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Drug-Drug Interactions in Cardiac and Cardiothoracic Intensive Care Units

An Analysis of Patients in an Academic Medical Centre in the US

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Abstract

Background: Mortality and morbidity are increased in patients experiencing drug-drug interactions. Unfortunately, there is a paucity of literature describing clinically significant drug-drug interactions occurring in the intensive care unit (ICU). Knowing the clinically significant drug-drug interactions allows the opportunity for prevention through knowledge and computer-assisted programmes.

Objective: To identify significant potential drug-drug interactions occurring in the cardiovascular ICU (CCU) and the cardiothoracic ICU (CTICU).

Study Design: Prospective, observational study conducted over a total of 8 weeks in February and March 2009.

Setting: CCU and CTICU in a major academic medical centre (Presbyterian Hospital, University of Pittsburgh Medical Centre).

Patients: All adult patients (≥18 years of age) admitted during 1 month in each ICU.

Intervention: Micromedex® and Lexi-Interact™ interaction databases were used to screen each patient's medication profile daily for the presence of potentially interacting drug pairs that would be considered a potential drug-drug interaction. A severity assessment using these databases was completed after a potential drug-drug interaction was identified.

Primary Outcome Measure: The frequency of significant drug-drug interactions, including those that were considered major or contraindicated, according to two commercially available interaction databases.

Results: Evaluations of 400 patient medication profiles were conducted, resulting in 225 profiles possessing one or more potential drug-drug interactions. A total of 1150 potential interactions were identified, resulting in 287.5 potential interactions per 100 patient-days. Of the 1150 potential drug-drug interactions,

458 were unique interacting drug pairs; 5–9% of the potential interactions were considered major or contraindicated. Many of the significant and frequent potential interactions involved blood coagulation modifiers, potential interactions that could result in QTc prolongation, and cytochrome P450 inhibition. Micromedex® and Lexi-Interact™ agreed on the severity ratings in 20.5% of the potential interactions.

Conclusions: Significant potential drug-drug interactions occur in the CCU and CTICU, highlighting the need for active surveillance to potentially prevent patient harm. Clinicians should also consider using two references for identifying interactions, due to the lack of congruence between sources.

Background

The Institute of Medicine's report "To Err is Human, Building a Safer Health System," has heightened the awareness of preventable medical errors.[1] Drug-drug interactions, a subclass of preventable medical errors, are particularly concerning because they are associated with an increase in patient morbidity and mortality.[2] The addition of computerized physician order entry (CPOE) to the medication order process is an opportunity to reduce medication errors and improve safety.[3] Clinical decision-support software, a component of CPOE systems, offers physicians guidance on dosing, formulary decision support, duplicate therapy, drug-allergy interactions and drug-drug interactions.[4] Specifically, computerized drug-drug interaction surveillance systems may assist in detecting and preventing clinically significant drug-drug interactions.[5]

Computerized drug-drug interaction surveillance systems yield a large number of false-positive alerts. Clinically insignificant alerts can lead to alert fatigue. For example, a clinician receives many insignificant alerts and then does not take preventive action when a clinically significant alert occurs due to oversight from alert volume.[6,7] Also, the interpretation of drug-drug interaction alerts, without clear clinical relevance of the interaction, may lead to differences in the perception of the interaction's seriousness and lack of necessary interventions.[8] Research has shown that a small number of alerts require intervention, and insignificant alerts should be suppressed to prevent alert fatigue.[9] It has also been demonstrated that categorizing drug-drug interaction alerts by severity in the computerized surveillance system increases compliance with clinical recommendations by 66%.[10]

Recently, an assessment of drug-drug interactions in an inpatient setting was conducted. This investigation differentiated between the clinically significant drug-drug interactions and those that contribute to alert fatigue.[11] This study was limited to drug-drug interactions in general care units. Different drug-drug interactions would be expected in the intensive care unit (ICU) because more medications are prescribed, medications are different from those in general care units, patients' physiological characteristics vary and vulnerability may be heightened. There have been review articles describing drug-drug interactions in the ICU, but there have been no prospective evaluations of clinically significant drug-drug interactions occurring in practice in critically ill patients.[12-15]

