Physician versus Computer Knowledge of Potential Drug Interactions in the Emergency Department

MARK I. LANGDORF, MD, MHPE, JOHN C. FOX, MD, RAKESH S. MARWAH, BS, BRIAN J. MONTAGUE, BS, MICHAEL M. HART, MD, PHD

Abstract. **Introduction:** Proliferation of Food and Drug Administration–approved drugs makes it impossible for emergency medicine (EM) faculty to stay current on potential interactions between drugs, and with diseases, laboratory tests, and ethanol. A computer database may augment physician knowledge. **Objectives:** To compare the performance of EM faculty and an "expert" emergency physician (EP) with that of a criterion standard computer database in identifying potential drug interactions, and to report the incidence of drug–ethanol and drug–laboratory test interactions. **Methods:** This was a retrospective review of 276 emergency department charts for drug, ethanol, lab, and medical history. Evaluation by both EM faculty and an "expert" EP of patient history was done to identify potential interactions, and comparison with the Micromedex Drug-Reax database for potential interactions (graded minor, moderate, or major) was made. Clinical significance of potential interactions was judged by a second EM faculty member. **Results:** Seventeen percent of the patients had potential drug–drug interactions, and 25% of these were judged to be clinically significant. Up to 52% of the patients had potential drug–ethanol interactions, while 38% of the patients could have potential drug–lab interactions. Sensitivity, specificity, and positive and negative predictive values of the EM faculty for potential drug–drug interactions compared with the computer were poor, at 14%, 58%, 6%, and 23%, respectively. The corresponding values for the "expert" EP were 25%, 86%, 26%, and 85%. The "expert" EP was statistically better than the EM faculty, but still less sensitive and predictive than the computer. **Conclusions:** A computer can aid the physician in avoiding potential drug interactions. Prospective validation of these findings should be done. **Key words:** emergency department; computer database; drug interaction; medical education; drugs; physician knowledge. ACADEMIC EMERGENCY MEDICINE 2000; 7:1321–1329

THERE have been 19,313 drugs approved by the Food and Drug Adminisration (FDA) over the years, and an average of 340 new drugs are added to the formulary each year (personal communication, Scott, GR, FDA, Rockville, MD, 1997). A major drug interaction software program lists more than 100,000 potential interactions between these drugs (personal communication, Micromedex Corporation, Denver, CO, 1997). It is clearly impossible, then, for the practicing emergency physician (EP) to stay current with all potentially serious interactions. Furthermore, drugs interact not only with each other, but also with patients' diseases, ethanol, and certain laboratory tests.

For 20 years, various computerized systems have been used, mostly by pharmacists and mostly for inpatients, to try to identify and avoid potential interactions. In one study[1] 28% of adverse drug events were judged preventable, and some of these were drug–drug or drug–disease interactions. (Others related to dose and frequency of administration.) Organized medicine has called attention to the problem in position papers,[2,3] but there has been no agreement to use a standard computer system that identifies potential interactions before the prescription is written. Proprietary pharmacy systems exist that perform this function, but require that all of a patient's prescriptions be filled at the same pharmacy or chain. Many software programs are commercially available and have been reviewed in the literature,[4–19] but these have not become widely used in the emergency department (ED).

There have been four analyses of the utility of computer-generated potential drug interactions in ED patients, three dealing with only drug–drug

From the University of California, Irvine Medical Center, Orange, CA (MIL, JCF, RSM, BJM, MMH).
Received May 8, 2000; revision received June 23, 2000; accepted July 3, 2000. Presented at the California Chapter, American College of Emergency Physicians Annual Scientific Assembly, Rancho Mirage, CA, May 1997; and the National American College of Emergency Physicians Annual Scientific Assembly, October 1998, San Diego, CA, October 1998.
Supported in part by the University of California, Irvine, Undergraduate Research Opportunities Program Grant designation "Marwah."
Address for correspondence and reprints: Mark I. Langdorf, MD, MHPE, Department of Emergency Medicine, Route 128, UCI Medical Center, 101 City Drive, Orange, CA, 92868, Fax: 714-456-5390; e-mail: milangdo@uci.edu

interactions,[20–22] and one including drug–disease interactions.[23] These have identified high-risk groups, such as elders[21–23] and those taking multiple medications.[22,23] Underlying these studies is the assumption that the computer does a better job than the physician, but to the best of our knowledge, this has never been systematically assessed. Furthermore, while potential drug–drug interactions have been studied, we believe the incidence of potential interactions between drugs and ethanol or laboratory tests have not been quantified. We know of only one report of potential drug–disease interactions.[23]

The objectives of this study were twofold:

1. to compare the performance of emergency medicine (EM) faculty and an "expert" EP physician with that of a criterion standard computer database

2. to report the incidence of potential drug–ethanol and drug–laboratory test interactions.

