DEVELOPMENT OF A COMPUTERIZED ADVERSE DRUG EVENT MONITOR

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ABSTRACT

Adverse events during drug therapy are receiving renewed attention. Some adverse drug events (ADEs) are identified only after the widespread clinical use of a drug. The Food and Drug Administration advocates post-marketing surveillance systems to provide early warnings of previously undetected ADEs. The identification of ADEs by U.S. hospitals is now required by the Joint Commission on Accreditation of Healthcare Organizations. We developed a series of computer programs and data files on the HELP System to help identify ADEs. The HELP System monitors laboratory test results, drug orders, and data entered through a computerized ADE reporting program. A nurse or pharmacist verifies computer alerts of possible ADEs. The computerized system identified 401 ADEs during the first year of use compared to 9 by voluntary reporting methods during the previous year ($p < 0.001$). This paper describes the development and early use of the computerized ADE surveillance system.

INTRODUCTION

Several hospitals have applied epidemiologic knowledge, methods, and reasoning to monitor adverse drug events [1]. An adverse drug event (ADE), is defined by the World Health Organization as "any response to a drug which is noxious, unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease" [2]. Type A ADEs are predictable and are based on known toxicities of drugs. Type B ADEs are not predictable and are allergic or idiosyncratic reactions. Pre-marketing studies do not always depict how drugs will be clinically used [3]. Therefore, some ADEs may only be identified after widespread clinical use. As a result, somce studies were developed specifically to determine ADE rates in hospitals. These studies showed that as many as 20 percent of hospitalized patients experience ADEs [4-9].

Hospitalized patients in the United States receive an average of nine different drugs during a single hospitalization [10]. For each course of drug therapy the rate of adverse events is five percent. The most common types of adverse events are nausea, drowsiness, diarrhea, vomiting and rash. Severe or life-threatening drug events occur in about 3 percent of patients or in 0.4 percent per course of drug therapy. Severe ADEs include arrhythmia, seizures, bone-marrow depression, central-nervous-system depression, fluid overload, and hemorrhage [7]. Ten percent of severe ADEs result in death [11]. Up to 140,000 deaths occur each year in the United States as a direct result of ADEs [12]. One seventh of all hospital days is devoted to the care of ADEs, at an estimated yearly cost of three billion dollars [13].

The appropriate use of drugs requires the understanding of the benefits and hazards for the patient. Therefore, the physician must have information on the frequency and severity of ADEs for a given drug. Voluntary reporting of ADEs by physicians and nurses was shown to be erratic, incomplete, and of questionable reliability [14-16]. The Food and Drug Administration reported that the best method of documenting ADEs is a concurrent surveillance system. The routine collection and analysis of suspected ADEs would provide early warnings of previously undetected ADEs [17,18]. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) now requires hospitals to develop a written policy for recording and reporting ADEs [19]. The JCAHO advocates that proper steps should be taken to reduce the incidence of ADEs within the institution.

Steps to decrease the number of ADEs cannot be taken if the events are not identified and reported. This paper describes a computerized approach to identify ADEs at our hospital through use of the HELP Hospital Information System. The development and use of the computerized ADE surveillance system is reported.

METHODS

The HELP (Health Evaluation through Logical Processing) Hospital Information System has been under development at the LDS Hospital and the University of Utah for 20 years [20]. The HELP System is clinically operational at LDS Hospital. LDS Hospital is a 500 bed, private, tertiary care hospital and a major teaching center for the University of Utah School of Medicine. The daily operation of the hospital is now dependent on the HELP System. One key feature of the HELP System is its computerized medical record that contains patient information from clinical areas such as the pharmacy and laboratory.

We developed a series of computer programs and data

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files on the HELP System to help identify ADEs (Figure 1). One computer program allowed nurses, pharmacists, and physicians to enter possible symptoms of ADEs. The program was available at over 500 computer terminals in the hospital. The user only had to identify the patient and choose the symptoms, i.e. rash, change in heart rate, etc, that may be caused by ADEs. Up to six different symptoms could be entered for each possible ADE. Pharmacists could use the program to report abrupt orders to stop or reduce the dosage of drugs. Nothing else was required of the user. We also incorporated the ADE reporting feature in the nurse bedside charting programs that were available on most of the nursing divisions at LDS Hospital.

