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RESEARCH ARTICLE

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Evaluation of Potential Drug-Drug Interactions (DDIs) Incidence in Critically ill Patients

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Abstract

Objectives: We evaluated the instances of potential Drug-Drug Interactions (DDIs) in critically ill patients in a private care center, Mumbai, India and studied the factors associated with these. **Methods:** This is a secondary data analysis of 107 individuals from an intensive care unit in Mumbai, India. We used Medscape's multidrug interaction checker to identify and analyse the pattern of potential DDIs. We used the poison regression models for count outcomes to adjust for potential confounders (age, sex, co-morbidities). **Key findings:** The total number of interactions was 433 [41.4% (95% Confidence Intervals [CI]: 37.6% - 45.6%)]. These interactions were highest in > 80 years (56.8%, 95% CI: 45.0% - 70.8%). About 28% (95% CI: 25.4% - 31.9%) interactions were classified as 'significant' and only 0.1% (95% CI: 0.0% - 0.5%) were classified as 'contraindicated' interactions. The interactions were significantly higher in individuals with cardiovascular diseases (CVDs) (Rate Ratio [RR]: 1.86, 95% CI: 1.45, 2.41). Patients with diabetes mellitus (DM) were significantly less likely to have interactions affecting distribution (RR: 0.17, 95% 0.04, 0.77) and metabolism (RR: 0.38, 95% CI: 0.22, 0.65). Patients with renal disorders had significantly lower pharmacokinetic interactions (RR: 0.46, 95% CI: 0.23, 0.91). **Conclusion:** Though minor interactions were common, the proportion of contraindicated and serious interactions was low. Physicians, probably, were careful while prescribing medications to patients with DM, liver and renal diseases. However, this apparently was not the case in patients with CVDs. Thus, along with regular monitoring, it is important to train and advocate information about drug interactions with physicians of all specialties.

Key words: Drug-drug interactions, Liver, Kidney, Cardio-vascular diseases.

INTRODUCTION

Drug-Drug Interactions (DDIs) are a threat to public health across the globe. These interactions may lead to provoke hospitalization, increase length of hospital stay, cost of treatment, morbidity,[1-3] and mortality[4] costing billions of dollars annually to both patients and healthcare service providers. However, these are an avoidable cause of patient harm.

Previous studies conducted in Europe and US have reported that the potential DDIs ranged from five to 80%.[5-9] A study in Iran showed that about 19.2% of potential DDIs were observed in inpatient settings.[10] In 2007, Twenty-three clinical studies conducted across the globe were meta-analysed. This meta-analysis concluded that DDIs were held accountable for 0.054% of emergency department visits, 0.57% of hospital admissions and 0.12% of re-hospitalizations.[1] Another meta-analysis and systematic literature review conducted to estimate prevalence of hospital admissions and / or visits associated with actual DDIs revealed that the median DDIs prevalence rate for hospital admissions was 1.1% (interquartile range [IQR] 0.4-2.4%) and that of for hospital visits was 0.1% (IQR 0.0-0.3%).[11] Elderly patients are found more vulnerable to DDIs compared to other age-groups[12] attributing to abatement of liver metabolism or kidney function.[13-14] A study conducted by Becker and colleagues in elderly population revealed that DDIs were responsible for 4.8% of hospital admissions.[1]

Drug interactions are of two types based on their *in-vivo* mechanism: pharmacokinetics and pharmacodynamics. Any alteration in drug's concentration due to interactions is pharmacokinetic interaction.[12] Alteration may occur due to one drug affecting other drugs' absorption, distribution, metabolism and / or excretion.[15] In pharmacodynamic interactions, the changes occur in drugs' pharmacologic and / or therapeutic effects as an outcome of interactions where the interacting drugs compete for particular receptors, resulting in additive, potentiating, synergistic and / or antagonistic effects of other drug at a specific target receptor.[16]

The present study intends to evaluate instances of potential DDIs occurring in critically ill patients in a private care center in Mumbai, India. We also studied the factors associated with the interactions in these patients

METHODS

Study Design and Study Site: The present study is a secondary data analysis of 107 individuals admitted in the intensive care unit (ICU) of tertiary care center over a period of three months (January 2015 to March 2015).

