Original Article

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Evaluation of Potential Drug-Drug Interactions in Patients of Emergency Medicine Department at a Tertiary Care Teaching Hospital: A Prospective Study

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Abstract

Background: Emergency medicine physicians have the responsibility to recognize and prevent drug-drug interactions (DDI) as they can lead to adverse outcomes. Using current DI resources can ease this seemingly overwhelming DDI burden greatly.

Objectives: To evaluate potential DDIs, nature and mechanism of these DDI and to identify common drug groups involved in these DDI in patients of all age groups admitted in emergency medicine department (ED) of a tertiary care teaching hospital.

Materials and Methods: Data of the patients admitted to ED was collected prospectively for 48 h from the time of admission over 2 months. Data was analyzed for potential DDIs by online Medscape DI checker software.

Results: A total of 156 patients were included in the study (M:F ratio 1.89:1). More than 95% patients had potential for DDI. The total number of potential DI was 1191 with a mean number of DDI of 7.63 ± 3.53. Pharmacodynamic DDIs were most common constituting 73%, followed by pharmacokinetic DDIs 24%. Significant DDIs were most common constituting 61.29% followed by serious DDIs (8.22%), contraindicated DDIs (0.58%) and minor DDIs (29.89%). The Most common involved drug groups in interactions were antimicrobials (8.74%), antiplatelets (4.19%), and steroids (4.19%).

Conclusion: Safeguards need to be introduced to prevent patients from receiving medications that have the potential to cause adverse DIs in the ED.

Key words: Drug-drug interactions, Emergency medicine, Potential

INTRODUCTION

Adverse drug reactions and drug-drug interactions (DDIs) present a growing concern in the health care setting. A number of studies have found that the incidence of drug interactions (DIs) ranges from 3%[1] to 30%.[2] DDI can lead to a variety of adverse events, and it has been suggested that preventable adverse events are the eighth leading cause of death in the United States.[3] While the beneficial effects of medication are manifold, medication use also implicitly involves a risk of DIs, side effects and other drug-related problems. Medicines are often used concomitantly with other drugs, and some degree of DDI occurs with concomitant use. The overall prevalence of DIs is 50-60% in the USA. It is estimated that DIs cause up to 3% of all hospitalizations.[4,5] This translates to nearly 2, 50,000 hospitalizations per year in the USA at a cost of $1.3 billion.[6]

However, most studies have used a variety of screening criteria and evaluate between 300 and 400 patients. The incidence of DDI or adverse events in an unselected emergency department population is unclear.[7] DDI are associated with significant morbidity, mortality, impaired

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quality of life and are primary drivers of hospital admissions.[8] A DDI is defined as a pharmacokinetic or pharmacodynamics influence of drugs on each other, which may result in desired effects, reduced efficacy, and effectiveness or increased toxicity.[9]

Many emergency medicine department (ED) patients are at risk for DIs because they are elderly receiving multiple medications. These interactions can vary from insignificant to potentially lethal. Because of the potential to cause adverse effects, it would be optimal for health care providers to routinely evaluate patient's medication lists to identify and resolve DDIs during each patient care encounter. Recognizing DIs is a daily challenge for physicians and remembering all potential interactions has become virtually impossible.[10]

The clinical reality, however, is that few emergency physicians have the time and training to systematically screen patients for DDIs. The ED represents a patient treatment area where new DDIs could easily be caused. A lack of routine screening for DDIs bypasses the screening that would otherwise detect DIs among inpatients. In addition, as many as 47% of patients admitted to the ED are already taking interacting medications.[11] New medications are added for the patient's benefit in the ED.

Although many DDIs exist, only a small part of these DDIs is clinically relevant.[12] Several factors have been identified that increase a patient's risk of DDIs. The highest risk for DDIs occurs in those patients with advanced age, those taking more than four medications, or those taking medications with a narrow therapeutic index, or requiring therapeutic drug monitoring.[13] According to previous studies, the number of medications used by patients is the best predictor for DDIs.[13] It is therefore not surprising that older patients, who often take many medications, are at the highest risk.

Patients with risk factors warrant extra caution when health care providers add new medications to their regimens. A European study of 1601 ambulatory elderly patients, taking an average of seven different drugs, found that 46.0% were at risk for at least one clinically important potential DDI.[14] Furthermore, it has been reported that about 40% of hospitalized patients had at least one potential drug-disease interaction.[15]

Emergency medicine physicians have the responsibility to recognize and prevent DDI as they can lead to adverse outcomes. Using current DI resources can ease this seemingly overwhelming DDI burden greatly. Overall, data on the occurrence and consequences of DDI alerts within hospitals are scarce. The underlying rationale for the study was to characterize DDIs among ED inpatients likely to have DDIs, in order to assess the potential need for the development of an intervention to monitor and detect DDIs, while the patient is being treated in the ED.

