Research Article   **Open Access**

Comparing Drug-Drug Interaction Severity for Clinician Opinion to Proprietary Databases

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Abstract/Summary

Purpose: Commercial clinical decision support software (CDSS) may overestimate the severity of drug-drug interactions (DDI) because of their broad application; whereas, clinicians with knowledge of the patient should be able to better assess DDI severity. The purpose of this project was to compare DDI severity for clinician opinion in the context of the patient's clinical status to the severity of proprietary databases.

Methods: This was a single-center, prospective evaluation of DDIs at a large, tertiary care academic medical center between October 11, 2010 and November 5, 2010 in a 10-bed cardiac intensive care unit (CCU). A pharmacist identified DDIs using two proprietary databases. The physicians (fellow and attending) and pharmacists (rounding and distribution) caring for the patients evaluated the DDIs for severity while incorporating their clinical knowledge of the patient. Severity was ranked on a scale ranging from A to D and X.

Results: A total of 61 patients were included in the evaluation and experienced 769 DDIs. The most common DDIs included: aspirin/clopidogrel (n=21, 2.7%), aspirin/insulin (n=21, 2.7%) and aspirin/furosemide (n=19, 2.5%). Pharmacists ranked the DDIs identically 73.8% of the time, compared to the physicians who agreed 42.2% of the time. Pharmacists agreed with the more severe proprietary database scores for 14.8% of DDIs versus physicians at 7.3%. Among the five contraindicated DDIs, two were rated as category B (minor severity/no action needed) and three as category C (moderate severity/monitor therapy) by the majority of the reviewers. Overall, clinicians agreed with the proprietary database 20.6% of the time while clinicians ranked the DDIs lower than the database 77.3% of the time.

Conclusions: Proprietary DDI databases generally label DDIs with a higher severity rating as compared to clinicians who are caring for patients. Developing a DDI knowledgebase for CDSS requires careful consideration of the source of the severity information and should include clinician input in order to create clinically meaningful alerts.

Introduction

Adverse drug events (ADEs) may occur due to medication errors (MEs), pharmacokinetic alterations, drug-drug interactions (DDIs) and drug-disease interactions, with research revealing that both the incidence and severity of ADEs are heightened in intensive care unit (ICU) patients [1,2]. An ADE is defined as an undesirable clinical manifestation that is consequent to and caused by the administration of medications, as well as events due to error [3]. Drug-drug interactions contribute to ADEs when the efficacy or toxicity of a medication is altered by the administration of another substance [4]. The concomitant administration of medications becomes problematic when the combination causes a reduction in the intended therapeutic effect or an increase in the expected toxicity profile of the medication(s) [4].

Automated clinical decision support systems (CDSS) within most computerized prescriber order entry (CPOE) programs have contributed to error reduction by prospectively identifying potential medication allergies, interactions or overdoses [5]. Automated alert systems may reduce the incidence of DDIs by 50% through an increase in the recognition of interacting drug pairs [6]. Notably, only 1 out of 15 interactions in a cardiac ICU is considered major or contraindicated by proprietary DDI databases [7]. CPOE related DDI alerts may be excessive and cause "alert fatigue."

Alert fatigue is defined as a desensitization of clinicians to the overwhelming number of DDI notifications that occur during medication order and verification and contributes to the override

of between 49 to 96% of alerts [5-6,8-12]. Only 11% of DDI alerts generated by CDSS are considered to be useful; however, 69% of useful alerts lead to a change in clinical management [13]. Clinical decision support systems must be further modified in an effort to improve the delivery of clinically relevant, useful information and decrease the number of unnecessary and invalid alerts.

Several methods to improve alerts have been suggested, such as refining alert specificity by linking alerts to clinically relevant patient parameters and customizing the system to include only a limited number of clinically important alerts [5,10,14-16]. Another method to develop alert systems is to tier these alerts based on the perceived

severity of the DDI [17]. The use of tiering systems has demonstrated a higher rate of compliance with DDI alerts; however, the optimal rationale for determining the severity of DDIs within tiering systems has not been fully elucidated. While these suggestions appear to logical, there is limited data testing their benefit, to our knowledge no evaluation of DDI severity has been completed in the presence of patient specific clinical data. The overarching goal of this quality improvement project is to improve the institution's DDI CDSS by identifying clinically relevant DDIs. The primary objective is to compare DDI severity based on clinician opinion and proprietary database determinations in the context of the patient's clinical status.