The ICU is reported to have the highest incidence of adverse drug events (ADEs) among hospital patient care units. The increased severity and frequency of ADEs due to culprit drugs has been demonstrated between the ICU and non-ICU environments.[16,17] We propose that there may also be differences between ICUs because practices and drug use varies by setting. The primary objective of this study was to identify significant potential drug-drug interactions that occur in the cardiovascular ICU (CCU) and the cardiothoracic ICU (CTICU), and to compare frequent and significant interactions between units. We hope to highlight potential interactions that are clinically relevant so that clinicians may consider

implementing preventative actions when faced with one of the significant interactions, thereby promoting safe medication use. The goal is to provide institutions developing computerized drug-drug interaction surveillance software with a foundation to use for the knowledge base of an alert system. The secondary objective of the study was to compare the severity ratings of potential drug-drug interactions in two commonly used patient care drug resources: the Micromedex® and Lexi-Interact™ interaction databases.[18,19]

Methods

This prospective study was approved by the University of Pittsburgh Institutional Review Board and was conducted over a 2-month time period (February and March 2009) at a tertiary care, university-based academic hospital (Presbyterian Hospital, University of Pittsburgh Medical Centre). Our institution has a drug-drug interaction surveillance system that alerts the centralized pharmacist at the prescription verification stage of order processing. This system does not filter any of the alerts, so that the pharmacist verifying the order receives alerts for minor to contraindicated potential interactions. The physician does not receive any drug-drug interaction alerts.

The clinical pharmacist (PLS), a member of the primary medical service caring for patients in the CCU and the CTICU, evaluated the potential drug-drug interactions that occurred during a 1-month time period in each of the two ICUs. The CCU contains ten beds and the CTICU contains 20 beds; ten of these beds are acute care and were included in this study. Patients were included if they were adults (≥18 years of age) and were cared for in one of the ICUs under observation during that particular month by the clinical pharmacist.

Drug Interaction Evaluation

Each patient's electronic medication list and medication orders in the chart were evaluated daily Monday through Friday during the study period. Additional medications that were added over the weekend were included in the analysis that occurred on Monday. Micromedex® and Lexi-Interact™ interaction databases were used to provide an objective and consistent assessment of the presence and clinical significance of potential drug-drug interactions.[18,19] This was accomplished by screening each patient's medication profile daily. When a potential drug-drug interaction was identified by at least one of the databases, the interacting drugs, doses, routes of administration and the database severity rating were recorded. The patient's sex and age were also recorded.

In compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996, patient-identifying information was not collected. On day one of the study, and when a new patient was initially admitted to the ICU, their entire active medication list was screened and all identified potential drug-drug interactions were recorded. Each subsequent day was considered a new patient encounter, and newly added medications from the previous 24 hours were screened against the remainder of the patient's medication profile for potential drug-drug interactions. Throughout the manuscript, 'evaluation' refers to each day that a patient's medication profile was screened for a potential drug-drug interaction. Ethical and professional obligation requires that the intensivist-led, primary care team is notified by the clinical pharmacist of potential drug-drug interactions that are considered to be clinically significant by the drug-drug interaction databases. The patient care team then took appropriate action.

Data Analysis

After a potential drug-drug interaction was identified, a severity assessment was conducted through the use of the Micromedex® and Lexi-Interact™ interaction databases. Patient identifiers were not collected, so the mean age and sex of the patients in the study were determined by assuming that each evaluation with the same sex and age paired together was the same patient. This assumption provides an estimate of the mean age and sex of the patients included in the study. Descriptive statistics were performed on the collected data to enable the development of a list of the most frequently occurring and clinically

significant potential drug-drug interactions. The results of the Micromedex® and Lexi-Interact™ interaction databases were assessed for agreement of severity ratings, and the number of potential drug-drug interactions identified by each interaction database was compared.

