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Potential Drug-Drug Interactions in Critically Ill Medical Patients: A Cross-Sectional Study

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ABSTRACT

Background: Drug-drug interactions (DDIs) commonly occurred in critically ill patients and may increase hospital lengths of stay and total cost. The aim of the present study is to evaluate frequency and levels of potential DDIs in critically ill medical patients.

Methods: In this cross-sectional study, medical records of critically ill patients admitted to the 16-bed intensive-care units of a teaching hospital were assessed according to the Micromedex® drug interaction and drug interaction fact®. The identified DDIs were categorized by levels of severity. The agreement between two resources was assessed.

Results: Our survey found 915 and 564 paired DDIs according to the Micromedex® and drug interaction fact®, respectively, amongst 120 patients. The prevalence of potential DDIs (pDDIs) was 87.7% and 91.7% with drug interaction Fact® and Micromedex®, respectively. Approximately, 80% of recruited patients, had at least three pDDIs based on Micromedex®. A significant moderate agreement between two drug interaction compendia was reported (Kappa= 0.41, 95% CI: 0.17-0.65, P<0.001). The serotonin syndrome, increasing the risk of bleeding and hyperkalemia were the major possible consequences of pDDIs; but none of them occurred.

Conclusion: Most of the observed interactions were mild to moderate in nature. However, major and contraindicated interactions are possible in critically ill patients. Therefore, monitoring of patients with possible major or contraindicated drug interaction is recommended.

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Introduction

prophylactic purposes. This situation may place them at a higher risk for potential drug-drug interactions (pDDIs). Drug interactions may increase hospital stay and total cost (1,2) which include drug-drug interactions, drug-food interactions and drug-disease interactions (3). A wide range of potential drug interactions have been found in previous studies (4-6). Common features among the majority of critically ill patients are their acuity, complex pathophysiologic states and the use of a large number of pharmacologic agents in their management. On average, these patients have six to nine drugs prescribed per day while being cared for in the critical care unit (6). Due to the complexity of the pharmacotherapy involved in the simultaneous use of several drugs and various therapeutic classes, critically ill patients are at an increased risk for

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DDIs. The prevalence of potential DDIs among critically ill patients was studied by many authors in different countries (7, 8, 9-13). DDIs, ranging from 48.7% to 61%, were reported by these studies.

Several available resources including Lexicomp®, Drug Interaction Checker®, Hansten and Horn's Drug interactions, Micromedex®, Drug interaction fact® (iFact®), and Stockley's Drug Interactions checker are valuable resources for this purpose (14). Interactions for FDA-approved medications could be assessed by Lexicomp® and iFact® (14). Totally, Lexicomp® and Micromedex® were the most common software used for drug interactions (15). The results from a systematic review showed that Micromedex® is the most popular software for interaction evaluation (16). Also, Micromedex®, Lexicomp®, and iFact® offer information about the outcome, severity, onset, and level of evidence for each interaction (16). Micromedex® and iFact® are most commonly used sources, because give more information about severity, mechanism of action, level of evidence, and management (17).

The aim of the present study was to evaluate potential drug-drug interactions in general intensive care units (ICUs) of a teaching hospital by Micromedex® and iFact® references.

Methods

A cross-sectional prospective study was conducted in the sixteen-bed ICU of the hospital affiliated with Kermanshah University of Medical Sciences, Kermansah, Iran. From July 2017 to March 2018, all patients admitted consecutively to the ICU were recruited in this study. Patients discharged within less than 72 hours were excluded. Permission was obtained from hospital administration to consult patient's medical record for research purpose.

Drug prescribed during the ICU stay were retrieved from medical records. Following information were collected: patient's age, gender, length of ICU stay, reasons for admission, detail of medication therapy provided in the hospital and severity and significance of drug interaction. All information was recorded on a standardized form.

The severity and significance of each paired drug interaction were analyzed using the drug interaction Fact® reference textbook (2015, 1st Edition) and Android application of the Micromedex® drug interaction (v. 2.0.0, 2014). The significance of drug interactions was categorized based on severity (contraindicated, major, moderate, and minor) and time of occurrence (rapid and delayed). Paired interactions were double checked and categorized according to the available updated resources including Micromedex® drug interaction and drug interaction Fact®. Potential drug-drug interactions defined according to severity, level of evidence and time of occurrence (14).