Study Population: We abstracted data from patients who were admitted to the ICU and stayed at least for 24 hrs and were prescribed more than four drugs during their stay in the ICU.

Tool used for evaluation: We abstracted the following data from clinical records: age, sex, clinical diagnosis, the medications that were prescribed (including the dose and route of administration). These data were being collected as a part of regular audit and monitoring. They were collected on a pre-designed 'drug interactions assessment sheet. We used a web based tool, Medscape's multidrug interaction checker to identify and analyse

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the pattern on potential DDIs (http://reference.medscape.com/drug-interactionchecker). The classification of DDIs based on Medscape were as follows: 1) Contraindication: Life-threatening interactions where concomitant use of medicines should be avoided; 2) Serious: Potentially Life-threatening; it requires medical intervention to minimize or prevent the serious adverse effects; 3) Significant: Results in potential deterioration of patients' clinical condition; may require an alteration in therapy; and 4) Minor: Effects are usually mild and may not require change in therapy.

The drug interactions were also classified based on the mechanism of drug interactions as: 1) Pharmacokinetic: Altered drug concentration by affecting on drugs' absorption, distribution, metabolism and excretion; and 2) Pharmacodynamic: altered drug effects (potentiating effect, synergistic effect, antagonistic effect and additive effect).

Statistical Analysis: We calculated the proportions and their 95% confidence intervals (CI) of the total number of interactions as well the number of interactions according to various categories (nature of interactions, pharmacokinetic/pharmacodynamic, types of pharmacokinetic interactions and types of efficacy interactions). We calculated the exact Poisson confidence intervals for these proportions. We then prepared a matrix to assess the interactions between different classes of drugs. Finally, we used the poison regression models for count outcomes to adjust for potential confounders (age, sex, co-morbidities). The models were built in the following sequence: null model; model with each explanatory variable; and multivariate model with all the explanatory variables. The study was approved by the Ethics Committee of Dr. L H Hiranandani Hospital for secondary data analysis.

RESULTS

The mean age (standard deviation) of these individuals was 60.6 (16.8) years. About 44% of these participants were females and 56% were males; there was no significant difference between the mean age of males and females (58.7[18.1] vs 63.0[14.8], p=0.20). The common co-morbidities were: cardiovascular diseases (47%); diabetes mellitus (33%); renal diseases (21%); and liver diseases (9%). The total number of drug prescribed to these 107 individuals was 1044; the median number (inter-quartile range) of drugs was 9 (IQR: 7 – 12). The median number of drugs was significantly higher (p=0.005) in individuals more than 80 years of age compared with other ages (Median: 11, IQR: 9.5, 13.5) (Figure 1a). However, there were no significant differences between the number of drugs prescribed among males and females (p=0.57) (Figure 1b).

Drug interactions

About 67% (72/107) of the individuals had DDIs. The total number of interactions in these individuals was 433; the proportion was 41.4% (95% CI: 37.6% - 45.6%). The proportion of interactions was highest in the age group of 80 years and above (56.8%, 95% CI: 45.0% - 70.8%) and lowest in individuals up to 39 years (24.7%, 95% CI: 15.7% - 37.1%). The proportion of interactions in individuals with co-morbidities were: cardiovascular (57.2%, 95% CI: 50.9% - 63.9%); diabetes mellitus (42.1%, 95% CI: 35.7% - 49.4%); renal diseases (38.0%, 95% CI: 30.5% - 46.8%) and liver diseases (12.4%, 95% CI; 6.8% - 20.8%).

Many of these interactions were significant (28.5%, 95% CI: 25.4% - 31.9%); however, the proportion of contraindicated interactions was low (0.1%, 95% CI: 0.0% - 0.5%). The proportion of pharmacodynamic (20.1%, 95% CI: 17.5% - 23.0%) and pharmacokinetic (21.4%, 95% CI: 18.6% - 24.4%) interactions were similar. The common types of pharmacokinetic interactions were those affecting metabolism (11.0%, 95% CI: 9.1% - 13.2%) and excretion (8.0%, 95% CI: 6.4% - 9.9%). We have presented the proportions and confidence intervals of various types of interactions in Table 1.