Results

Upon completion of the data collection for the two units, 400 evaluations of patient medication profiles were conducted, with 200 evaluations in each unit. Of these 400 evaluations, 225 evaluations revealed one or more potential drug-drug interactions: 116 in the CTICU and 109 in the CCU. Assessment of the patient demographics in the evaluations that revealed a potential drug-drug interaction indicated the mean age to be 62 ± 15.7 years and that 57.3% were male. Overall, 1150 total potential drug-drug interactions occurred, with each unit recording 575 potential interactions. This resulted in 287.5 potential drug-drug interactions per 100 patient-days. Of the 1150 potential drug-drug interactions, 458 were unique drug pairs, with 296 unique drug pairs in the CCU and 213 in the CTICU. The most common potential drug-drug interactions, identified through at least one of the databases, included ten interacting drug pairs, which accounted for 22.5% (259/1150) of the potential interactions. These interacting drug pairs are reported in table I, along with the most frequently occurring potential drug-drug interactions for each unit. Out of all the potential drug-drug interactions identified, anticoagulants and antiplatelet agents were involved in 32.3% (186/575) of the potential interactions in the CCU, and 26.3% (151/575) of those in the CTICU.

The most clinically significant potential drug-drug interactions based on the database severity assessments are listed in table II. Potential interactions were included in this table if evaluation through Micromedex® and Lexi-Interact™ indicated the potential interaction to be contraindicated or major. The CCU showed 4.7% (14/296) and the CTICU 8.9% (19/213) interacting drug pairs that were considered major drug interactions or contraindicated drug combinations.

Upon evaluation of the congruence of severity ratings between Micromedex® and Lexi-Interact™, of the 458 unique potential drug-drug interaction pairs identified, both databases agreed on the severity rating in only 20.5% (94) of the potential interactions. Upon assessing the total number of unique potential drug-drug interaction pairs identified by each database, Micromedex® identified 50.4% (231/458) and Lexi-Interact™ 86.9% (398/458) of the potential interactions. Of the 65 potential interactions that Lexi-Interact™ identified as contraindicated or major, Micromedex® did not identify 16. Of the 97 potential interactions that Micromedex® identified as contraindicated or major, Lexi-Interact™ did not identify 13. The differences between the severity assessments of the identified potential drug-drug interactions from Micromedex® and Lexi-Interact™ interaction databases are displayed and compared in table III.

Discussion

Potential drug-drug interactions are frequent in the cardiac ICUs, occurring at a rate of 287.5 per 100 patient-days. This substantial number of alerts could cause alert fatigue. Approximately one of 15 potential drug-drug interactions were considered major or contraindicated despite a drug-drug interaction alerting system occurring during the order verification process by the centralized pharmacist. The clinical significance of a drug-drug interaction is difficult to assess without patient-specific information. In the clinical practice setting, practitioners have access to patient data and are aware of the risk versus benefit of continuing the two interacting medications. Therefore, it would be useful if the prescriber receives the alert so that significance is accurately assessed. Another prevention mechanism could be to have a pharmacist working with the patient care team aiding with the order verification process, since they have additional insight into the patient's conditions compared with the centralized pharmacist.

The documentation and tracking of ICU-specific ADEs rarely occurs, which prevents institutions from determining the number of ADEs in the ICU.[20] Most institutions rely on voluntary reporting of ADEs for surveillance, which results in

Table I. The ten most frequently occurring drug-drug interactions (DDIs) in the cardiovascular intensive care unit (CCU) and cardiothoracic intensive care unit (CTICU)

