples of medication errors include overdoses, underdoses, medications which are inappropriate given patient characteristics, orders for medications to which the patient is known to be allergic, and orders for interacting combinations of medications. Few medication errors actually result in ADEs and only a minority of ADEs are caused by medication errors. Bates, et al.[4] noted that 20% of 25 ADEs identified by chart review were caused by medication errors.

The goal of this project was to try to prevent medication errors and ADEs due to drug-drug interactions. Although the literature describes thousands of drug-drug interactions of varying severity,[5] previous studies have found that clinically important drug-drug interactions are relatively infrequent. Folli, et al.[6] found that out of 500 errors in 100,000 medication orders, only 9 were related to drug-drug interactions (overdoses and underdoses were much more common). The HELP system's drug alert monitor[7] finds only one important drug-drug interaction approximately every 500 patient-days. Medication orders that result in drug-lab interactions are twice as common. Out of 10,000 medication orders, Bates, et al.[4] found only one drug-drug interaction that caused an ADE. Even though serious drug-drug interactions are low frequency events, the resulting adverse events (while completely preventable!) may be devastating. The highly publicized death of Libby Zion a decade ago[8] was felt to be due partially to an interaction between meperidine and phenelzine. Indeed, this case caused a grand jury to suggest that computerized drug-drug interactions programs be considered for all level one hospitals in New York State. Additionally, malpractice suits resulting from drug-related injuries are difficult to defend[9] and although pharmacists often can detect medication orders that will result in an interaction, humans are fallible.[10]

We decided to implement an automated detection scheme because the data required to detect drug-drug interactions are present in our hospital information system,[11] because detecting such interactions is computationally relatively straightforward, and because of the potential importance of even a single such event.

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METHODS

Setting: Brigham and Women's Hospital (BWH) is a 751-bed tertiary care hospital in Boston, Massachusetts. The Brigham Integrated Computer System (BICS) provides administrative, financial, and clinical computing services at the hospital.[11] A computerized pharmacy application is used by pharmacists to manage patients' medications. The BICS database contains a list of the medications that each patient is currently receiving.

Knowledge acquisition: We used empiric data on adverse events at BWH[4],[12] and surveyed the pharmacy literature to determine which drug-drug interactions may be life-threatening. Fifty-two serious interactions were identified. Eighteen of the pairs involved warfarin. Examples of other alerts are digoxin-quinidine (possible digoxin toxicity), antiotensin converting enzyme (ACE) inhibitors-potassium sparing diuretics (possible hyperkalemia), meperidine-monoamine oxidase (MAO) inhibitors (potentially fatal), and terfenidine-erythromycin (arrhythmia risk). The full list of interactions is available from the authors on request. For computational purposes, the data were stored in a database consisting of 3 fields: 1) drug A, 2) drug B, and 3) the message to be displayed if the patient is receiving both drugs. A knowledge base editor was created to facilitate knowledge base maintenance. For each interaction, the editor allows the drug names and the alerting message to be entered in a "slot-filling" approach. The editor also allows links to be created between the drug names and specific elements in the BWH drug database.

Linkage of drug names to BWH drug database: The BWH drug database consists of 9000 packages which, for management purposes, are collected into "rollup" groups (Figure 1). For example, all of the various erythromycin packages used in the hospital are contained in the erythromycin rollup group. The rollup categories were inadequate (i.e., too specific) for use in drug interactions. For example, MAO inhibitors (as in the meperidine-MAO inhibitor interaction) are contained in multiple rollup groups (e.g., phenelzine, tranylcypromine, etc.). We therefore created the concept of a "drug family" which is a collection of rollup groups (Figure 1) to be used in the drug interaction database. The drug interactions were therefore defined as interactions between pairs of drug families. Any individual patient's medication profile is defined in terms of drug packages however the associated drug families can be discerned by following the links shown in Figure 1.

Preliminary work and modification of knowledge structure: A program was written which reviewed all inpatients' computerized medication profiles and detected when patients were receiving pairs of interacting drugs. When the program was tested, it was found that many patients (60 per day) were generating alerts, yet there were few instances of clinical significance. A closer review of the interactions revealed why.

Twenty-eight (28) of the interactions were found to be mediated by alterations in measurable physiologic parameters such as potassium (K^+), prothrombin time (PT), urea nitrogen (BUN), creatinine, calcium, and various drug levels. For example, the life-threatening consequences of warfarin-related interactions involve an elevation of the PT which makes the patient more susceptible to hemorrhage and the simultaneous administration of potassium-sparing diuretics and potassium products may elevate the serum K^+ to dangerously high levels. Often, however, even when a patient is receiving both drugs in an interacting pair, the laboratory test which would be affected by the interaction remains normal, in which case an alert would not be necessary.