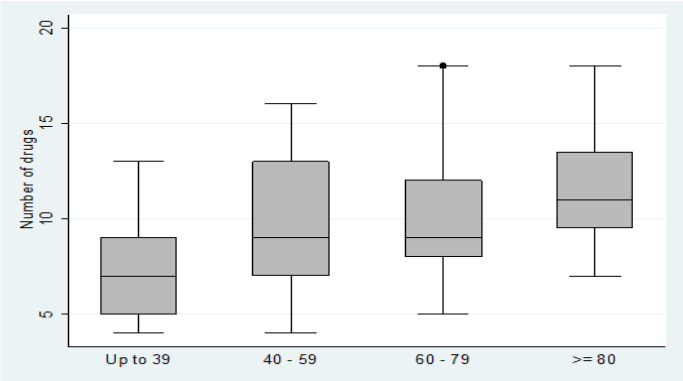

Figure 1a: Box plots of number of drugs across age groups in 107 individuals in Mumbai, India.

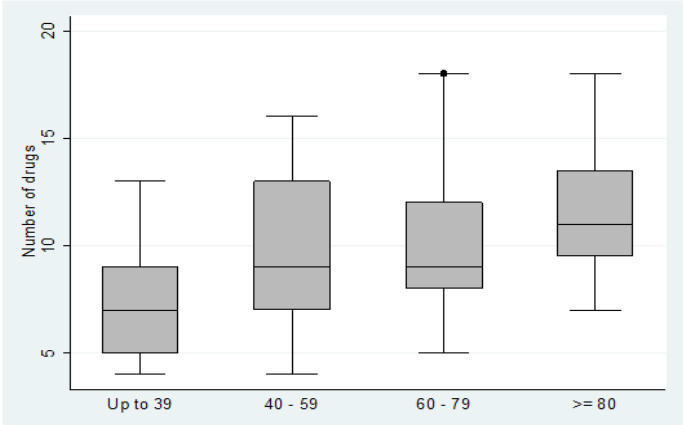

Figure 1b: Box plots of number of drugs according to gender in 107 individuals in Mumbai, India.

Table 1: Table showing the proportion of various types of interactions in 107 individuals in Mumbai, India

	Estimate	95% Confidence intervals
All Interactions	41.4%	37.6% - 45.6%
Nature of Interactions		
Contraindicated interactions	0.1%	0.0% - 0.5%
Serious interactions	2.2%	1.4% - 3.3%
Significant interactions	28.5%	25.4% - 31.9%
Minor interactions	10.6%	8.7% - 12.8%
Type of Interactions		
Pharmacodynamic interactions	20.1%	17.5% - 23.0%
Pharmacokinetic interactions	21.4%	18.6% - 24.4%
Affecting absorption	0.6%	0.2% - 1.3%
Affecting distribution	2.2%	1.4% - 3.3%
Affecting metabolism	11.0%	9.1% - 13.2%
Affecting excretion	8.0%	6.4% - 9.9%
Types of efficacy interactions		
Potentiation effect	11.1%	9.2% - 13.3%
Synergism effect	11.7%	9.7% - 13.9%
Antagonism effect	12.5%	10.4% - 14.8%
Additive interactions	6.2%	4.8% - 7.9%

Table 2: Table showing the proportion of interactions between different classes of drugs in 107 individuals in Mumbai, India