Definition of severity

- Contraindicated: combination of medications is contraindicated
- Major: concomitant use may cause life threatening adverse events that need further interventions
- Moderate: concomitant use may worsen patient medical status
- Minor: didn't need any alteration in therapy.

Documentation:

- Established: interaction proved to occur in well stablished study
- Probable: very likely but not proved in clinical trials
- Suspected: may occur but need trial to prove
- Possible: very limited data support, but can occur
- Unlikely: clinical effects of interaction is uncertain

Time of occurrence:

- Rapid: occur within 24 hours
- Delayed: occurred later (more than days to weeks)

For major or contraindicated interactions, patient's status was followed to identify the occurrence of interactions.

The documentation, severity and the onset of interactions were calculated in each pDDIs according to the description of Micromedex® and iFact®. Logistic regression was applied to identify the association of occurrence of pDDIs with patient's age, gender, length of ICU stay and number of prescribed medications.

Potential food-drug interactions were not included in the present study and for establishing food and drug interaction (such as phenytoin, warfarin, levofloxacin, levodopa), nurse staff were instructed to separate enteral feeding from interacting drugs.

Microsoft Excel 2010 and Statistical Package for Social Science (SPSS) v.21 were used for the analyses. Categorical and continuous variables were reported as the number and percentage as well as median or mean, respectively. The correlation between the number of prescribed medications and DDIs was captured using the bivariate Spearman rank correlation test. Finally, the agreement between two compendia was calculated by Cohen's kappa test. Kappa value over 0.81 was considered as excellent, 0.61-0.8 as good, 0.41 to 0.6 as moderate, and below 0.4 as poor. A P value of less than 0.05 was considered statistically significant.

Results

A total of 350 patients were admitted in the general ICU during the study period. Totally, 120 patients (34.3%) with a mean age of 56.1 ±17.1 years were included in the study. The majority of the recruited patients were male (N=64, 53.3%). The median duration of ICU stay was 12 (4-71) days. Cerebrovascular accidents (N=34, 28.3%) and respiratory disease including asthma and chronic obstructive pulmonary disease (N=14, 11.6%) were responsible for 40% of ICU admission. Further, the number of concomitant prescription medications ranged from 2 to 27 (median: 14) and more than half of our population took at least 14 drugs.

From the medical chart of 120 patients, we detected 260 paired interactions responsible for overall interactions in our patients. Cardiovascular medications were involved in more than 132/260 (50.7%) of unique paired interactions. 564 pDDIs were found by iFact® and 915 by Micromedex®. The number of paired drug-drug interactions among recruited patients according to the compendia is reported in Table 1. Regarding the severity, 91.7% (110/120) of the patients had at least one pDDI based on Micromedex® resource. This prevalence was 87.7% according to drug interaction Fact®. Approximately 80% of the recruited patients had at least three pDDIs based on Micromedex®. Considering the two interaction sources, more than half of the patients had at least four pDDIs. The number of pDDIs according to the Micromedex® significantly increased with the number of prescribed medications (r=0.8, P<0.001). Similar results were also obtained by the iFact® (r=0.71, P<0.001). The prevalence of major pDDIs was 16% and 35% based on iFact® and Micromedex®, respectively (Table 1). The distribution of pDDIs based on the onset, severity, and documentation has been presented in Table 1. According to Micromedex®, only 14.1% of potential DDIs had excellent documentation. However, only 3.9% of interactions had established documentation according to the drug interactions in iFact®.

Table 1. Number of paired drug-drug interaction, severity, time to occurrence and level of evidence in recruitted patients according two compendia.

Micromedex®		iFact®	
Number of interactrion			
No	8.3% (10/120)	13.3% (16/120)	
1-3	19.2% (23/120)	30.8% (37/120)	
4-6	16. 7% (20/120)	29.2% (35/120)	
≥7	55.8% (67/120)	26.7% (32/120)	
Severity			
Minor:	74/915 (8.1%)	Minor:	164/564 (29.1%)
Moderate:	500/915 (54.6%)	Moderate:	310/564 (54.9%)
Major:	328/915 (35.8%)	Major:	90/564 (15.9%)
Contraindicated	13/915 (1.4%)		
Time to occurrence			
Rapid:	22.3% (204/915)	Rapid:	73.1%(412/564)
Delayed:	41.2% (377/915)	Delayed:	26.9% (152/564)
Not-specified:	36.5% (334/915)		
Level of evidence:		Established: 22/564 (3.9%)	
Excellent: 129/915 (14.1/%)		Probable: 96/564 (17.1 %)	
Good: 399/915 (43.6%)		Suspected: 164/564 (29.1%)	
Fair: 387/915 (42.3%)		Possible: 231/564 (40.9%)	
Unknown: 0		Unlikely: 51/564 (9.1 %)	