METHODS

Study Design. We conducted a retrospective chart review of 276 consecutive patients presenting to a university hospital ED. The study qualified for exempt registration by the UC Irvine Institutional Review Board.

Study Setting and Population. The ED is a Level I trauma center with an annual census of 38,000. The hospital is a 463-bed, former county institution serving a significant proportion of indigent patients. Medicaid and county insurance patients comprise 35% of ED patients, while 40% are self-pay and 21% have commercial insurance.

Study Protocol. Research assistants were trained to abstract data from ED charts, including where to find drug history, alcohol use, laboratory tests, and past and present disease states. These were recorded in predefined areas of the ED medical record. Urgent care charts lacked these prompts to record data, and so were excluded. Because of the standardized form of the ED chart, assessment of interobserver variability was not thought to be necessary. An EM resident and faculty assisted as needed. In the ED, charts were filed as they were completed, by date, but in no other particular order. The ED records from three consecutive days were analyzed according to explicit criteria on standardized data sheets. While exact patient census was not available on the days chosen, approximately 280 patients would have been seen in the main ED over three days, excluding the urgent care census. Therefore, we believe we achieved a consecutive series of ED patients.

The research assistants, while aware of the aim of the study, had neither medical training in nor knowledge of drug interactions. All charts were reviewed prior to accessing the computer database, to eliminate bias in data collection. They recorded all medications, prior to the ED visit, in the ED, and upon discharge. We did not verify medication history. The patient's alcohol history was a required element on the ED chart under social history, so this was frequently recorded.

We entered these data in the 1997 Micromedex Drug-Reax database, and recorded potential drug–drug, drug–disease, drug–lab, and drug–ethanol interactions. We define a drug–disease interaction when a drug exacerbates a pre-existing medical condition. This is distinct from an adverse effect, where a drug brings about a new medical condition. Further, a drug–laboratory interaction occurs when a drug interferes with a laboratory measurement, thus giving a false reading.

The computer program identifies potential drug interactions with myriad diseases without regard to whether the patient actually has the disease. The computer grades potential interactions as minor, moderate, or major. The software program defines "minor" interactions as those that would have limited clinical effects, and manifestations may involve an increase in frequency or severity of side effects, but would generally not necessitate a major alteration of therapy. "Moderate" interactions may result in an exacerbation of patient condition and/or necessitate an alteration of therapy. "Major" interactions are those that are life-threatening and/or necessitate medical intervention to minimize or prevent serious adverse effects.

We then gave the data sheets to eight board-certified EPs (the EM faculty), approximately 35 patients each, and asked them to record both the presence and the severity of the potential interactions. We also asked them whether they thought potential interactions were "clinically significant," defined as necessitating a change in management. All 276 data sheets were also analyzed by an "expert" physician, an EM faculty member with a PhD degree in pharmacology, 20 years of practice experience, and a particular interest in emergency medications.

We assessed whether the potential interactions identified by the computer, but missed initially by the physician, were clinically important. A second physician reviewed the data sheets and recorded which potential interactions were important, i.e., those that would change patient management, and which were trivial. There was no attempt to assess whether any actual drug-related problems occurred.

Measurements and Key Outcome Measures. We calculated the sensitivity, specificity, and posi-

TABLE 1. Most Common Potential Drug–Drug Interactions, and Their Level of Severity, Identified by Computer

Drug	Drug	Effect	Severity	Incidence (n = 168)
Aspirin	Verapamil	Increased risk of bleeding	Moderate	2
Haloperidol	Cogentin	Anticholinergic effect	Moderate	2
Potassium	Hydrochlorothiazide + triamterene	Hyperkalemia	Major	1
Nitroglycerin	Heparin	Decreased anticoagulant effect	Moderate	1
Ibuprofen	Atenolol	Decreased atenolol effect	Moderate	1
Gemfibrozil	Glyburide	Hypoglycemia	Moderate	1
Warfarin	Ciprofloxacin	Increased risk of bleeding	Moderate	1
Warfarin	Ranitidine	Increased risk of bleeding	Moderate	1
Midazolam	Fentanyl	Respiratory depression	Moderate	1
Carbamazepine	Phenobarbital	Decreased carbamazepine effect	Minor	1
Lidocaine	Cimetidine	Lidocaine toxicity	Minor	1
Ranitidine	Phenytoin	Phenytoin toxicity	Minor	1
Cimetidine	Diazepam	Diazepam toxicity	Minor	1
Fluoxetine	Trazodone	Trazodone toxicity	Minor	1

tive and negative predictive values for the general EM faculty vs the criterion standard computer and for the "expert" EP vs the computer. We assessed whether the "expert" physician achieved closer agreement with the computer than the general EM faculty. Because the computer reports any possible potential drug interaction with myriad diseases, and the faculty did not, we do not report comparisons between the faculty identification of potential drug–disease interactions and that of the computer.