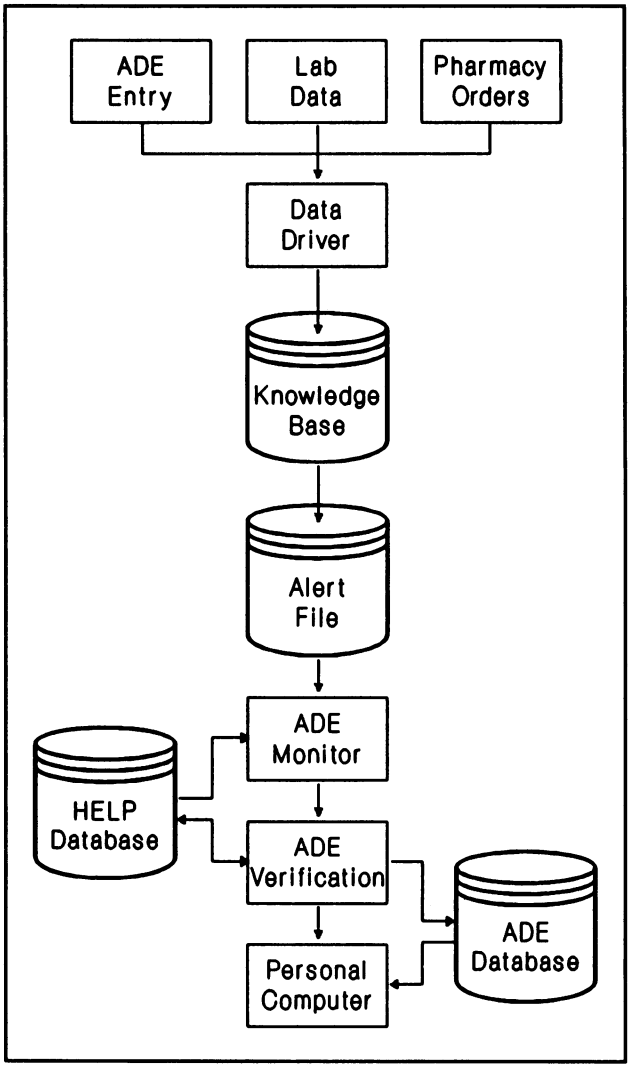

Figure 1. Programs and files developed for the Adverse Drug Event monitor.

The "data driver" on the HELP System was expanded to monitor all symptoms entered through the ADE reporting program, certain laboratory test results, and specific pharmacy orders. The "data driver" automatically activated the knowledge base on the HELP System when the key information was stored in the HELP database [21]. We then developed new frames in the knowledge base to identify possible ADEs (Table 1). The knowledge base identified patients with specific chemistry test results that were above or below specified levels. Drug level tests and orders for drugs that are commonly used to treat ADEs also were monitored by the knowledge base. Logic was added to the knowledge base to reduce some false positive alerts. For example, the knowledge base did not flag a patient with a creatinine clearance below 50 ml/min if the patient's admission diagnosis involved renal disease. The knowledge base stored each possible ADE in an alert file.

TABLE 1
SIGNALS USED TO ACTIVATE THE ADE KNOWLEDGE BASE

ADE Reporting Program	Drug Levels (continued)
Laboratory Data	Gentamicin peak >10
Chemistry	Gentamicin trough > 2
SGOT > 150	Tobramycin peak > 10
SGPT > 150	Tobramycin trough > 2
Bilirubin > 10	Amikacin peak > 25
Alkaline Phosphatase > 350	Amikacin trough > 10
Potassium > 6.5	Pharmacy Orders
BUN > 50	Prednisone
Creatinine Clearance < 50	Diazepam
Hematology	Diphenhydramine/calamine
Eosinophil % > 6	Calamine
Platelets < 50	Vitamin K
White blood count < 2.5	Digibind
Drug Levels	Sodium polystyrene sulfonate
Carbamazepine > 10	Kaolin/pectin
Digoxin > 2	Diphenoxylute/atropine
Lidocaine > 5	Opium
N-acetyl procainamide > 20	Paregoric
Procainamide > 10	Loperamide
Phenobarbital > 45	Activated charcoal
Phenytoin > 20	Diphenhydramine
Quinidine > 5	Protamine
Theophylline > 20	Steroid cream
Cyclosporin > 100	Epinephrine
Vancomycin peak > 40	Naloxone
Vancomycin trough > 10	Phenytoin
Gentamicin peak > 10	Phenobarbital

Each day at 8:00 A.M. an ADE Monitor program was activated by the HELP "time driver" and listed all patients alerted with possible ADEs during the previous 24 hours. The ADE monitor accessed the HELP database and appended pertinent patient information to each ADE alert. The ADE monitor report listed the alerted patients according to hospital location. Either a clinical pharmacist (SLP) or study nurse (SBB) followed up on each possible ADE.