Methods

This was a single-center, prospective evaluation of potential DDIs at a large, tertiary care academic medical center. Data collection was conducted between October 11, 2010 and November 5, 2010 in a 10-bed cardiac intensive care unit (CCU). The protocol was approved by the institution's Quality Improvement Committee.

Each patient admitted to the CCU during the study period was assessed for potential DDIs. Patients' medication administration records were reviewed for all DDIs on the first day of the study for all patients and subsequent patient admissions were reviewed on the day of arrival to the CCU. After the initial medication record review, additional potential DDIs were identified daily when a new drug was ordered. All medications, including one-time orders and as needed orders, were assessed. Drug-drug interactions that occurred during the weekend and evening were evaluated by the participants on Monday and the following day, respectively. Patients were followed throughout their entire stay in the CCU.

A clinical pharmacist (MJA) generated patient-specific DDI reports using Micromedex © and LexiComp © drug interaction software and identified all potential DDIs involving medications that were currently prescribed to patients in the CCU [18,19]. Individual DDIs were assessed only once for each patient during the study period. The list of potential DDIs with the interaction mechanism was provided to the physicians (attending and fellow) caring for the patients, the clinical pharmacist rounding with the team (MJA) and a second non-rounding clinical pharmacist (AA) who was verifying the medication orders. A sample of this DDI report is included in Table 1. The clinical pharmacistshad both completed pharmacy residencies in pharmacy practice and critical care pharmacy, while the physicians were both cardiologists. The physicians and pharmacists were asked to rate the severity of each potential DDI while incorporating their clinical knowledge of the patient. The rating scale provided to the clinicians utilized rankings ranging from A to D and X and is detailed in Table 2 [18,19]. The severity scores for all potential DDIs assessed by multiple clinicians and those assigned to the DDIs by proprietary databases (Micromedex © and Lexicomp ©) were compared.

Results

A total of 61 patients were included in the evaluation and 769 potential DDIs were identified, of which 419 were unique DDIs (i.e.

DDI	Micromedex ©	Lexicomp ©
aspirin + clopidogrel	Concurrent use of CLOPIDOGREL and ASPIRIN may result in an increased risk of bleeding.	Antiplatelet Agents may enhance the adverse/ toxic effect of Salicylates. Increased risk of bleeding may result

Table 1: Drug-Drug Interaction Example.

Rating	Designation	Explanation	
X	Contraindicated	Avoid combination	The drugs are contraindicated for concurrent use
D	Major	Consider therapy modification	The interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse events
C	Moderate	Monitor therapy	The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy
B	Minor	No action needed	The interaction would have limited clinical effects. May include an increase in the frequency or severity of the side effects but generally would not require a major alteration in therapy.
A	Unknown	No known interaction	Unknown

Table 2: Drug-Drug Interaction Rating Scale[18,19]

	Micromedex ©	Lexicomp ©
A	6	0
B	81	43
C	524	243
D	73	148
X	4	1
Total	688	435

Table 3: Drug-Drug Interactions by Severity.

Drug-Drug Interaction	N	%	Micromedex ©	Lexicomp ©
aspirin + clopidogrel	21	2.7	B	C
aspirin + insulin	21	2.7	C	Not Identified
aspirin + furosemide	19	2.5	C	C
aspirin + heparin	19	2.5	D	C
aspirin + nitroglycerin	19	2.5	C	B
insulin + metoprolol	15	2.0	C	C
atorvastatin + clopidogrel	11	1.4	Not Identified	B
clopidogrel + heparin	10	1.3	D	C
clopidogrel + simvastatin	10	1.3	Not Identified	B

Table 4: Most Common Drug-Drug Interactions Identified.

occurred only once). Discrepancies between the proprietary databases were noted, with Lexicomp © identifying 688 DDIs and Micromedex © identifying 435 DDIs. Simultaneous identification of DDIs by both databases occurred for only 353 listed interactions. Among the interactions identified by the databases, discrepancies were noted in relation to the severity rating (Table 3). The most commonly database-identified DDIs included: aspirin and clopidogrel (n=21, 2.7%), aspirin and insulin (n=21, 2.7%) and aspirin and furosemide (n=19, 2.5%) (Table 4).