To assess the ability of the computer to aid physician recognition of potential drug interactions, we report the proportion of computer-generated, but physician-missed, interactions that were judged clinically significant.

Data Analysis. We used chi-square (True Epistat, Version 5.0, Epistat Services, Richardson, TX) to determine whether the proportions of correct answers regarding drug interactions were statistically different between the general EM faculty and the "expert" physician, with the computer serving as the final criterion standard. Statistical significance was set at $p < 0.05$ by convention. We used Kendall's tau-b (SAS Institute, Cary, NC) as a measure of concordance between the responses of the general EM faculty and the "expert" physician, ranging from -1 to 1, where -1 indicates complete discordance, and 1, complete concordance.

RESULTS

Sixty-five percent of the patients said they took medications prior to the ED visit. Thirty-nine percent were medicated in the ED, while 61% received a discharge prescription for a new drug. Overall, 227 patients (82%) were exposed to at least one medication prior to, during, or after the ED visit, while 168 (61%) were exposed to at least two drugs, giving rise to a possible drug–drug interaction. Pre-ED visit drugs, ED drugs, and discharge drugs averaged 2.4, 1.8, and 1.2 per patient, respectively. We found 32 potential drug–drug interactions for 29 of the 168 patients who took or received at least two drugs (17% of patients). Of these, eight interactions were classified as major, 17 moderate, and seven minor. Table 1 lists 15 of the most common and potential drug–drug interactions identified by computer.

There were 131 potential drug–disease interactions for 109 of the 227 patients exposed to at least one drug (48%). These 131 interactions were classified by the computer as major in 28, moderate in 99, and minor in four. Table 2 lists the most common potential drug–disease interactions identified by computer. However, the patient actually had the disease, either pre-existing or identified during the ED visit, in only five of these 227 cases (2.2%).

For 87 of the 227 patients exposed to at least one drug (38%), the computer identified 111 potential drug–lab interactions. Table 3 describes the most common potential drug–lab interactions, regardless of whether the patient had the laboratory test ordered. However, the patient had the suspected interacting laboratory test ordered in the ED in only five of 227 cases (2.2%). These are listed in Table 4.

For 119 of the 227 patients exposed to at least one drug (52%), the computer identified 132 potential drug–ethanol interactions. The most common interactions are listed in Table 5. Fifty patients (18%) were recorded on the ED chart as ethanol users/abusers. Of these 50 patients, 29 (58%) used or were given drugs that had potential interactions with alcohol. Because of the retrospective nature of this study, we could not determine whether pa-

TABLE 2. Most Common Potential Drug–Disease Interactions Identified by Computer

Drug	Disease	Effect	Severity	Incidence (*n*)
Nonsteroidal anti-inflammatory drugs	Peptic ulcer disease (PUD)	Worsens PUD	Moderate	50
Trimethoprim–sulfamethoxazole	Systemic Lupus erythematosus (SLE)	Worsens SLE	Moderate	16
Prednisone/dexamethasone	Diabetes mellitus	Hyperglycemia	Major	11
Prednisone/dexamethasone	Hypertension (HTN)	Worsens HTN	Major	11
Prednisone/dexamethasone	Congestive heart failure	Fluid retention	Moderate	11
Prednisone/dexamethasone	Peptic ulcer disease	Worsens PUD	Moderate	11
Nonsteroidal anti-inflammatory drugs	Gout	Hyperuricemia	Moderate	10
Albuterol/metaproterenol	Hypertension	Worsens HTN	Moderate	10
Furosemide	Diabetes mellitus	Hyperglycemia	Moderate	5
Furosemide	Gout	Hyperuricemia	Moderate	5
Dexamethasone	Glaucoma	Worsens glaucoma	Major	3

TABLE 3. Most Common Potential Drug–Lab Interactions

Drug	Lab Test	Effect	Severity	Incidence (*n*)
Trimethoprim–sulfamethoxazole	Theophylline level	False increase	Moderate	15
Cephalexin	Theophylline level	False increase	Moderate	11
Methylprednisolone	Digoxin level	False increase	Moderate	11
Aspirin	Serum glucose	False increase	Moderate	10
Aspirin	Acetaminophen level	False increase	Moderate	10

TABLE 4. Patients with Potential Drug–Lab Interactions Where Lab Was Actually Ordered (One Occurrence Each)

Drug	Lab Test	Effect	Severity
Iron	Fecal occult blood	False positive	Moderate
Aspirin	Serum glucose	False elevation	Moderate
Cimetidine	Fecal occult blood	False positive	Moderate
Trimethoprim–sulfamethoxazole	Serum theophylline	False elevation	Moderate
*Phenergan	Urine salicylate	False positive	Minor

*Patient overdosed on ibuprofen. Urine toxicology screen ordered.

tients used alcohol concurrently with the interacting drug, or whether they abstained from alcohol when taking medications. Table 6 describes the most common potential drug–ethanol interactions in documented ethanol users.

