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RESEARCH ARTICLE

Drug-drug interaction study in an intensive care unit: An assessment of prevalence, nature, and severity of the medications involved

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ABSTRACT

Background: Intensive care unit (ICU) patients are at an increased risk of drug-drug interactions (DDIs) due to polypharmacy and pharmacokinetic changes in critically ill patients. Adverse drug reactions in hospitals caused by DDIs pose a significant risk to the patient's health outcome with an additional economic burden on the health -care system. **Aims and Objectives:** This study was conducted to measure the prevalence and nature of potential DDIs (pDDIs) as primary objective and to know the severity of pDDIs and association of pDDIs with the length of stay in ICU (if any) as a secondary objective. **Materials and Methods:** This was a 2-month, prospective, observational study that was conducted in an ICU of ESIC Medical College and Hospital, Gulbarga. Drugs.com interaction database was utilized to screen patient's medication profiles for DDIs and for severity assessment. **Results:** Of 112 study population, 755 pDDIs were identified, averaging 6.74 interactions per patient. About 6.9% (52/755) were major, 75.9% (573/755) were moderate, and 19.9% (150/755) were minor DDIs. The most frequent drug pairs involved in pDDIs in major, moderate, and minor were rifampin and isoniazid (15.4%), furosemide and pantoprazole (4.01%), and digoxin and spironolactone (8%), respectively. **Conclusions:** DDIs occur frequently in the ICU. Nature and Severity of medications related to DDIs in an ICU differ from other hospital ICU settings. Based on the prescribing pattern in an ICU, a database at an institutional level can be developed so as to decrease the burden of interactions and overall result in improved patient safety.

KEY WORDS: Drug-drug Interactions; Drug Interaction Database; Intensive Care Unit

INTRODUCTION

A drug interaction is defined as a variation in the effect of a drug when it is administered with another drug. The outcome may be in the change of action of either drug or on the adverse effect profile.[1]

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Drug-drug interactions (DDIs) in an intensive care unit (ICU) are often associated with adverse events, longer ICU stays, and end-organ impairment. Increased risk of adverse drug events related to DDIs can be attributed to polypharmacy, seriously ill patients, and pharmacokinetic distinctiveness of the administered medications.[2]

DDIs contributing to adverse drug reactions amount about 5% in hospitals, and the greater part of which is preventable.[3] The problem of DDIs within hospital setup deserves extra consideration due to additional medications prescribed and frequent changes in a number of drugs or dose may be larger. Therefore, DDIs occur more often within hospitals than in an

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outpatient setting.[4] A wide variation of research data exists for the prevalence of DDIs in ICUs with range between 67% and 90.02%.[5-9]

Considering the scarcity of data describing the prevalence, nature, and severity of pDDIs for the ICU population in Indian settings, the present study aims to measure the prevalence and nature of pDDIs as primary objective and to know the severity of pDDIs and association of pDDIs with length of stay in ICU (if any) as secondary objective. With these objectives, we hope to highlight potential interactions and their severity so that clinicians may consider implementing preventative actions, thereby promoting safe medication use and suggesting modifications in the prescribing patterns in these patients.

MATERIALS AND METHODS

Study Design

This study was prospective, observational in nature, conducted in an ICU and Department of Pharmacology, ESIC Medical College and Hospital, Gulbarga, Karnataka, from May 2018 to July 2018. The study was started after obtaining approval from the Institutional Human Ethics Committee (Protocol No.05ESICMCGLB/IEC/2018-19). Patients of either sex, aged 18 years or older, admitted to ICU for >24 h, with at least two medications on prescription and willing to provide informed consent were included in the study. Patients stay in ICU for <24 h, age lesser than 18 years, and not willing to give written consent were excluded from the study. Based on recent (August-November 2017) medical records, approximately 40 patients on monthly basis were admitted in an ICU, so therefore minimum of 80 patients as sample size were considered in our study.

Drug Interaction Evaluation

On day 1 of the study and with each new admission to the ICU, the patient's demographic profile and medication profiles were screened for DDIs. Each subsequent day was considered a new patient evaluation and newly added medications were evaluated against the existing medication profile for the presence of DDIs. Drugs.com interaction databases were utilized to screen each patient's medication orders in the chart for DDIs. This database ranked the severity of the potential DDIs as minor, moderate, major, or unknown.[10] On identification of a DDI, the database severity rating along with interacting drugs, doses, and routes of administration was recorded. Data analysis for the present report was done using Microsoft Excel worksheet and SPSS version 21.0. $P < 0.05$ was considered to be statistically significant.