We therefore altered our knowledge structure to include the concept of a "relevant lab test" (Figure 2). The database structure of a drug interaction was extended to include a list of 0 or more relevant laboratory tests for each interaction. Each relevant laboratory test is described by 4 elements: 1) the name of the lab test, 2) a threshold value, 3) an inequality operator ("<" or ">") to

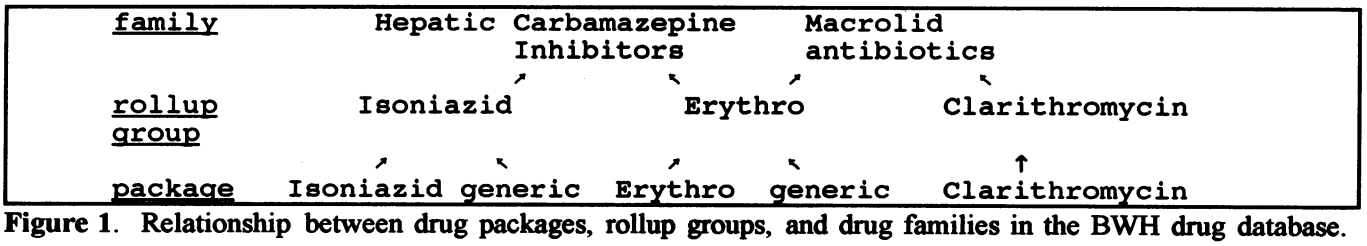

Figure 1. Relationship between drug packages, rollup groups, and drug families in the BWH drug database.

Drug interaction data			Relevant laboratory tests			
Family A	Family B	Message	Labname	Threshold	Operator	Within
K-sparing diuretics	Potassium	Hyperkalemia →	Potassium	4.7	>	4 days
Cyclosporine	Erythro	Renal Failure →	BUN	25	>	3 days
		↳	Creatinine	2.5	>	3 days
Digoxin	Quinidine	Dig toxicity →	Digoxin	2.0	>	5 days
Barbiturates	Warfarin	Warfarin less effective →	Protime	13	<	3 days
etc.						

Figure 2. Knowledge structure for drug-drug-lab interactions.

indicate if "greater-than" or "less-than" the threshold is of concern, and 4) a "days-within" value indicating within how many days the test should have been performed.

The algorithm for alert detection was modified so that, even if both drugs were present in a patient's medication profile, the drug interaction alert would be suppressed if, for all of the "relevant labs" for that interaction 1) none of the last 3 test results were above or below (as indicated by the inequality operator) the threshold value, and 2) the laboratory test had been done within the "days-within" value.

For example, a patient receiving both potassium and potassium-sparing diuretics would only have the interaction reported if one of the three most recent serum potassium measurements was above 4.7 or if the serum potassium had not been measured in the last 3 days; a patient receiving both phenytoin and chloramphenicol would generate an alert only if any of the 3 most recent dilantin levels were above 20 or if no dilantin measurement has been performed within 4 days. Threshold values (i.e., K^+>4.7) were set so the alerts would be presented before the values became dangerous. The knowledge base editor was expanded so relevant labs could easily be defined.Since drug-drug interactions now often involve laboratory tests, we refer to these alerts as drug-drug-lab interactions, or DDLIs.

Program operation: The DDLI detection program runs daily at 7 a.m. All patients' medications are reviewed and the program generates reports which are reviewed later in the day by clinical pharmacists working in the hospital's four satellite pharmacies. The reports include relevant pharmacy, laboratory and demographic data (Figure 3). The pharmacists 1) review the alerts for significance, 2) collect further clinical information if necessary, and 3) contact a clinician if warranted. We decided to do background (batch mode) detection of interactions rather than real-time detection at the time of pharmacist data entry because a physician order entry project is under development[13] which soon will make programs relying on pharmacist entry of medication data obsolete.

Evaluation: For a 3-week period, data detailing the frequency and distribution of generated alerts were collected. We measured how often our modified knowledge structure suppressed an alert because a laboratory threshold value was not exceeded. We also kept data in two of the satellite pharmacies on 1) whether the patient's medications were changed as a result of the alert, and 2) how often additional data were required to establish the clinical significance of the alert.

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================ Drug-drug alerts -- 03/26/93, Alert # 6 ==================
Patient PATIENT, A in room 11D-72
MR #: 999-99-99-9 Age: 73   Sex: M
Patient on COUMADIN and BACTRIM.  Possible PROLONGED BLEEDING TIME
Patient had same alert recently on 03/23/93, 03/24/93, 03/25/93
  drug name                          dose          rt   sch      start date
WARFARIN SODIUM                       12.5 MG       PO   HS         03/23/93
TRIMETHOPRIM/SULFA                    160 MG        PO   BID        03/24/93
Relevant laboratory tests with age/sex specific normal values:
PT          37.3   03/25/93 10:20A  [nl:10 - 13]
PT          28.4   03/24/93  9:43A  [nl:10 - 13]
PT          26.4   03/23/93 10:37A  [nl:10 - 13]
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Figure 3. Example of alert generated by DDLI detection program.