Tables 7 and 8 show the comparison between the physicians and the computer. We list sensitivity, specificity, and predictive values, with the computer serving as the criterion standard for identifying interactions.

In addition, the tables compare the general EM faculty with one "expert" physician, and answer the question, "Did the 'expert' physician come closer to the computer criterion standard than the general EM faculty?" To compare sensitivities, specificities, and predictive values between the "expert" physician and the EM faculty, both relative to the computer criterion standard, we analyzed physician decisions regarding whether there was a potential interaction for each patient. We used chi-square analysis to compare the proportions of correct responses, and report statistical significance where the computer identified an interaction ("positive interaction") and where it did not ("no interaction").

Regarding Tables 7 and 8, the total number of patients at risk for potential drug–drug interactions was 167, while for potential drug–lab and drug–ethanol interactions, it was 227. The tables list sample sizes appropriate for the calculations in question. For example, there were 29 patients with computer-identified potential drug–drug interactions, so the EM faculty and "expert" physician each had 29 opportunities to agree or disagree with the criterion standard computer. Thus, the sample size (number of decisions) for chi-square is double the patient sample size, or 58. Conversely, there were 138 (167 − 29) patients with no interaction, an equally important determination. Both the EM faculty and the "expert" physician had 138 chances to agree or disagree with the computer, hence, the doubling of the sample size to 276.

For potential drug–drug interactions, sensitivity for the EM faculty was no different from that

for the "expert" physician (p = 0.50). However, specificity was significantly better for the "expert" physician compared with the EM faculty (p = 0.000001). Accuracy of the EM faculty was 47%, while the "expert" physician was accurate 77% of the time. The advantage of the "expert" physician rested entirely in identifying the absence of potential drug interactions when the computer said none existed. The EM faculty and "expert" physician were equally poor at identifying true-positive potential interactions.

For potential drug–ethanol interactions, the EM faculty and the "expert" physician were similar in their concordances with the computer in identifying patients who truly had potential interactions (p = 0.99), but the "expert" physician was statistically better at correctly identifying the absence of potential drug–ethanol interactions. In the aggregate, the "expert" physician was statistically better (p = 0.0l) than the EM faculty. For potential drug–lab interactions, the EM faculty and the "expert" physician were equally poor in sensitivity, identifying only two and none, respectively, of the 87 potential drug–lab interactions found by the computer. Specificities were equivalent and almost 100% because both groups rarely, if ever, identified an interaction.

In Tables 9 and 10, we report only those potential interactions that the physicians judged to be clinically significant.

The Kendall's tau-b statistic for potential drug–drug interaction, comparing the EM faculty with the "expert" physician, was −0.235 for all patients. This indicates a minor to moderate discordance of opinion, with the "expert" physician being correct more often. The advantage of the "expert" physician over the EM faculty lies almost entirely in

TABLE 5. Most Common Potential Drug–Ethanol Interactions by Computer

Drug	Effect	Severity	Incidence (*n*)
Acetaminophen	Hepatotoxicity	Moderate	87
Codeine	Sedation	Moderate	18
Hydrocodone	Sedation	Moderate	18
Meperidine	Sedation	Moderate	10
Aspirin	Gastrointestinal bleeding	Moderate	10

TABLE 6. Most Common Potential Drug–Ethanol Interactions in Documented Ethanol Users

Drug	Effect	Severity	Incidence (*n*)	Frequency (% of 50)
Acetaminophen	Hepatotoxicity	Moderate	17	34%
Hydrocodone	Sedation	Moderate	5	10%
Codeine	Sedation	Moderate	4	8%
Nitroglycerin	Hypotension	Moderate	3	6%
Morphine	Sedation	Moderate	3	6%
Aspirin	Gastrointestinal bleeding	Moderate	3	6%

TABLE 7. Comparison of Emergency Medicine (EM) Faculty and "Expert" Emergency Physician (EP) with Computer Database*

		Sensitivity (%)		Positive Interactions		Specificity (%)		No interactions
Interaction	*n*	EM Faculty	"Expert" EP	p	*n*	EM Faculty	"Expert" EP	p
Drug–drug	58	14	25	0.50	276	58	86	0.000001
Drug–ethanol	238	70	71	0.99	216	34	59	0.00039
Drug–lab	174	2	0	0.48	280	98	99	0.61