	Analgesics	Anti-microbials	Anti-asthmatics	Drugs acting on CVS	Drugs acting on CNS	Cortico-steroids	Immuno-suppressants	Antidiabetics	Proton pump inhibitors	Miscella-neous
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Analgesics	0 (0)									
Antimicrobials	9 (32)	10 (10)								
Anti-asthmatics	1 (4)	2 (2)	0 (0)							
Drugs acting on CVS	6 (21)	35 (36)	8 (53)	149 (49)						
Drugs acting on CNS	11 (39)	12 (12)	4 (27)	25 (8)	7 (10)					
Corticosteroids	0 (0)	4 (4)	0 (0)	12 (4)	2 (3)	0 (0)				
Immuno-suppressants	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	3 (12)	2 (20)			
Antidiabetics	0 (0)	7 (7)	0 (0)	35 (11)	3 (4)	5 (19)	0 (0)	8 (13)		
Proton pump inhibitors	0 (0)	12 (12)	0 (0)	10 (3)	4 (6)	0 (0)	3 (30)	0 (0)	0 (0)	
Miscellaneous	1 (4)	5 (5)	0 (0)	26 (9)	2 (3)	0 (0)	0 (0)	3 (5)	4 (12)	1 (2)
Total	27 (3)	92 (9)	15 (1)	280 (27)	69 (7)	26 (2)	10 (1)	58 (6)	29 (3)	41 (4)

Table 3: Table showing the rate ratios and 95% confidence intervals of different types of interactions in 107 individuals in Mumbai, India

	All Interactions	Significant Interactions	Minor Interactions	Pharmacodynamic Interactions	Pharmacokinetic Interactions
Age group (years)					
Up to 39	Reference	Reference	Reference	Reference	Reference
40 – 59	1.47 (0.93 – 2.32)	2.92 (1.40 – 6.10)	0.54 (0.28 – 1.03)	15.18 (2.09 - >100)	0.83 (0.50 – 1.38)
60 - 79	1.34 (0.84 – 2.11)	2.43 (1.16 – 5.09)	0.52 (0.27 – 1.00)	12.90 (1.78 – 93.75)	0.82 (0.49 – 1.35)
≥ 80	1.59 (0.97 – 2.61)	2.41 (1.11 – 5.25)	0.88 (0.42 – 1.84)	16.36 (2.21 - >100)	0.92 (0.52 – 1.63)
Sex					
Female	**Reference**	**Reference**	**Reference**	**Reference**	**Reference**
Male	1.18 (0.96 – 1.44)	1.13 (0.89 – 1.44)	1.04 (0.71 – 1.54)	1.31 (0.98 – 1.75)	1.06 (0.80 – 1.39)
Co-morbidities					
Cardiovascular diseases	1.86 (1.45 -2.41)	2.67 (1.92 – 3.72)	0.91 (0.57 – 1.45)	1.88 (1.27 – 2.78)	0.58 (0.41 – 0.81)
Diabetes Mellitus	0.90 (0.72 – 1.12)	0.75 (0.57 -0.98)	1.39 (0.88 – 2.20)	1.33 (0.97 – 1.81)	0.97 (0.69 – 1.37)
Renal Disorders	0.96 (0.74 – 1.22)	0.83 (0.61 – 1.14)	1.26 (0.81 – 1.94)	0.93 (0.65 – 1.32)	0.46 (0.23 – 0.91)
Liver diseases	0.36 (0.21 – 0.62)	0.29 (0.13 – 0.62)	0.46 (0.20 – 1.08)	0.26 (0.11 – 0.65)	0.20 (0.12 – 0.33)

Class of drugs and DDIs

Out of total 1044 drugs prescribed and 433 potential DDIs observed, the drug classes associated with potential DDIs were analgesics [28 (2.7%)], antimicrobials [97 (9.3%)], anti-asthmatics [15 (1.4%)], drugs acting on the cardiovascular system [306 (29.3%)], drugs acting on the central nervous system [71 (6.8%)], corticosteroids [26 (2.5%)], immunosuppressants [10 (0.96%)], anti-diabetics [61 (5.8%)] and proton pump inhibitors [33 (3.2%)]

Most of the interactions were observed between cardiovascular drugs – cardiovascular drugs [149 (34.4%)], followed by cardiovascular drugs – anti-microbials [35 (8.1%)], cardiovascular drugs – anti-diabetic drugs [35 (8.1%)] and cardiovascular drugs – drugs acting on CNS [25 (5.8%)]. Additional details of the interactions between classes of drugs are provided in Table 2.