An ADE verification program was developed and was used by the pharmacist and nurse monitors to evaluate the possible ADEs. The verification program used the Naranjo method to determine the probability of the ADE (definite, probable, possible, negative) [22]. Computer alerts of possible ADEs that led to the identification of a definite, probable, or possible ADE were classified as "true alerts." The evaluator entered the drug causing the event with a detailed description of the patient's specific symptom(s).

Each verified ADE also was classified by severity. Mild ADEs did not require a change in dosage of drug, drug therapy, or an increase in the length of hospitalization. Moderate ADEs required a change in drug therapy, specific treatment, or resulted in an increase in the length of hospitalization. Severe ADEs were potentially life threatening, caused permanent damage, or contributed to the death of the patient. The verified ADE was stored in the patient's computerized medical record on the HELP System. The verification program then accessed the HELP database and appended other pertinent patient information to an expanded verified ADE record. The expanded ADE record was then stored in the ADE database (Table 2).

The pharmacists and nurses in the hospital were instructed how to identify ADEs and how to use the ADE reporting program. The instruction was undertaken from April through June, 1989. Because of nurse turn-over, continuing education was also performed and ADE education was included during nurse orientation. The nurses and pharmacists were told to enter any possible ADE symptom(s) and not be concerned about false alerts.

TABLE 2
DATA STORED IN ADE DATABASE

Patient hospital number
Drug causing reaction
Time ADE was first noticed
Time drug causing ADE was first received
Medical record number
Sex
Age
Race
Admission date and time
Flag (how ADE was first identified)
Naranjo probability score
Admission diagnosis
Number of drugs received
Number of drugs received before ADE
ADE Symptom(s)
Service
Physician
Division
Severity of the ADE
Type of ADE
Hospitalized because of the ADE Y/N
Last lab results before ADE

After we used the computerized ADE monitor for 17 months (October, 1990) we downloaded the records of verified ADEs to a personal computer. A control population of 2,733 patients from the HELP database also was downloaded to the personal computer. The control patients were randomly selected from hospitalized patients who received drugs during the same time period but did not have verified ADEs. Stepwise logistic regression was used on the data from the ADE database to identify patients that were most likely to experience ADEs. Models also were developed to identify patients likely to experience ADEs to specific drugs. Control populations consisting of randomly selected patients who received the specific drugs but did not have verified ADEs were used for each drug model.

Similar statistical methods were used to improve the logic in the knowledge base and reduce false positive ADE alerts. For example, patients with false positive diphenhydramine alerts were compared to patients with true positive diphenhydramine alerts. The analysis was used to determine reasons, other than treating ADEs, physicians ordered diphenhydramine. The statistical analysis was compared with the experience of the two ADE monitors (SLP, SBB). The logic in the knowledge base was subsequently enhanced based on the analysis.

RESULTS

There were nine (0.04%) ADEs voluntarily reported through incident reports at LDS Hospital among 25,142 patients discharged from May 1, 1988 to May 1, 1989. From May 1, 1989 to May 1, 1990, the computerized ADE surveillance system identified 401 (1.7%) verified ADEs among 23,297 patients discharged. The verified ADEs occurred in 366 different patients. The average Naranjo score was 9 (range 3-12). Two-hundred and forty-one ADEs were definite (score > = 9), 156 were probable (score 5-9), and only 4 were possible (score 1-4). Fifty-eight (15%) of the ADEs were severe and 343 were moderate. No verified ADE was classified as mild. There were 341 type A ADEs and 60 type B. The average length of hospitalization for patients with ADEs was 13 days compared to only 5 days for patients not experiencing ADEs. Patients with ADEs received an average of 33 different drugs (15 before the ADE) compared to 13 for patients without ADEs.