The most frequent potential drug-drug interactions with possible adverse events are reported in Table 2. The potential interaction between aspirin and heparin (27/915, 2.9%) was the most prevalent, followed by aspirin/furosemide (19/915, 2.1%) and aspirin/metoprolol pDDIs (15/915, 1.6%), respectively. No adverse events related to pDDIs occurred during the study period.

Table 2. The most frequent potential drug-drug interactions with probable adverse events.

Interaction	Frequency	Possible Results	Severity/ evidence (Micromedex ®)	Severity/ evidence (iFact®)
Aspirin /heparin	27	Bleeding	Major/excellent	Major/possible
Aspirin /furosemide	19	Decrease diuresis	Moderate /good	Minor/ possible
Aspirin / metoprolol	15	Decrease anthypertensive effects	Moderate/ good	Minor/ possible
Spironolacton/potassium chloride	14	Hyperkalemia	Major/fair	Major/ established
Omeprazole/diazepam	12	Prolonged sedation	Minor/good	Moderate/ possible
Furosemide/ phenytoin	12	Decrease furosemide activity	Minor/fair	Minor/ possible
Furosemide/hydrocortisone	11	Hypokalemia	Moderate /fair	No data
Midazolam/ sufentanil	11	Oversedation/respiratory suppression	Major/good	No data
Spironolacton/ Aspirin	10	Decrease spironolacton efficacy (dose dependenent)	Moderate/ fair	Minor/ suspected
Aspirin / clopidogrel	9	Bleeding	Major/ fair	Moderate/ suspected
Aspirin /enoxaparin	9	Bleeding	Major/good	Major/ possible
Atorvastatin/ clopidogrel	9	Stent thrombosis	Moderate/excellent	Minor/ possible
Amlodipine/ phenytoin	9	Reduce amlodipine efficacy	Moderate/fair	No data
Ciprofloxacin/ metoprolol	9	Bradycardia/hypotension	Minor/good	No data
Ciprofloxacin /hydrocortisone	9	Increase risk of tendon rupture	Moderate/excellent	No data
Losartan/ potassium chloride	9	Hyperkalemia	Moderate/fair	No data
Captopril /Aspirin	9	Reduced captopril efficacy	Moderate /excellent	Moderate/ possible

Contraindicated interactions according to Micromedex® were seen in 1.3% (12/915) of pDDIs (Table 3). Serotonin syndrome and hyperkalemia were the main consequence of these possible contraindicated interactions. However, no patients met the criteria for serotonin syndrome or severe hyperkalemia (K+>6.5meq/l) in our study.

Table 3. Possible frequency and consequence of contraindicated interactions.

Interactions	Frequency	Consequence	Leading to adverse effect
Carbamazepine/Linezolid	1/12 (8.3%)	Serotonin syndrome	Not occured
Fluconazole/Tacrolimus	1/12 (8.3%)	Tacrolimus nephrotoxicity	Not occured
Spironolacton/Triamteren-hydrochlorothiazide	3/12 (25%)	Hyperkalemia	Not occured
Selegiline / Escitalopram	2/12 (16.7%)	Serotonin syndrome	Not occured
Nortriptyline/ Selegiline	2/12 (16.7%)	Serotonin syndrome	Not occured
Citalopram/ Selegiline	2/12 (16.7%)	Serotonin syndrome	Not occured

Furthermore, there was a moderate positive correlation between duration of ICU stay and number of prescribed medications (r: 0.56, P<0.001).

Also, a significant low correlation was seen between duration of ICU stay and number of pDDIs according to the iFact® and Micromedex®. (r: 0.47, r: 0.46, respectively, P<0.001)

There was a significant moderate agreement in interaction severity between the two drug interaction compendia, iFact® and Micromedex®. (Kappa= 0.41, 95% CI: 0.17-0.65, P<0.001)

No significant differences were observed between the two genders in terms of age distribution (P: 0.09), duration

of ICU stay (P: 0.5) and number of pDDIs (base on iFact® and Micromedex®, P: 0.5, for both)

The duration of ICU stays (P: 0.006), number of prescribed medications (P: 0.04), number of pDDIs based on iFact® (P: 0.004) and micromedex® (P: 0.006) in the population ≥ 60 years were significantly higher than those of patients <60 years old.