Drug-drug interaction	n (%)	DDI description
Total DDIs (both units) [n = 1150]		
Aspirin [acetylsalicylic acid]/insulin	49 (4.26)	Aspirin may increase the hypoglycaemic effect of insulin
Aspirin/heparin	43 (3.74)	Aspirin may enhance the anticoagulant effects of heparin
Aspirin/clopidogrel	35 (3.04)	Clopidogrel may enhance the adverse/toxic effects of the salicylates; increased risk of bleeding may result
Bisacodyl/famotidine	32 (2.78)	Use of famotidine with bisacodyl may decrease the effectiveness of bisacodyl
Aspirin/furosemide	20 (1.74)	Salicylates may diminish the effects of loop diuretics
Clopidogrel/heparin	20 (1.74)	Antiplatelet agents may enhance the anticoagulant effect of anticoagulants
Insulin/metoprolol	18 (1.57)	β-Adrenergic receptor antagonists ('β-blockers') may enhance the hypoglycaemic effects of insulin
Aspirin/calcium chloride	16 (1.40)	Concomitant use of calcium may diminish the effectiveness of the aspirin
Atorvastatin/clopidogrel	13 (1.13)	Atorvastatin may diminish the antiplatelet effect of clopidogrel
Metronidazole/tacrolimus	13 (1.13)	Metronidazole may decrease the metabolism of calcineurin inhibitors
CCU DDI [n = 575]		
Aspirin/heparin	30 (5.22)	Aspirin may enhance the anticoagulant effects of heparin
Aspirin/clopidogrel	18 (3.13)	Clopidogrel may enhance the adverse/toxic effects of the salicylates; increased risk of bleeding may result
Aspirin/insulin	17 (3.00)	Aspirin may increase the hypoglycaemic effect of insulin
Clopidogrel/heparin	14 (2.43)	Antiplatelet agents may enhance the anticoagulant effect of anticoagulants
Atorvastatin/pantoprazole	10 (1.74)	Proton pump inhibitors may increase the serum concentrations of HMG-CoA reductase inhibitors ('statins')
Atorvastatin/clopidogrel	10 (1.91)	Atorvastatin may diminish the antiplatelet effect of clopidogrel
Aspirin/furosemide	9 (1.57)	Salicylates may diminish the effects of loop diuretics
Insulin/metoprolol	9 (1.57)	β-Blockers may enhance the hypoglycaemic effects of insulin
Clopidogrel/pantoprazole	8 (1.39)	Proton pump inhibitors may diminish the effect of clopidogrel
Aspirin/lisinopril	7 (1.22)	Salicylates may diminish the antihypertensive effects of ACE inhibitors
Aspirin/nitroglycerin	7 (1.22)	Use of aspirin with nitroglycerin may result in an increase of nitroglycerin concentrations; may result in additive platelet function depression
CTICU DDI [n = 575]		
Aspirin/insulin	32 (5.56)	Aspirin may increase the hypoglycaemic effect of insulin
Bisacodyl/famotidine	32 (5.56)	Use of famotidine with bisacodyl may decrease the effectiveness of bisacodyl
Bisacodyl/calcium chloride	23 (4.00)	Use of calcium with bisacodyl may decrease the effectiveness of bisacodyl
Aspirin/clopidogrel	17 (3.00)	Clopidogrel may enhance the adverse/toxic effects of the salicylates; increased risk of bleeding may result
Aspirin/calcium chloride	16 (2.78)	Concomitant use of calcium may diminish the effectiveness of the aspirin
Aspirin/heparin	13 (2.26)	Aspirin may enhance the anticoagulant effects of heparin
Metronidazole/tacrolimus	13 (2.26)	CYP3A4 inhibitors (metronidazole) may decrease the metabolism of calcineurin inhibitors
Aspirin/furosemide	11 (1.91)	Salicylates may diminish the effects of loop diuretics
Fentanyl/metronidazole	10 (1.74)	CYP3A4 inhibitors (metronidazole) may increase the serum concentration of fentanyl
Insulin/metoprolol	9 (1.57)	β-Blockers may enhance the hypoglycaemic effects of insulin

CYP = cytochrome P450.

substantial underreporting.[21] With adverse drug-drug interactions being a subset of ADEs, underreporting may misrepresent the occurrence of these events. This study prospectively evaluates the presence of potential drug-drug interactions in the vulnerable ICU population and may be

Table II. Most clinically significant drug-drug interactions based on database ratings[a]