**n* represents the number of decisions by faculty and the "expert" EP.

TABLE 8. Comparison of Emergency Medicine (EM) Faculty and "Expert" Emergency Physician (EP) with Computer Database*

		Positive Predictive Value (%)			Negative Predictive Value (%)	
Interaction	*n*	Faculty	"Expert" EP	*n*	Faculty	"Expert" EP
Drug–drug	89	6	26	245	23	85
Drug–ethanol	282	54	66	172	51	65
Drug–lab	6	40	0	448	62	62

**n* represents the number of decisions by faculty and the "expert" EP.

TABLE 9. Proportion of Potential Interactions Identified by Computer, but Missed by an Emergency Medicine Faculty Member, that Were Then Judged to Be Clinically Significant.

Interaction	Number of Computer-identified, Physician-missed Interactions	Number of Interactions that Are Clinically Significant (*n*)	Percentage of Computer-identified, Physician-missed Interactions that Are Clinically Significant
Drug–drug	24	5	21%
Drug–ethanol	78	20	26%
Drug–lab	119	2	2%
All interactions	221	27	12%

TABLE 10. Proportion of Potential Interactions Identified by an Emergency Medicine Faculty Member, but Missed by the Computer, that Were Judged to Be Clinically Significant

Interaction	Number of Physician-identified, Computer-missed Interactions	Number of Interactions that Are Clinically Significant (*n*)	Percentage of Physician-identified, Computer-missed Interactions that Are Clinically Significant
Drug–drug	80	36	45%
Drug–ethanol	94	17	18%
Drug–lab	3	0	0%
All interactions	177	53	30%

predicting the lack of potential interaction when one does not exist. The Kendall's tau-b for patients with potential interactions was −0.043, indicating little difference of opinion between the "expert" physician and the EM faculty. However, the Kendall's tau-b for patients without potential drug interactions was −0.286, indicating that the "expert" physician differed in opinion from the EM faculty to a moderate degree. From the specificity analysis, it is clear that the "expert" physician was superior to the EM faculty, identifying the absence of a potential interaction when none existed (specificity 86% vs 58%). The two groups did not substantially agree with each other in patients with potential interactions, and both groups fell equally short of the computer (sensitivities of only 14% and 25%, respectively).

Table 9 outlines the proportion of potential interactions missed initially by one physician, but caught by the computer, which a second faculty member then judged to be clinically significant. Potential drug–lab interactions were rarely judged clinically significant because the laboratory test was ordered only twice in patients with a possible interaction. However, potential drug–lab interactions were identified by the computer 119 times, 40 of which (33.6%) were judged by a second faculty as clinically significant. Excluding potential drug–lab interactions then, the rate of clinically-significant potential drug–drug and drug–ethanol, computer-identified but physician-missed, interactions was 25% (25/102). Examples of these are: 1) aspirin and verapamil causing an increased risk of bleeding; 2) nitroglycerin and heparin causing a decreased anticoagulant effect; 3) gemfibrozil and glyburide causing hypoglycemia; 4) warfarin and ciprofloxacin causing an increased risk of bleeding; and 5) warfarin and ranitidine causing an increased risk of bleeding.

Table 10 describes the proportion of potential interactions identified by physicians, but missing from the computer database, which a second faculty member confirmed to be clinically significant. It is the converse of Table 9.

Table 11 summarizes the proportion of patients at risk for potential drug interactions, and categorizes the severity of these (note that these are patients, not numbers of interactions as reported above in the text).

The faculty identified potential drug–drug interactions that the computer missed. These omissions fell into several categories. Regarding oversedation, the computer frequently did not report potential interactions between two different opioids (n = 22), opioids and antiemetics (n = 11), two anticholinergic/antiemetic agents (n = 7), and benzodiazepines and either opioids (n = 3) or barbiturates (n = 1). These potential interactions were validated in a common medical text.[24]

The faculty did not find significant omissions with potential drug–disease interactions. However, they identified that the computer missed significant potential problems with ethanol. Its potential interactions with myriad other sedatives, including benzodiazepines, antidepressants, opioids, anticholinergics/antiemetics/antipsychotics (n = 27), were not contained in the database. Furthermore, ethanol's effect on the development or exacerbation of gastritis or peptic ulcers was similarly overlooked by the computer (n = 27). Potential interactions that cause or exacerbate gas-

TABLE 11. Proportion of Patients at Risk for Potential Drug Interactions, and Corresponding Severity