To detect risk factors of pDDIs, duration of ICU stay and number of prescribed medications were introduced in multiple linear regression analysis. This model was significant for pDDIs in both resources. (P <0.001, adjusted R2: 0.58 and 0.48 for Micromedex ® and iFact®, respectively). The number of prescribed medications was an independent variable which predicted the number of pDDIs. (P<0.001). In other word, for every 0.8 increase in number of prescribed medications an extra pDDI was observed.

Discussion

In the present study, the pDDIs in critically ill patients were evaluated by two different reliable references. Our results indicated high pDDIs prevalence in general critical care units. According to our study, a higher number of pDDIs was detected by Micromedex® compared to iFact®. This could suggest the higher reliability and completeness of Micromedex® (18). Furthermore, a significant moderate agreement was observed between the two references.

In this study, we used two compendia for assessing pDDIs in each patient during ICU stay. Most previous studies used only one source to examine pDDIs in their designs (19-21). The high prevalence of pDDIs in our study has been in line with the findings obtained by previous studies (15, 19, 22, 23). However, several study did not reported high rate of pDDIs (20, 22-24). Ismail et al reported pDDIs of 74.5% in critically ill medical patients and 13.9% of interactions were categorized as contraindicated and 52.2% were major (22). In another study order of orders of 369 patients were revied for possible paired interactions, author reported incidence of 89% in ICU patients, most of interactions were moderate and important (25). However, in our study more than 90% of patients had at least one interaction, reviewing patients' medications during ICU stay and the number of used resources are two important factors which influenced the prevalence of pDDIs in this study.

Although no complete drug interaction resource is available (26), Micromedex® is considered as one of the most accurate and comprehensive resources (15, 16). Janković et al., evaluated potential interactions in critically ill patients with Micromedex®, Epocrates® and Medscape®, they showed Medscape® was detected the most pDDIs software followed by Epocrates® and Micromedex® (19).

Despite the high prevalence of potential drug-drug interactions in critically ill patients, most of the interactions in our study were mild-moderate and established based on case studies or pharmacologic mechanisms.

Previous studies have reported different severity of drug-drug interactions. Based on our knowledge, major pDDIs accounted for 2.4% to 52% of all interactions (21, 27). Further, major pDDIs accounted for up to 35% of all interactions at least based on one resource. Almost similar results were reported by others (28).

Although duration of hospital stay increased the rate of interaction, however, the correlation was not significant. Moura et al., showed prolonged hospital stay significantly increased number of interactions (29).

Bleeding was the main observation of potential major DDIs, where combination of aspirin and heparin/low molecular weight heparins potentiates the anti-thrombosis efficacy which is commonly used in patients with acute ischemic stroke (28). Previous studies showed patients who received cardiovascular medications had a higher risk for pDDIs (12). Similar results were also observed in our population.

Contraindicated interactions occurred in 1.31% of paired interactions, but no endpoint related to pDDIs (serotonin syndrome and severe hyperkalemia) occurred in the present study. In Vanham's study, adverse drug events related to major drug interactions occurred in 4% of patients (21).

As mentioned previously, the number of prescribed medications was the only independent risk factor for pDDIs. The number of medications, duration of ICU stay, age >55 years, male sex, comorbidity scores, some prescribed medications (e.g. antiarrhythmic and anticonvulsant) and surgery during hospitalization were identified as independent risk factors for pDDIs in other studies (19, 30).

Before drawing any definite conclusion, the results of our study should be interpreted with these limitations. First, the study was cross-sectional in which a limited number of patients were included. Therefore, we recommend further study with a larger sample size to detect pDDIs across different populations in critically ill patients. Secondly, comorbidity scores and their relationship with pDDIs were not evaluated. Finally, established food and drug interactions were not included.

Despite high rate of pDDI in our study, most interactions are mild or moderate in nation. And some major interactions (spironolactone and potassium supplements) are used frequently to maintain potassium levels. Therefore, monitoring of patients who received multiple medications

with possible major interactions is recommended to prevent pDDIs in critically ill patients.

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