RESULTS

Overall, 323 patient medication profiles of 112 patients were evaluated in an ICU over the 8-week study period. Table 1 shows general characteristics of study population. Of 112 patients, 60.7% were males and 39.3% were females. Their age ranged between 18 and 87 years with a median age of 55 (interquartile range: 42–65) years with majority grouped in age group between 40–59 years (35.7%) and 60–79 years (35.7%).

Table 2 shows association between variables such as gender, age, and ICU stay with pDDIs. A total of 580 ICU days were spent with a median length of ICU stay accounting for 4 (interquartile range 2–7) days. Drug interactions were most commonly seen in male patients attributing to 61.5% ($n = 56$), in patients aged ≥55 years attributing to 57.1% ($n = 52$), and 58.2% ($n = 53$) in those who stayed in ICU for at least 4 days. No association was found for gender ($P = 0.71$), age ($P = 0.115$), and ICU stay ($P = 0.38$), with drug interactions.

Frequency and Mechanisms of pDDIs

Of total 112 study population, 91 showed 755 pDDIs, averaging 6.74 interactions per patients with prevalence rate of 81.25%. An Average number of drugs prescribed per patient were 9.15. Of 755 interactions, 6.9% ($n = 52$) were major, 75.9% ($n = 573$) were moderate, and 19.9% ($n = 150$) were minor. The first five commonly observed major, moderate, and minor interactions and their frequencies are shown in Tables 3-5, respectively. The most frequently occurring pDDIs in major, moderate, and minor were the combination of rifampin and isoniazid (15.4%), furosemide and pantoprazole (4.01%), and digoxin and spironolactone (8%), respectively.

DISCUSSION

Patients admitted in an ICU are at increased risk of pDDIs due to their critical clinical conditions, with additional

Table 1: Characteristics of the study population (n=112)

Characteristics	*n* (%)
Age (*)	
(years)	
18–39	24 (21.4)
40–59	40 (35.7)
60–79	40 (35.7)
≥80	08 (7.1)
Gender	
Male	68 (60.7)
Female	44 (39.3)
Comorbidities	
Cardiovascular disease	10 (33.3)
Respiratory disease	09 (30.0)
Diabetes mellitus	04 (13.3)
Central nervous system disease	03 (10.0)
Others	04 (13.3)

*Denotes mean (SD) (52.92±17.02), median (55), interquartile range (42–65)

Table 2: Association between the variables gender, age, ICU stay and pDDIs

Number of patients				
Variables	**Interaction *n*=91**	**No interaction *n*=21**	**Odds ratio (95% CI)**	***P* value**
Gender				
Male	56	12	1.2 (0.46−3.14)	0.71
Female	35	09		
Age (years)				
<55	39	13	0.46 (0.17−1.22)	0.12
≥55	52	08		
ICU stay*, days				
<4	38	11	0.65 (0.25−1.69)	0.38
≥4	53	10		

*Denotes mean (SD) (5.20±4.36), median (4), interquartile range (2−7) P <0.05 is considered to be statistically significant, pDDIs: Potential drug-drug interactions, CI: Confidence interval

Table 3: Major interactions (*) (*n*=52)

Interacting drug pair	Frequency (%)	Mechanism of DDI
Rifampin/isoniazid	8 (15.4)	Concomitant use of rifampin and isoniazid increases the risk of hepatotoxicity
Ondansetron/tramadol	6 (11.5)	Concomitant use of ondansetron with tramadol may potentiate the risk of serotonin syndrome
Rifampin/pyrazinamide	5 (9.6)	Concomitant use of rifampin and pyrazinamide enhances the risk of hepatotoxicity
Hydrocortisone/levofloxacin	4 (7.7)	Levofloxacin combined with hydrocortisone increases the risk of tendinitis and tendon rupture
Spironolactone/potassium chloride	3 (5.8)	Concomitant use of spironolactone and potassium chloride may result in hyperkalemia

*Denotes percentage (6.9), DDI: Drug-drug interactions

Table 4: Moderate Interactions (*) (*n*=573)

Interacting drug pair	Frequency (%)	Mechanism of DDI
Furosemide/pantoprazole	23 (4.01)	Chronic use of pantoprazole can cause hypomagnesemia when combined with furosemide
Atorvastatin/pantoprazole	20 (3.5)	Pantoprazole may increase the plasma concentrations of atorvastatin and the associated risk of myopathy
Clopidogrel/pantoprazole	17 (2.9)	Pantoprazole may reduce formation of the active metabolite of clopidogrel and reduced therapeutic efficacy
Atorvastatin/clopidogrel	14 (2.4)	Atorvastatin may reduce the metabolic activation of the clopidogrel and its antiplatelet effects
Furosemide/salbutamol	13 (2.3)	Furosemide with salbutamol may increase the risk of hypokalemia