Interacting drug pairs	Frequency[b]	Mechanism of drug-drug interaction
CCU		
Amiodarone/ranolazine	1	CYP3A4 inhibitors (e.g. amiodarone) may increase the serum concentration of ranolazine
Atazanavir/simvastatin	1	CYP3A4-inhibitor protease inhibitors (e.g. atazanavir) may increase the serum concentration of HMG-CoA reductase inhibitors ('statins')
Linezolid/noradrenaline (norepinephrine)	1	Monoamine-oxidase inhibitors may enhance the vasopressor effect of α/β-adrenergic receptor agonists
Amiodarone/azithromycin	1	Azithromycin may enhance the QTc prolonging effects of amiodarone
Amiodarone/moxifloxacin	1	Moxifloxacin may enhance the QTc prolonging effects of amiodarone; effects may be additive
Amiodarone/ciprofloxacin	1	Ciprofloxacin may enhance the QTc prolonging effects of amiodarone
Aspirin [acetylsalicylic acid]/citalopram	3	Selective serotonin reuptake inhibitors may enhance the antiplatelet effect of aspirin
Aspirin/duloxetine	2	Serotonin/noradrenaline reuptake inhibitors may enhance the antiplatelet effect of aspirin
Aspirin/heparin	30	Aspirin may enhance the anticoagulant effects of heparin
Aspirin/ketorolac	1	NSAIDs may enhance the adverse/toxic effects of the salicylates; increased risk of bleeding may result
Aspirin/warfarin	3	Salicylates may enhance the anticoagulant effects of vitamin K antagonists
Atazanavir/tenofovir	1	Tenofovir may decrease the serum concentration of atazanavir; atazanavir may increase the serum concentration of tenofovir
Atorvastatin/diltiazem	1	Diltiazem (CYP3A4 inhibitor) may decrease the metabolism of statins
Carvedilol/clonidine	1	β-Adrenergic receptor antagonists ('β-blockers') may enhance the rebound hypertensive effect of α_2-agonists
Clonidine/metoprolol	1	β-Blockers may enhance the rebound hypertensive effect of α_2-agonists
Colchicine/metoprolol	1	β-Blockers may enhance the rebound hypertensive effect of α_2-agonists
Colchicine/pravastatin	1	Colchicine may enhance the myopathic (rhabdomyolysis) effect of statins and may increase the serum concentrations
Fluconazole/fluoxetine	2	QTc-prolonging agents may enhance the effects of other QTc-prolonging agents; CYP2C9 inhibitors (fluconazole) may decrease the metabolism of CYP2C9 substrates (fluoxetine)
Ritonovir/simvastatin	1	CYP3A4 inhibitor (ritonavir) protease inhibitors may increase the serum concentration of statins
CTICU		
Linezolid/sertraline	1	Monoamine-oxidase inhibitors (linezolid) may enhance the serotonergic effect of selective serotonin reuptake inhibitors; may lead to serotonin syndrome
Atropine/potassium chloride	1	Anticholinergic agents may increase the ulcerogenic potential of potassium chloride
Adrenaline (epinephrine)/linezolid	2	Monoamine-oxidase inhibitors may enhance the vasopressor effect of α/β-agonists
Linezolid/noradrenaline	1	Monoamine-oxidase inhibitors may enhance the vasopressor effect of α/β-agonists
Amiodarone/azithromycin	2	Azithromycin may enhance the QTc-prolonging effects of amiodarone
Amiodarone/fentanyl	3	CYP3A4 inhibitors (amiodarone) may increase the serum concentration of fentanyl
Amiodarone/fluconazole	1	Fluconazole may enhance the QTc-prolonging effects of amiodarone; effects may be additive
Aspirin/escitalopram	1	Selective serotonin reuptake inhibitors may enhance the antiplatelet effect of aspirin
Aspirin/heparin	13	Aspirin may enhance the anticoagulant effects of heparin
Aspirin/warfarin	1	Salicylates may enhance the anticoagulant effects of vitamin K antagonists
Ciprofloxacin/sotalol	1	Ciprofloxacin may increase the QTc-prolonging effects of sotalol
Clonidine/labetalol	1	β-Blockers may enhance the rebound hypertensive effect of α_2-agonists
Clopidogrel/lansoprazole	1	Proton pump inhibitors may diminish the effect of clopidogrel