The number of potential DDIs evaluated by each clinician differed due to alternating times of direct patient care being provided by each clinician, with pharmacists 1 and 2 evaluating 769 potential DDIs, physician 1 evaluating 240 potential DDIs and physician 2 evaluating 575 potential DDIs. Both pharmacists evaluated all 769 potential DDIs while both physicians evaluated only 192 potential DDIs. Interaction severity agreement differed between the proprietary databases and evaluators (Figure 1), with Micromedex © and Lexicomp © agreeing for 39.4% of interactions, pharmacists agreeing for 73.8% of interactions and physicians agreeing for 42.2% of interactions. All evaluators agreed on the severity rating only 17.7% of the time, while pharmacists agreed with the Micromedex © and Lexicomp © database rating 8.5%

Figure 1: Drug-Drug Interaction Severity By All Sources.
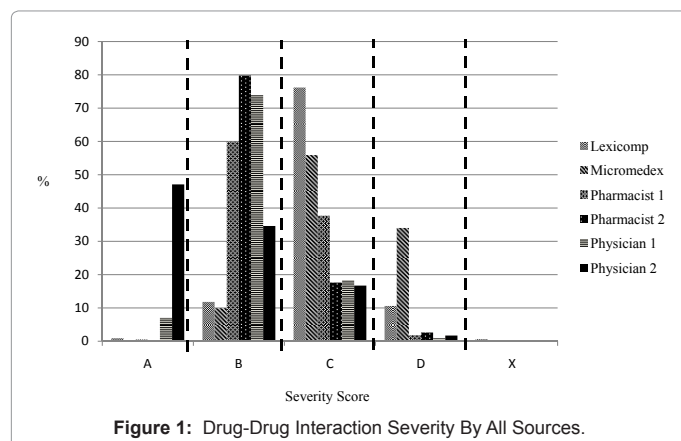
Evaluator(s)	N	%
Micromedex® and Lexicomp®	139/353	39.4
Pharmacists	568/769	73.8
Physicians	81/192	42.2
Pharmacists and Physicians	34/192	17.7
Pharmacists and Micromedex ©	37/435	8.5
Pharmacists and Lexicomp ©	167/688	24.3
Physicians and Micromedex ©	10/192	5.2
Physicians and Lexicomp ©	13/192	6.8
Pharmacists and More Severe Rating	115/769	14.8
Physicians and More Severe Rating	14/192	7.3

Table 5: Drug-Drug Interaction Agreement Between Evaluators.

More Severe Database Category	Clinicians Rated More Severe than Database	Agreement Between Clinicians and Database	Clinicians Rated Less Severe than Database	Total
A	8	7	0	15
B	25	151	8	184
C	16	299	1242	1557
D	0	27	554	581
X	0	0	16	16
Total DDIs assessed	49 (2.1%)	484 (20.6%)	1820 (77.3%)	2353

Table 6: Drug-Drug Interaction Severity Agreement.

and 24.3% of the time, respectively, while physicians agreed with the Micromedex © and Lexicomp © database rating 5.2% and 6.8% of the time, respectively. Also, the clinician evaluations were compared to the more severe database rating provided for each interaction. Pharmacists agreed with the more severe proprietary database rating for 14.8% of potential DDIs versus physicians at 7.3%. (Table 5)

Furthermore, an evaluation of DDI severity agreement was conducted as illustrated in Table 6. Clinicians agreed with the severity rating from the proprietary database 20.6% of the time while ranking the DDI less severe than the database 77.3% of the time and more severe than the database only 2.1% of the time.

Finally, an evaluation of contraindicated DDIs was conducted to determine their potential clinical relevance. A total of five (0.7%) contraindicated DDIs were discovered during the evaluation (Lexicomp ©: 4, Micromedex ©: 1). Among the five contraindicated DDIs, two were rated as category B (minor severity/no action needed) and three as category C (moderate severity/monitor therapy) by the majority of the evaluators, with the other interactions having discrepant evaluator ratings (Table 7).

Drug-Drug Interaction	Pharmacist 1	Pharmacist 2	Physician 1	Physician 2
atropine + potassium chloride	B	B	B	-
clopidogrel + fluoxetine	C	C	B	B
magnesium + sodium polystyrene sulfonate	B	B	B	-
metoclopramide + prochlorperazine	C	C	C	-
midazolam + olanzapine	C	C	B	-

Table 7: Clinician Severity Rating of Contraindicated Drug-Drug Interactions.

Discussion

Quite similar to ADEs, DDIs are complicated to evaluate, especially when attempting to decipher severity. The overall agreement between 4 healthcare professionals in our study was 17%, which is the same frequency of agreement for 5 healthcare professionals in their assessment of ADEs [20]. While previous comparisons of DDI severity between databases has been demonstrated and proprietary databases have been compared to clinician opinion, to our knowledge this has not been done in the context of knowledge for the patients' condition. [7,16,21,22]. A major finding in this study is noting that the severity of DDIs is consistently over interpreted by proprietary databases compared to healthcare professionals opinion in the context of the patient care data.