Potential Interaction	No (%) of Patients (n = 276)	No. (%) Minor	No (%) Moderate	No. (%) Major	Total No. (%) with Potential Interactions
Drug–drug	168 (60.9%)	6/168 (3.6%)	16/168 (9.5%)	7/168 (4.2%)	29/168 (17.3%)
Drug–disease	227 (82.2%)	3/227 (1.3%)	88/227 (38.8%)	18/227 (7.9%)	109/227 (48.0%)
Drug–ethanol	227 (82.2%)	n/a	n/a	n/a	119/227 (52.4%)*
Drug–lab	227 (82.2%)	n/a	n/a	n/a	87/227 (38.3%)†

*Micromedex reports potential drug–ethanol interactions for all patients, regardless of presence and quantity of ethanol use. Severity, therefore, is not relevant. Only 50 patients were recorded as alcohol users, and 29/50 (58%) of these had potential drug–alcohol interactions.

†Micromedex reports potential drug–lab interactions for all patients, regardless of whether the suspect laboratory test was ordered. In reality, only 5/87 (5.7%) patients had the suspect lab ordered.

trointestinal bleeding were omitted as well (n = 2).

DISCUSSION

Drugs can interact with one another through myriad mechanisms, including impaired or enhanced absorption, induction or inhibition of enzymes, changes in first-pass metabolism, protein binding displacement, effects on renal excretion, and direct and indirect receptor effects.[25] It is unrealistic to expect the EP to be familiar with all of these mechanisms, and the multitude of drugs that interact.[26] The actual harm done to patients by drug interactions is difficult to quantify, but probably small. Only three studies, all of hospitalized patients, have identified potential drug–drug interactions, and then performed chart review to assess clinical effect.[27–29] Potential interactions in these studies occurred in 7.7%, 4.7%, and 11.1% of patients, respectively, while the rates of actual interactions were 0.7%, 0.1%, and 1% (aggregate n = 8,626). To generalize, available evidence shows that 2.1% of potential interactions are clinically important by retrospective review by implicit clinical criteria.

The identification and severity of potential drug interactions from a database represent a judgment by the consultant to the software maker. In the Micromedex database, documentation for some listed interactions is "poor" and based on case reports or small retrospective case–control studies. As such, the computer may overstate the severity of interaction and gives no estimate of frequency. While some of the drug combinations listed in the tables are clinically used together, the interactions do exist on both a physiologic and clinical basis. For example, the verapamil–aspirin interaction causing increased bleeding is based on two case reports and a small study. Eighteen patients had impaired platelet aggregation with verapamil,[30] and three had significant hemorrhages and prolonged bleeding times when verapamil was added to a stable aspirin regimen.[31,32]

The physicians could not be blinded to the study hypothesis, because the study aim became evident when one physician assessed another's discrepancy with the computer. This could lead to bias by either judging "missed" interactions as clinically insignificant to protect one's colleagues, or affirming the interaction because of the computer's authority.

Three other studies have assessed the frequency of drug–drug interactions as a subset of all adverse drug reactions.[33–35] They found 2.7%, 6.5%, and 2.6%, respectively (aggregate n = 620), for a weighted average of 3.5%. Clearly, drug interactions are a small subset of all adverse drug events.

We know of no studies in the ED that have documented clinical harm due to drug interaction. A surrogate for this is whether an experienced physician would alter treatment based on knowledge gained from a computer. We found 32 potential drug interactions for 29 of the 168 patients who had at least two drugs (17%). The EM faculty identified only one-fourth of these potential interactions, and five of the 24 missed interactions (21%) were judged clinically significant. A similar study found potential drug interactions for 30% of ED patients (61/201), and reported changes in management for 25% (15/61) as well.[22]

In the study design, we assumed the computer program would be an appropriate criterion standard against which to measure the physicians. This assumption deserves scrutiny. We were surprised that the EM faculty identified 174 potential interactions that the computer missed (80 drug–drug, 94 drug–ethanol). A second physician validated the clinical importance of these interactions in 30% of cases (45% of drug–drug, 18% of drug–ethanol). Conversely, the computer generated 102 (24 drug–drug and 78 drug–ethanol) potential interactions of which the physician was unaware, and 25% of these were clinically significant. Therefore, it was more likely that the physician identified a clinically important potential interaction missing from the database, than the computer identified one that the physician missed. Clearly, computerized information is a useful adjunct to

physician knowledge and judgment, not a substitute. Though the computer is flawed as a criterion standard, absent a better one, it must serve this function at present.

In an evaluation of ED drug interactions in patients 65 aged years and older, Hancock et al.[20] found that 2.7% of the patients visiting an ED had drug interactions between their existing medications and those newly prescribed. Our study found a much higher rate (17%), but we assessed all potential interactions: among pre-existing drugs, those given in the ED, and discharge drugs.