Poisson Regression Models

We found that the total number of interactions were significantly higher in individuals with cardiovascular diseases (CVDs) compared with those that did not have the disease (Rate Ratio [RR]: 1.86, 95% CI: 1.45, 2.41). Furthermore, these individuals also had higher 'significant interactions' (RR: 2.67, 95% CI: 1.92, 3.72) and 'pharmacodynamic interactions' (RR: 1.88, 95% CI: 1.27, 2.78). The other significant interactions in individuals with CVDs were: affecting excretion; synergistic effect interactions; and antagonistic effect interactions. Interestingly, patients with liver diseases had a significantly lower total interactions compared with those that did not have liver diseases (RR: 0.36, 95% CI: 0.21, 0.62). The other interactions which were lower in individuals with liver diseases were: significant interactions; pharmacodynamic interactions; pharmacokinetic interactions; and interactions with synergistic effect.

Patients with diabetes mellitus were less significantly to have interactions affecting distribution (RR: 0.17, 95% 0.04, 0.77) and metabolism (RR: 0.38, 95% CI: 0.22, 0.65). Similarly, patients with renal disorders had significantly lower pharmacokinetic interactions (RR: 0.46, 95% CI: 0.23, 0.91). We have provided the estimates and 95% confidence intervals for these interactions in Tables 3 and 4.

DISCUSSION

Since decades, combination drug therapy had become an essential tool to manage multiple disease conditions. However, multiple drugs when administered together may react with each other ending up amplifying or diminishing the effects of drugs, causing harm to the patients. This may occur due to either increased drug effects leading to toxicity or decreased drug effects causing therapeutic failure.[12,17]

Monitoring of DDIs is essential to minimize patient harm and to achieve optimum treatment efficacy. There are a lot of open to access drug interaction checker softwares available. For this particular study, web-based software – Medscape's Multidrug Interaction Checker was used to evaluate potential DDIs. The software provides an evidence-based information regarding DDIs and also categorizes them as per their severity (contraindicated, serious, moderate and minor).[18]

In our study, the instances of potential DDIs (67.28% of patients) was higher compared with the findings observed by Smithburger *et al.* (56.25%),[19] Vonbach *et al.* (56.2%)[9] and by Uijtendaal *et al.* (54%).[20] However, it was lower than that observed by Doubova *et al.* (80%)[5] and by Kothari *et al.* (71.50%).[21] The instances of potential DDIs were high in males compared with females; a finding similar to those observed by Moura *et al.*[3]

In the study, elderly patients were found more vulnerable – a strong relationship between increasing age, co-morbidities, number of drugs prescribed and frequency of potential DDIs.[12,22] In general, most of the patients had at least two co-morbidities. The common conditions were cardiovascular diseases were the most common, followed by diabetes mellitus, kidney diseases and liver diseases.

Majority of potential DDIs were observed with cardiovascular drugs. Most of them paired up with other cardiovascular drugs, anti-microbials, anti-diabetic drugs, drugs acting on CNS and others. Other studies also conclude that drugs acting on CVS are the one that get most frequently paired up for interactions, followed by NSAIDs. [1,3,5,23,24]

In this study, most of the interactions were significant in nature, followed

Table 4: Table showing the rate ratios and 95% confidence intervals of different types of interactions in 107 individuals in Mumbai, India