Computerized screening of diphenhydramine orders identified the most ADEs, 168 (42%) (Table 3). The nurses reported only 45 (11%) of the verified ADEs. However, 58 percent of the nurses' reports were "true alerts" compared to only 13 percent for the diphenhydramine order alerts. Pharmacists did not report any ADEs. The computer surveillance generated nine false positive alerts for every true alert. Following up on the possible ADE alerts required one person an average of two hours per day five days a week. Monitoring laboratory test results had the lowest true positive rate, 21 of 966 (2.2%).

There were 98 individual drugs that caused verified ADEs. The drugs were from 15 different drug classes, the most frequent categories being analgesics, antibiotics, and cardiovascular agents. Morphine caused 89 ADEs, followed by meperidine, 28, oxycoclone/acetaminophen, 21, warfarin, 21, and digoxin, 18.

The model to identify patients likely to experience ADEs was developed from data on 731 ADEs identified from May 1, 1989 through October 31, 1990. We found that five different types of patient variables (sex, service, underlying disease, physician, and the number of different drugs received) were identified by the model. The model indicated that oncology patients and women with complicated labor were most likely to experience ADEs. Morphine accounted for 130 (18%) of the 731 ADEs. The model based on patients with ADEs to morphine identified some of the same variables (Table 4). The morphine

TABLE 3
ALERTS OF VERIFIED ADEs

Type of Alert	True Alerts (%)	No. Alerts (% True)
Diphenhydramine orders	168 (42)	1280 (13)
Nurse reports	45 (11)	77 (58)
Naloxone orders	44 (11)	417 (11)
Vitamin K orders	22 (6)	235 (9)
Diphenoxylate/atropine orders	20 (5)	157 (13)
Digoxin level > 2	19 (5)	219 (9)
Lidocaine level > 5	9 (2)	49 (18)
Theophylline > 20	9 (2)	36 (25)
Procainamide > 10	8 (2)	19 (42)
Platelets < 50	8 (2)	189 (4)
White blood cell count < 2.5	8 (2)	93 (9)
Loperamide order	6 (2)	56 (11)
Paregoric order	4 (1)	63 (6)
Gentamicin trough > 2	3 (1)	130 (2)
Quinidine > 5	3 (1)	7 (43)
Sodium ploystyren sulfonate orders	3 (1)	47 (6)
SGOT > 150	2 (<1)	137 (2)
Phenytoin > 20	2 <(1)	30 (7)
Vancomycin trough > 10	2 (<1)	6 (33)
Tobramycin trough > 2	2 (<1)	8 (25)
Phenytoin orders	2 (<1)	171 (<1)
Diphenhydramine/calamine orders	2 (<1)	19 (11)
Steroid cream orders	2 (<1)	15 (13)
Epinephrine orders	2 (<1)	71 (3)
Potassium > 6.5	1 (<1)	8 (13)
Creatinine clearance < 50	1 (<1)	89 (1)
Eosinophil % > 6	1 (<1)	9 (11)
Calamine orders	1 (<1)	10 (10)
Digibind orders	1 (<1)	3 (33)
Activated charcoal orders	1 (<1)	13 (8)
All others	0 (0)	794 (0)
TOTAL	401 (100)	4457 (9)

TABLE 4
RISK FACTORS IDENTIFIED FOR ADEs TO MORPHINE

Factor	Coeffecient
Age 33 - 38	0.7600
Female	1.152
Medical Service	1.326
Gynecology Service	3.100
Hernia of abdominal cavity	1.505
Abnormality of organs of pelvis	2.566
Diseases of the lung	1.756
Disorders of the gallbladder	1.245
One physician	1.147
12 - 14 different drugs	0.6732
17 - 20 different drugs	1.330
More than 46 different drugs	1.266
Constant	-6.198

model indicated that women in the gynecology service with abnormal organs of the pelvis were the most likely patients to experience ADEs to morphine.

During 17 months of computer surveillance of ADEs, there were 235 of 2,015 (12%) diphenhydramine alerts that identified true ADEs. The statistical comparison between the true- and false-positive diphenhydramine alerts confirmed the additions to the logic suggested by the nurse and pharmacist ADE monitors. New rules were developed to identify reasons for ordering diphenhydramine other than treating ADEs. For example, diphenhydramine was frequently ordered with diazepam for patients undergoing heart catheterization. Diphenhydramine was ordered for its sedative effect and not to treat ADEs. Thus, we tried to identify reasons other than to treat ADEs for ordering diphenhydramine. The new logic to reduce false-positive diphenhydramine alerts was added to the knowledge base. After two months, the new logic increased the true-positive diphenhydramine alert rate from 12 percent to 23 percent.