It appears that computer programs used to alert physicians to potential interactions have varying capabilities. This is well documented in a series of software evaluations by Poirier and Giudici.[4,5,7–18] The most recent comparison found programs that identified all of ten important potential interactions, or as few as five of ten.[5]

In a similar study using a program called Drug Master Plus, Goldberg et al.[23] found an almost threefold higher incidence of potential drug–drug interactions (47% vs 17%) in a county and community hospital population. They also found a higher number of potential interactions per patient (2.5 vs. 1.1) than the current study. Conversely, the same study found less than half of the potential drug–disease interactions (21% vs 48%). While it is possible that differing physician expertise is responsible, the discrepancy is more likely due to inconsistent content of computer databases.

It is useful to examine the power of the study to discriminate between the EM faculty and the "expert" physician. We found no difference between groups in the ability to correctly identify potential drug–drug interactions for patients who had them (n = 29). We also found the EM faculty to have an accuracy of approximately 50%. If a clinically important improvement of the "expert" physician over the EM faculty is 30%, $\alpha = 0.05$ and $\beta = 0.80$, a sample size of 45 interactions would be required to demonstrate a statistically significant difference in performance. Therefore, in this subset of patients, the study has a high likelihood of type II error.

Limitations and Future Questions

Our drug–ethanol interaction analysis deserves comment. Since documentation of alcohol use on the ED chart was inconsistent, and a high percentage of general ED patients use alcohol, we instructed the EM faculty reviewing cases to assume all patients were drinkers. We did not confirm whether patients drank or abstained from drinking while taking medications that interact with alcohol. Therefore, our finding of 52% of patients with a potential drug–ethanol interaction is likely overstated. Advice against driving while taking sedating medicines is routine. Alcohol use should be similarly discouraged.

Reporting potential drug–lab interactions, as in Table 3, does not imply that the physician should forgo ordering the test. Nevertheless, the result must be interpreted with the knowledge that the value may be falsely increased.

We recognize that this study tested the knowledge of only one physician "expert," and his performance is not generalizable. Furthermore, our study design judged potential interactions merely qualitatively. We recognize that medication dose, alcohol levels, and disease severity would have significant impact on the magnitude of potential interactions. The judgment of potential drug interactions by physicians was subjective. Following computer identification of a potential interaction, a physician judged clinical significance. This was confirmed or refuted by a second physician, but disagreements between the two physicians were not adjudicated by a third. In addition, some drug combinations, while potentially harmful, are used clinically because of a positive benefit–risk ratio. Our study identified these combinations as potentially problematic, despite their clinical use.

Future research should focus on a prospective program, where real-time potential drug interactions are identified and corrected during the ED visit. This will require a user-friendly database with prescription writing capability, and automatic warnings for interactions, improper dose, or previously noted allergy. A web-based version is currently under commercial development, but not yet ready for widespread use.

Conclusions

With the immense formulary of FDA-approved drugs, it is beyond the scope of the EP to accurately identify all potentially harmful drug interactions. In this test of physician knowledge of potential drug interactions, all physicians fared poorly compared with the criterion standard computer database. Conversely, the computer database has significant omissions, and may not be an appropriate criterion standard. An "expert" EP was more specific but just as poorly sensitive as the general EM faculty for potential drug–drug and drug–ethanol interactions, indicating that further education is not likely to raise the level of physician knowledge to that of the computer. Potentially, up to 52% of patients have drug–ethanol interactions, while 38% of patients could have drug–lab interactions. A computer can aid the physician in avoiding potential interactions. Prospective validation should follow.

Statistical analysis was performed by Robert Newcombe, PhD, Department of Statistical Consulting, University of California, Irvine (compensated). The authors give special thanks to the EPs whose knowledge they tested.