Table 1. Distribution of 160 drug-drug-lab interactions (DDLIs) captured over a 3 week period from two satellite pharmacies.

ACE inhibitors and potassium	53%
Warfarin and other drugs	25%
Neuromuscular blockers and aminoglycosides	6%
Cyclosporin and erythromycin	6%
Phenytoin and other drugs	4%
Maalox and doxycycline	2%
Theophylline and other drugs	2%
Others	2%

RESULTS

The application has been in use since April 1993. The 3 week evaluation took place in June 1993. During the evaluation period, an average of 21.8 DDLI alerts per day were generated for the hospital as a whole. A further 38.3 alerts per day that might have been presented were suppressed because a relevant laboratory test did not exceed a threshold. Data were collected from two satellite pharmacies for 160 alerts. Table 1 shows the distribution of the alerts. Angiotensin converting enzyme (ACE) inhibitors/potassium and warfarin-related interactions accounted for 78% of the alerts.

Eight (5%) of the alerts were clinically significant. Five (3% of all interactions) led to a documented change in therapy (Table 2). This corresponds to a rate of about one clinically significant drug-drug interaction per 500 patient-days. Table 2 shows that the clinical circumstances surrounding the interactions requiring changes in therapy were potentially very serious (i.e., hyperkalemia, theophylline and digoxin toxicities, and excessive anticoagulation). Three interactions (2%) resulted in changes in medication administration times so that medications would not be administered concurrently (Maalox and doxycycline).

Pharmacists required additional data (e.g., medication administration times, other medication data, other laboratory data, etc.) to determine clinical significance in 18% of the alerts.

The program continues to be used routinely.

DISCUSSION

Although the DDLI detection program described here has a low specificity -- only 5% of interactions reported to BWH pharmacists led to immediate changes in medication therapy -- Table 2 shows that the program helped avert some potentially serious conditions. Gardner[7] reports that the physician compliance with the LDS Hospital drug alert detection system is near or at 100%, i.e., physicians nearly always change their prescriptions in response to alert messages. Several factors could account for the discrepancy between the two systems' performances including the differences in the knowledge bases and the fact that at LDS Hospital, pharmacists subjectively categorize alerts as "information-oriented" or "action-oriented" (the specificity figures apply only to the action-oriented alerts). It is interesting that the frequency of significant interactions found in this study was very similar to that found by Gardner (both about one per 500 patient-days).

Table 2. Interactions resulting in changes in medication therapy (with relevant laboratory results). Theoph = theophylline levels, PT = prothrombin time, K = potassium levels, Dig = Digoxin levels.

Interaction found	Lab	Result	Action taken
1) Ciprofloxacin-theophylline	Theoph	22.5	decrease theophylline
2) Warfarin-trimethoprim/sulfa	PT	37.3	decrease warfarin
3) ACE inhibitor-potassium	K	4.9	D/C potassium
4) ACE inhibitor-potassium	K	5.4	add furosemide
5) Digoxin-quinidine	Dig	2.2	change digoxin to every other day

Because a patient's medication profile continued to be scrutinized as long as the patient was in the hospital, it is unlikely that the screened-out alerts were clinically relevant (because an alert would have been generated if the laboratory value changed or if the test was not repeated shortly). A new medication started just prior to discharge, however, may have resulted in an adverse situation that would not have been discovered until after discharge. The scope of this project was limited to the inpatient setting.

The specificity of the BWH alerts could likely be increased if the threshold limits on the laboratory tests were changed. For example, BWH cardiologists like to keep the potassium values of cardiac patients "on the high side", i.e., close to 5. Many cardiac patients receiving ACE inhibitors and potassium thus generate DDLI alerts. These alerts could be squelched by increasing the potassium threshold value from 4.7 to, say, 5.0 or 5.1. However, the pharmacists are apprehensive about missing another patient's potassium that is creeping up. The pharmacists do not mind reviewing the small number of false positives that are generated and thus far have not asked for the threshold values to be changed. About 5-10 alerts per satellite per day are generated and review of the alerts is very quick (1-2 minutes) if additional data are not needed.

Another factor that may contribute to the low specificity is that in our study the BWH pharmacists only documented medication changes of which they were certain. It is possible that physicians, having been informed of a possible adverse situation may have changed the patient's medications at a later time, or otherwise modified their prescribing habits in response to the information, even though they did not respond immediately to the information.

Subjectively, the pharmacists feel the program provides them with worthwhile information and make time in their day to generate and review the alert report.

CONCLUSIONS

We developed a drug-drug interaction detection scheme that automatically reviews all BWH patients' medication profiles. We added the concept of a "relevant lab" for interactions mediated by changes in physiological parameters. We developed a knowledge base editor to manage rules and the linkages to the database. Over a 3 week period, 5 serious drug interactions (one per 500 patient-days of care) were detected that led to changes in patients' therapies. The program continues to be in routine clinical use.

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