Age group (years)	Affecting Distribution	Affecting metabolism	Affecting excretion	Potentiation effect	Synergistic effect	Antagonism effect
Up to 39	Reference	Reference	Reference	Reference	Reference	Reference
40 – 59	1.24 (0.22 – 6.94)	0.57 (0.31 – 1.03)	4.09 (0.54 – 31.24)	1.21 (0.57 – 2.61)	10.25 (1.40 – 75.27)	0.82 (0.42 – 1.59)
60 - 79	1.90 (0.37 – 9.70)	0.65 (0.36 – 1.16)	3.50 (0.46 – 26.90)	1.58 (0.75 – 3.32)	7.42 (1.00 – 54.86)	0.61 (0.31 – 1.20)
≥ 80	1.29 (0.17 – 9.46)	0.93 (0.47 – 1.87)	3.08 (0.38 – 24.57)	1.89 (0.81 – 4.34)	11.46 (1.52 – 86.57)	0.63 (0.29 – 1.37)
Sex						
Female	**Reference**	**Reference**	**Reference**	**Reference**	**Reference**	**Reference**
Male	6.98 (1.60 – 30.35)	1.17 (0.79 – 1.73)	0.62 (0.39 – 0.97)	1.30 (0.88 – 1.92)	1.16 (0.80 – 1.69)	1.21 (0.84 – 1.75)
Co-morbidities						
Cardiovascular diseases	2.30 (0.81 – 6.53)	1.15 (0.75 – 1.76)	4.61 (2.12 – 10.01)	1.30 (0.84 – 2.00)	1.75 (1.07 – 2.88)	2.58 (1.58 – 4.19)
Diabetes Mellitus	0.17 (0.04 – 0.77)	0.38 (0.22 – 0.65)	0.89 (0.55 – 1.44)	0.43 (0.26 – 0.70)	1.06 (0.70 – 1.61)	0.91 (0.61 – 1.37)
Renal Disorders	1.58 (0.52 – 4.79)	1.36 (0.86 – 2.15)	0.54 (0.28 – 1.05)	1.37 (0.86 – 2.17)	0.89 (0.55 – 1.44)	1.10 (0.71 – 1.68)
Liver diseases	0.43 (0.06 – 3.34)	0.50 (0.22 – 1.17)	0.29 (0.07 – 1.20)	0.53 (0.23 – 1.23)	0.29 (0.09 – 0.93)	0.38 (0.14 – 1.04)

by minor interactions and serious interactions. Contraindicated interaction was found in only 0.1% of the case; this proportion was lower compared with a proportion of as reported in a study conducted by Juárez-Cedillo *et al*.[25] The significant type of interactions was found prominently in patients with cardiovascular co-morbidities; whereas, minor type of interactions was observed more in diabetic patients. No significant difference was found in pharmacokinetic (21.4%) and pharmacodynamic (20.1%) interactions.

The most frequently observed pharmacokinetic interactions' mechanism was the one affecting drug metabolism. The least common was the one affecting drug absorption. The most common pharmacodynamic mechanism of interactions were those having antagonizing effect on either of the interacting drugs and the least common was that to be having additive effects.

In general, it was observed that patients with CVDs had higher rates of interactions (various types) and patients with liver diseases, diabetes mellitus and renal diseases had significantly lower rates of interactions. It is possible that physicians are more careful about drug interactions while prescribing medications in patients with liver diseases or renal diseases (due to its role in metabolism and excretion of many drugs). However, this may not be the case while prescribing medications for cardiovascular diseases. Thus, it is important to train and advocate information about drug interactions with all specialties. Furthermore, an important strategy will be to have monthly or quarterly meetings with each specialty, rather than an all hospital meeting to ensure reduction in drug interactions in the hospital.

The study was conducted in a single hospital; hence it may not be representative of the prescription of drugs in the general population. Furthermore, since the hospital staff was aware that prescriptions are being audited regularly, they may have been more careful in prescribing the medications. Thus, we may have underestimated the DDIs. Finally, we have analysed data for only one time point. A longitudinal analysis of DDIs will be useful to provide information on the prescription patterns of physicians over time.

CONCLUSION

Nonetheless, the study provides useful information on DDIs. Though significant and minor interactions were common in this group, the proportion of contraindicated and serious interactions was relatively low. Thus, regular audits of prescription and monitoring of DDIs will help in reduction of these interactions, particularly in patients admitted to intensive care units. We also found that physicians, probably, were careful while prescribing medications to patients with liver and renal disorders or those diagnosed with diabetes mellitus. However, this was not the case while prescribing medications to patients with CVDs. Thus, along with regular monitoring, it is important to train and advocate information about drug interactions with physicians of all specialties.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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