References

1. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. JAMA. 1995; 274:29–34.
2. American Society of Hospital Pharmacy. 1992 draft guidelines on preventable medication errors. Am J Hosp Pharm. 1992; 49:640–8.
3. AMA Board of Trustees Report: Medication (Drug) Errors in Hospitals, April 1994, Chicago, IL, Resolution 512, I-93.
4. Poirier TI, Giudici RA. Evaluation of drug interaction microcomputer software: comparative study. Hosp Pharm. 1991; 26:30–3, 37.
5. Poirier TI, Giudici RA. Evaluation of drug interaction microcomputer software: an updated comparison. Hosp Pharm. 1995; 30:888–90, 893–4.
6. Jankel CA, Martin BC. Evaluation of six computerized drug interaction screening programs. Am J Hosp Pharm. 1992; 49: 1430–5.
7. Poirier TI, Giudici RA. Drug interaction microcomputer software evaluation: Drug Therapy Screening System (DTSS). Hosp Pharm. 1990; 25:738–41, 4.
8. Poirier TI, Giudici RA. Drug interaction microcomputer software evaluation: the medical letter drug interactions program. Hosp Pharm. 1990; 25:458–61.
9. Poirier TI, Giudici RA. Drug interaction microcomputer software evaluation: S-O-A-P. Hosp Pharm. 1990; 25:342–7.
10. Poirier TI, Giudici RA. Drug interaction microcomputer software evaluation: Rx/Triage. Hosp Pharm. 1990; 25:136–40.
11. Poirier TI, Giudici RA. Evaluation of drug interaction microcomputer software: Dambro's Drug Interactions. Hosp Pharm. 1990; 25:30–3, 72.
12. Poirier TI, Giudici RA. Drug interaction microcomputer software evaluation: Drug Master 89. Hosp Pharm. 1989; 24: 1003–6.
13. Poirier TI, Giudici RA. Drug interaction microcomputer software evaluation: Therapeutic Software's Adverse Interactions. Hosp Pharm. 1989; 24:936–40.
14. Poirier TI, Giudici RA. Evaluation of drug interaction microcomputer software: drug interactions III. Hosp Pharm. 1989; 24:522–6.
15. Poirier TI, Giudici RA. Evaluation of drug interaction microcomputer software: Medicom Micro Plus. Hosp Pharm. 1989; 24:273–7.
16. Poirier TI, Giudici RA. Evaluation of drug interaction microcomputer software: Part 1—Hansten Drug Interaction Knowledge Base Program. Hosp Pharm. 1988; 23:1062–5, 1070, 1079.
17. Poirier TI, Giudici RA. Evaluation of drug interaction microcomputer software: Part 2—Drug Interactions Advisor. Hosp Pharm. 1989; 24:125–8, 144.
18. Poirier TI, Giudici RA. Drug interaction microcomputer software: PDR's drug interactions and side effects diskettes. Hosp Pharm. 1990; 25:839–42, 851.
19. Goldberg RM, Mabee J, Mammone M, et al. A comparison of drug interaction software programs: applicability to the emergency department. Ann Emerg Med. 1994; 24:619–25.
20. Hancock D, Kennington JM, Beckner RR, Quick G. Emergency department medication and drug interaction evaluation. Hosp Pharm. 1992; 27:129–32.
21. Beers MH, Storrie M, Lee G. Potential adverse drug interactions in the emergency room: An issue in the quality of care. Ann Intern Med. 1990; 112:61–4.
22. Herr RD, Caravati EM, Tyler LS, Iorg E, Linscott MS. Prospective evaluation of adverse drug interactions in the emergency department. Ann Emerg Med. 1992; 21: 1331–6.
23. Goldberg RM, Mabee J, Chan L, Wong S. Drug–drug and drug–disease interactions in the ED: analysis of a high-risk population. Am J Emerg Med. 1996; 14:447–50.
24. Gilman AG, Rall TW, Nies AS, Taylor P. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed. New York: Pergamon Press, 1990, pp 362, 427, 428, 499.
25. McInnes GT, Brodie MJ. Drug interactions that matter: a critical reappraisal. Drugs. 1988; 36:83–110.
26. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. JAMA. 1997; 277:312–7.
27. Ford DR, Rivers NP, Wood GC. A computerized detection system for potentially significant adverse drug–drug interactions. J Am Pharm Assoc. 1997; 17:354–7.
28. Puckett WH Jr, Visconti JA. An epidemiological study of the clinical significance of drug–drug interactions in a private community hospital. Am J Hosp Pharm. 1971; 28:247–53.
29. Kwan TC, Wahba WW, Wildeman RA. Drug interactions: a retrospective study of its epidemiology, clinical significance and influence upon hospitalization. Can J Hosp Pharm. 1979; 32:12–6.
30. L-Lacoste L, Lam JY, Hung J, Waters D. Oral verapamil inhibits platelet thrombus formation in humans. Circulation. 1994; 89:630–4.
31. Verzino E, Kaplan B, Ashley JV, Burdette M. Verapamil–aspirin interaction. Ann Pharmacother. 1994; 28:536–7.
32. Ring ME, Martin GV, Fenster PE. Clinically significant anti-platelet effects of calcium channel blockers. J Clin Pharmacol. 1986; 26:719–720.
33. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA. 1995; 274:35–43.
34. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med. 1991; 324:377–84.
35. Bates DW, O'Neil AC, Boyle D, et al. Potential identifiability and preventability of adverse events using information systems. J Am Med Inform Assoc. 1994; 1:404–11.