DISCUSSION

Computerized ADE surveillance identified significantly more ADEs (9 vs. 401, $p < 0.001$) than the traditional method used at LDS Hospital. Previously, ADEs were reported through voluntary incident reports completed by nurses. The report required the nurse to decide what drug caused the event, describe the event and what actions were taken to correct the problem. The nurse also was required to have the nursing supervisor and attending physician verify and sign the form. This process demanded extra time from already busy individuals. During the educational training for ADE reporting, some nurses stated that they were unaware of the need to report ADEs. Others were aware, but did not see the value of ADE reporting.

While the new ADE reporting program simplified ADE reporting and nurses and pharmacists appeared to be more aware of ADEs, most still saw ADE reporting as extra work. Therefore, even with a simplified reporting mechanism, voluntary identification of ADEs was low. Some nurses stated that "we" found out about the ADEs without their use of the ADE reporting program. Nonetheless, we believe that ADEs were not identified because of low nurse reporting. This study demonstrated that most ADEs (89%) would not have been reported without computer screening of laboratory tests and drug orders. Other studies have shown that pharmacists identify most ADEs at some hospitals [23]. One disappointing result of this study was finding that pharmacists at LDS Hospital did not report any ADEs.

The current pharmacy knowledge base on the HELP System alerts the pharmacist when a drug is ordered to which the patient has an allergy. However, the computer is only aware of drug allergies if the patient or another person makes this fact known at the time of admission. Information on ADEs was not entered as part of a patient's computerized medical record before computerized ADE surveillance. The ADE verification program now stores a record containing the drug and the probability score for the verified ADE in the patient's computerized medical record. We also developed a way to store this information in the Master Patient Index at Intermountain Health Care (IHC). LDS Hospital is one of 23 hospitals owned by IHC. The Master Patient Index will contain a permanent abstract of every patient visit to an IHC hospital. A new pharmacy program will use the Master Patient Index to identify patients with previous ADEs. Thus, information about previous ADEs will be available to the prescribing physicians and may be used to prevent ADEs during subsequent hospitalizations.

The statistical analysis identified patients who were most likely to experience ADEs to morphine. Logic to

identify high-risk patients could be added to the current pharmacy knowledge base on the HELP System. Physicians could then be alerted when they ordered morphine or other drugs for high-risk patients. However, we found that physicians were generally aware of which drugs frequently caused ADEs and often wrote standing orders for drugs such as diphenhydramine or naloxone to be used if ADEs occurred. In some situations, physicians would rather treat moderate ADEs than change the drugs they normally use. If there are not alternative, equally effective drugs, the risk of moderate ADEs appears to be acceptable to physicians.

Our attempt to reduce false positive diphenhydramine alerts found that diphenhydramine was often ordered with amphotericin B and with blood products to prevent ADEs. This process of drug prophylaxis probably prevented certain mild and moderate ADEs. Patients that were alerted because they received diphenhydramine, but did not have any signs or symptoms of ADEs, were not counted as having ADEs during this study. This may help explain a lower ADE rate at LDS Hospital than reported by other studies [4-9). Those studies, however, included mild ADEs. Other recent studies that do not include mild ADEs report much lower ADE rates [15,16). The computerized ADE surveillance system described here did not report mild ADEs. Another reason for a low ADE rate at LDS Hospital is the HELP pharmacy package. The screening of drug orders by the HELP System prevents ADEs by alerting pharmacists of drug-drug, drug-food, drug-laboratory, and drug-patient incompatibilities. Pharmacists follow up on the "action oriented" computer alerts and physician compliance was 100 percent in 1989 [24).

A weakness of the computer ADE surveillance was the high false positive rate. The nursing reports of ADEs were fairly reliable (58% true positives). Without better reporting by nurses and pharmacists, we must continue to rely on monitoring laboratory tests and drug orders. The prophylactic use of drugs such as diphenhydramine caused many false-positive alerts. As more ADE data are collected, we will improve the computer logic and try to reduce the false-positive rate. More data and analysis also are needed to identify methods to prevent severe ADEs. Nonetheless, we believe that concurrent surveillance of the type described here is a necessary step in the development of methods to identify and prevent ADEs.

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