Our study showed that proprietary DDI databases often rate DDIs as a higher severity than clinicians at the bedside who are caring for the patients. This may be due, in part, to the clinician's understanding of the patient's medical problems and the necessity to treat patients with a specific drug combination while monitoring for ADRs caused by that therapy, whereas the databases are simply reporting all DDIs that may occur. However, this does bring up an interesting question: Should proprietary DDI database rankings be modified or is it important that these warnings are given to providers in order to promote safe medication use? Our study also identified several contraindicated DDIs amongst patients. None of these contraindications seemed clinically relevant, based on the administration route in use and the ADRs associated with their concomitant use. However, it is important that all contraindicated DDIs be reported, with the responsibility falling upon the clinicians to make a risk vs. benefit assessment of the situation.

Similar ratings between the pharmacist reviewers and physician reviewers were noted in this study. This is most likely explained by the differing levels of exposure and training received by each provider group. At our institution, all DDI alerts are reported to pharmacists at the time of order entry, whereas physicians only see a small number of DDI alerts. Additionally, many pharmacists receive training regarding DDIs during formal education, which may contribute to an increased familiarity. The background of the pharmacists involved in this study may have contributed to their ranking of the DDIs, in that their previous training made them more aware of DDIs and their impact on patients. Additionally, the cardiologists involved in this study have an extensive knowledge of medications typically used in the CCU and understand the DDIs that can and do occur in their patients.

In this prospective evaluation, the most commonly identified DDIs were typical based on the patient population studied. It is no surprise that interactions involving aspirin, clopidogrel, insulin and furosemide were most commonly identified, as these medications are administered to almost every patient treated in the CCU. Approximately 12 DDIs were identified per patient during the CCU stay. Drug-drug

interactions have been associated with an increase in patient morbidity and mortality [23]. Mouraand colleagues found that the median ICU length of stay (LOS) among patients with at least one DDI was significantly longer than patients not experiencing DDIs (12 days vs. 5 days), while Reis and colleagues showed that 7% of ADEs corresponded to DDIs amongst a cohort of patients treated in an intensive care unit [24,25]. The ramifications of unresolved DDIs can be far reaching, especially amongst critically ill patients. On the contrary, some DDIs must be tolerated due to the risk-benefit assessment associated with the treatment in question (i.e. bleeding risk vs. in-stent thrombosis risk associated with concomitant aspirin and clopidogrel in patients post-stent) therefore limiting the DDI significance.

Development of a DDI knowledgebase requires careful consideration of the source of the severity information to avoid excessive alerts and create clinically meaningful alerts. DDI systems provide evidence behind most of their alerts but clinicians must be aware that some alerts are based on theoretical interactions that utilize known CYP enzyme system inhibitors, inducers and substrates to determine potential DDIs. Many of these DDIs do not have clinically-relevant case reports to substantiate the hypothetical interaction [26].

Drug-drug interaction knowledgebase development should consider patient-specific information, such as patient demographics, risk factors for the development of DDIs, laboratory values, radiology reports, electrocardiogram information and hemodynamic values. These systems should also be tailored based on the clinician and patient care environment. Physician and pharmacist alerts should differ to help provide the most clinically relevant information to each provider. Additionally, alerts could be tailored based on patients being treated in the ICU and non-ICU patient care areas. The legal ramifications of these differences must be explored to determine the most appropriate manner in which to report differing information.

Limitations

This setting of this product was an academic medical center, and therefore the results may not be generalizable to community hospitals. The patient population was limited to those being treated in the CCU, where specific medications are commonly used that may not be used in all ICUs, limiting the validity of this study in other environments. A differing number of alerts were assessed by each evaluator, due to the time spent in the patient care service. This could have contributed to the differing rankings of each evaluator. Only two drug databases were used in the study, although these are the two most commonly used alert systems in our institution.

Conclusion

Knowledgebase development for CDSS should be structured to limit alert fatigue and optimize patient outcomes. This project demonstrates that in the context of patient care knowledge with the ability to assess risk-benefit for drug therapy the severity of DDIs ranked by clinicians is frequently less severe than proprietary databases. It may be best to develop a DDI knowledgebase for CDSS with clinician input and adjust alerting systems for specific patient populations.

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