Continued next page

Table II. Contd

Interacting drug pairs	Frequency[b]	Mechanism of drug-drug interaction
Clopidogrel/pantoprazole	3	Proton pump inhibitors may diminish the effect of clopidogrel
Dopamine/phenytoin	1	Dopamine may enhance the hypotensive effect of phenytoin
Fentanyl/fluconazole	3	CYP3A4 inhibitors (fluconazole) may enhance the effects of fentanyl
Hydrocortisone/warfarin	1	Corticosteroids may enhance the anticoagulant effect of warfarin
Prednisone/warfarin	1	Corticosteroids may enhance the anticoagulant effect of warfarin
Sotalol/voriconazole	2	QTc-prolonging agents may enhance the effects of other QTc-prolonging agents

a Drug-drug interactions must be considered major or contraindicated in Micromedex® or Lexi-Interact™ to be included in this table.

b Number of occurrences during 4-week observation.

CCU = cardiovascular intensive care unit; **CTICU** = cardiothoracic intensive care unit; **CYP** = cytochrome P450.

useful as a benchmark for the identification and tracking of ICU-specific drug-drug interactions.

Many of the significant potential drug-drug interactions shared one of three common mechanistic categorizations including (i) potential interactions affecting cardiac electrical conductance producing an additive QTc prolonging effect; (ii) potential interactions enhancing antiplatelet or anticoagulant effects; and (iii) potential interactions involving the cytochrome P450 (CYP) enzyme system, specifically CYP3A4 inhibitors. The antiplatelet and anticoagulant potential interactions are of particular concern because several of these were also identified as frequently occurring interactions. In the CCU and CTICU, 32.3% and 26.3%, respectively, had one or more antiplatelet or anticoagulant medications as potentially interacting drugs.

Potential drug-drug interactions are frequent in the cardiac ICUs, with anticoagulants and antiplatelet drugs being the most common interacting drug groups. Patients in the CCU and CTICU are at a higher risk for bleeding due to the nature of their condition and the anticoagulation therapy required during or after the procedures these patients undergo.[22,23] Extensive bleeding can occur following cardiac bypass surgery, and has been shown to increase morbidity and mortality.[24,25] Furthermore, ICU patients, in general, have a predisposition to gastrointestinal bleeding, which occurs at a rate of 15–50%.[26] The potential drug-drug interactions identified in this study include commonly used anticoagulant therapies that may be necessary in patient care; however, these drug combinations further increase the risk of bleeding in cardiac ICU patients. A heightened awareness of these drug-drug interactions, and a patient-specific assessment of bleeding risk, would assist the clinician in proactive decisions concerning whether to continue administration of the interacting drugs, choose alternative agents or reduce the dosage of the anticoagulants. This is an integral component of an improved medication safety system.

The use of a computerized drug interaction surveillance system may be a helpful tool to identify and prevent drug interactions of clinical significance.[3] However, a common problem with these systems is that they identify a large number of drug-drug interactions with unclear clinical significance or irrelevance, which can lead clinicians to alert fatigue.[27] In this instance, the regularly occurring false alarms may prompt clinicians to ignore all of the alerts, which could result in the overriding of a lethal drug-drug interaction warning.[28] Many interactions in this study required no clinical action, such as the interaction of bisacodyl with famotidine. A recent study demonstrated that categorizing drug-drug interaction alerts by severity increases acceptance of clinical recommendations not to prescribe the drugs simultaneously.[10] This highlights the importance of our study in elucidating the most significant alerts, not necessarily the most common alerts, in providing data for developing a clinical drug interaction surveillance system.

The Institute for Safe Medication Practices (ISMP) is a non-profit organization that devotes its activities to the prevention of medication errors and the promotion of safe medication use.[29]

Table III. Database severity rating congruence[a]

Micromedex® and severity assessment	Lexi-Interact™ severity assessment	Number of interactions (n = 458)
Contraindicated	Contraindicated	1
Contraindicated	Major	5
Contraindicated	Moderate	0
Contraindicated	**No reaction reported**	**2**
Major	Major	28
Major	Moderate	47
Major	**No reaction reported**	**11**
Moderate	Major	15
Moderate	Moderate	64
Moderate	Minor	4
Moderate	No reaction reported	40
Minor	Moderate	6
Minor	Minor	1
Minor	No reaction reported	7
No reaction reported	**Major**	**16**
No reaction reported	Moderate	200
No reaction reported	Minor	11

a Bold text denotes interactions that were considered major or contraindicated by one database, but were not reported as an interaction in the other database.