*Denotes percentage (75.89), DDI=Drug-drug interactions

Table 5: Minor interactions (*) (*n*=150)

Interacting drug pair	Frequency (%)	Mechanism of DDI
Digoxin/spironolactone	12 (8)	Spironolactone may reduce the tubular secretion of digoxin
Aspirin/furosemide	10 (6.7)	Aspirin may blunt the diuretic and natriuretic response to loop diuretics
Aspirin/spironolactone	9 (6)	Salicylates may impair the tubular secretion of canrenone
Pantoprazole/aspirin	7 (4.7)	Coadministration with PPIs may decrease the oral bioavailability of aspirin
Digoxin/salbutamol	6 (4)	Combined use with salbutamol results in decrease in serum digoxin levels

*Denotes percentage (19.87), DDI: Drug-drug interactions, PPIs: Proton-pump inhibitors

comorbidities and polypharmacy. However, the situation becomes more alarming in the settings where DDIs are not taken into considerations during their routine clinical practice. In our study, the prevalence rate of pDDIs (81.25%) was higher with an average of 6.74 interactions per patient. The frequency of interactions in major, moderate, and minor were 6.9%, 75.89%, and 19.87%, respectively. In our study, the most frequently occurring pDDIs in major, moderate, and minor were the combination of rifampin and isoniazid (15.38%), furosemide and pantoprazole (4.01%), and digoxin and spironolactone (8%), respectively.

The mean length of ICU stay of patients in our study was 5.20 ± 4.36 days. However, the median length of stay (4 days) and interquartile range (2–7 days) in our study was slightly greater than the study conducted by Uijtendaal *et al*. (median:

2.9 days; interquartile range: 1.7–6.8 days) which could be attributed to variations in the disease pattern.[11]

In our study there was no association found for age and ICU stay, with DDIs. These findings were corroborated by the study conducted by Lima *et al*.[6] investigating pDDIs in intensive care patients. However, the association for the gender with DDIs was not significant and inconsistent when compared to a study conducted by Lima *et al*.[6] which could be explained by smaller sample size and shorter duration of the study.

The average pDDIs per patients in our study were found to be 6.74, which was greater than the study conducted by Uijtendaal *et al*.[11] (1.7 pDDIs per patient) which could be explained by the higher burden of drug prescribed per patient (average 9.15) in our study, use of different database, and also not taking into account of laboratory values, clinicians' inputs to review the patients medication profile and discussions on relevant pDDIs. The prevalence rate of pDDIs in our study was found to be 81.24% which is reasonably higher in comparison with the studies conducted by Ismail *et al*.[12] (74.5%) and y Reis and Cassiani[7] (70%). In this context of findings, proper review by clinical pharmacist, clinical insight by clinicians, and proper monitoring system are crucial in an ICU for timely identification of pDDIs and for the prevention strategy which could possibly explain the difference in prevalence rate in our study.

Severity levels of pDDIs are important for the management of adverse effects caused by DDIs. In the present study, 75.89% of the pDDIs were moderate in severity. A study conducted by Egger *et al*.[13] (70%) and Abideen *et al*.[9] (64.15%) showed a similar result. Therefore, it is evident from our findings that, in most of the cases, patients are at high risk of adverse outcomes related to pDDIs, and proper monitoring system in place would reduce the burden of interactions.

Although not all drug interactions are preventable, keeping abreast with the knowledge of common drug interactions that are clinically relevant, their mechanisms and risk factors involved are the keys to prevent these events. This knowledge will enable health-care providers to choose appropriate therapeutic regimens, formulations, and dosing schedules that are safer for patients and to provide better quality care.

The strength of this study is that it is conducted in actual clinical conditions in an ICU of an academic hospital with diverse patient's population, providing good background for identifying pDDIs and their common mechanisms involved. A limitation of this study is that it is limited to a single center with smaller sample size, which may limit the generalizability of this study. Although the database showed many pDDIs and their clinical consequence, in practice, it is cumbersome to attribute clinical outcomes to complex pDDIs and in severely ill with comorbid conditions in ICU patients.

CONCLUSIONS

The prevention of DDIs is an important aspect of patient safety. This study illustrates the large number of DDIs (6.74 pDDIs per patient) that were detected in an ICU and could help clinicians not only in preventing DDIs but also for generating relevant signals based on their clinical discretion and database. Based on the prescribing pattern in an ICU of tertiary care hospital, a database at institutional level could provide thorough knowledge of these and can decrease burden of interactions between drugs in medication profile and overall resulting in improved patient safety.

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