This organization has developed a list of medications that are considered 'high-alert'. These drugs are considered to lead to a greater risk of injury when misused. The ISMP considers several of the medications that we identified as frequently occurring drug-drug interactions in their 'high-alert' medication list; specifically, the interactions involving heparin, insulin and metoprolol. These 'high-alert' medications were involved in four of the six most frequently occurring potential drug-drug interactions identified in this study. The importance of patient monitoring needs to be stressed to prevent the development of an ADE.

Micromedex® and Lexi-Interact™ interaction databases were both used to identify and provide consistent and objective analysis of potential drug-drug interactions. These two databases were chosen because they are readily accessible and highly used by practitioners. Upon comparison of the identified potential interactions and the assigned severity rating from each database, the results depicted a lack of congruence. The observation that of the 65 interactions that Lexi-Interact™ considered contraindicated or major, Micromedex® did not identify 16, and that of the 97 potential interactions that Micromedex® considered contraindicated or major, Lexi-Interact™ did not identify 13 is of concern. This is because if a clinician used just one database to screen for drug-drug interactions, there is the possibility that a contraindicated or major interaction would not be identified. The variation we identified between Micromedex® and Lexi-Interact™ was similar to the previously published studies evaluating other interaction databases.[30,31] The assessment of drug-drug interactions in patient care should include consulting more than one reference in order to not miss a potentially significant alert.

Limitations

One limitation of our study is that, to ensure confidentiality, patient identifiers were not collected. Therefore, the mean age and sex calculated may be slightly different from that reported if patient identifiers were able to be collected. The setting of this study, a large university hospital, with its diverse patient population, lends itself to generalization to other cardiac ICUs having a similar drug-drug interaction surveillance system

in place (only centralized, dispensing pharmacists receive alerts), but not to other types of ICUs and community hospitals. Institutions that have no drug-drug interaction surveillance system activated may have more potential drug-drug interactions prescribed; conversely, institutions with a system that filters alerts based upon severity would have fewer.

Another possible limitation would be that a centralized pharmacist would intervene upon an interaction before it was evaluated. To assure that these drug-drug interactions were captured, a review of all verbal and written medication orders for the previous 24 hours was carried out. A review also occurred daily of a log of pharmacy interventions, where centralized pharmacists document when they intervene upon an ADE, including drug-drug interactions.

In compliance with HIPAA and the University of Pittsburgh Institutional Review Board, patient-identifying information was not collected and, therefore, patients could not be followed over time. This prevented the collection and assessment of patient outcomes. Although no outcomes were collected, one could speculate that the critically ill patient is at a greater risk for severe drug-drug interactions – due to their changing organ function, altered drug disposition and altered protein binding – that might result in outcomes that could complicate a patient's care.[15] One study demonstrated that most drug-related events that led to death occurred in patients who were seriously ill and were receiving high-risk medications.[31]

Conclusions

The identification and prevention of potential drug-drug interactions is an important aspect of patient care in the ICU. We identified major and contraindicated potential drug-drug interactions occurring in cardiac ICU patients. For those institutions that do not have computerized drug interaction surveillance systems, more aggressive monitoring may be needed to prevent patient harm. Hospitals that have a computerized drug-drug interaction surveillance system that does not filter interactions based on severity should also consider modifications to avoid alert fatigue and the possibility of overlooking clinically significant alerts. Implementation of a computerized drug-drug interaction surveillance system, based on interaction severity, could use the data described in this study as a foundation to develop a knowledge base. Because of the disagreement in the severity ratings of the potential drug-drug interactions by the two utilized interaction databases, we strongly recommend that clinicians should consider using two resources to screen for potential drug-drug interactions in patients' medication regimens and when using interaction databases to develop the knowledge base for decision support software.

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