Therefore, our study objectives were,
1. To evaluate potential DDIs
2. To identify nature and mechanism of DDIs
3. To identify common drug groups involved in DDIs

MATERIALS AND METHODS

A prospective observational, cross-sectional study was carried out over a period of 2 months in the ED after obtaining written approval by Institutional Review Board and from head of ED. All patients admitted to ED were enrolled in the study after taking written informed consent from the patient/legal guardian. Patients with very critical condition as per the clinician's opinion were excluded from the study. Demographic data like name initials, age, gender, occupation, address were recorded. The complete prescription was recorded in case record form for first 48 h. Patient admitted in the ED of our institute were transferred to their respective specialty after 48 h of initial stabilization. Hence, data was collected for the first 48 h. Confidentiality of all the patients' data were maintained. Data analyzed for potential DDI by using online Medscape DI checker software, textbooks, and reference books.[16,17] DIs judged by the Medscape DI checker software to be of serious, significant, contraindicated and minor varieties. Fischer exact test and Pearson correlation coefficient test were used to assess the relationship between quantitative variables.

Statistical Analysis

Data analyzed by Microsoft excel 2010®, Microsoft Corporation Pvt. Ltd, USA and statistical software SPSS 21.0.

RESULTS

In our study, prescriptions of 156 patients admitted in the ED were collected for first 48 h and analyzed.

Age

The mean age was 53.38 ± 16.84 years. About 37 (23.71%) patients presenting to ED were 61-70 years of age followed by 30(19.23%) patients belonged to 51-60 years of age group. Male: Female ratio was 1.9:1.

Co-morbid Conditions

Most frequent co-morbid condition were hypertension 59 (37.82%), diabetes mellitus 35 (22.43%), ischemic heart

disease 33 (21.15%) and chronic obstructive pulmonary disease 11 (7.05%).

Drugs Use Pattern

Total 156 patients received 1635 drugs, number of drugs prescribed per patient being 9.99 ± 2.55 (mean ± SD).

DDI

A total of 149 (95.51%) prescriptions had potential for DDIs out of 156 prescriptions. The total number of potential DDIs was 1191 with a mean number of DDIs 7.63 ± 3.53. Demographic variables and nature of potential DDIs are illustrated in Table 1. The association between DDIs, male gender ($P = 0.04$) and age >40 years, $P = 0.05$) was statistically significant using Fischer exact test. The association between DDIs and number of drugs prescribed more than 5 was statistically extremely significant ($P < 0.0001$) using Fischer exact test (Table 2).

Nature and Mechanism

Pharmacodynamic DDIs were most common constituting 73%, followed by pharmacokinetic DDIs 24% and unknown 3%. Significant DDIs were most common constituting 61.3% followed by serious DDIs (8.22%), contraindicated DDIs (0.58%) and minor DDIs (29.9%). Contraindicated DDIs were seen with linezolid and dopamine/norepinephrine in 5 patients. Minor DDIs were not analyzed. Examples of serious and significant pharmacodynamic DDIs are shown in Table 3. Examples of serious and significant pharmacokinetic DDIs are shown in Table 4.

Common Drug Groups

The most common involved drug groups were antimicrobials (8.74%), steroids (4.19%), antiplatelets (4.19%), diuretics (3.59%), anticoagulants (3.23%), angiotensin converting enzyme (ACE) inhibitors + AT_1 antagonists (2.87%) and β blockers (2.75%) (Figure 1). The number of drugs prescribed were in correlation with increasing age of the patient ($r = 0.85$, $P = 0.05$) using Pearson correlation coefficient test. The number of potential DDIs were correlated with the number of drugs prescribed ($r = 0.74$, $P < 0.0001$) using Pearson correlation coefficient test (Figure 2).

Table 1: Demographic variables and nature of potential DDIs (*n*=156)

Demographic variable	Mean±SD (range in years)	Total (%)
Age	53.38±16.84 (12-85)	156 (100)
Male	50.78±13.83 (12-91)	(59.71)
Female	54.93±15.13 (16-85)	(40.29)
Number of drugs prescribed	9.99±2.55 (4-16)	1635 (100)
Potential for DDI	7.63±3.53 (0-34)	1191 (100)
Mechanism of potential for DDI		
Pharmacodynamic interaction (pd)	5.57±4.24 (0-29)	869 (72.96)
Pharmacokinetic interaction (pk)	1.82±0.70 (0-9)	284 (23.85)
Unknown mechanism of interaction	0.24 (0-2)	38 (3.19)
Clinical types of potential for DDI		
Serious drug interaction	0.62±0.70 (0-5)	98 (8.22)
Significant drug interaction	4.68±4.24 (0-21)	730 (61.30)
Contraindicated drug interaction	0.04 (0-2)	7 (0.58)
Minor drug interaction	2.28 (0-12)	356 (29.90)

DDI: Drug-drug interactions, SD: Standard deviation

Table 2: Different variables and DDIs

Variables	Patients without DDIs on their prescription	Patients with DDIs on their prescription	*P* value*
Gender			
Male	2	100	0.04
Female	5	49	
Age range (years)			
≤40	4	32	0.05
More than 40	3	117	
Number of drugs prescribed			
≤5	4	3	<0.0001
≥5	3	146	
Co-morbid condition			
Diabetes	0	35	0.35
Non-diabetes	7	114	
Hypertension	1	58	0.25
Non-hypertensive	6	91	
Ischemic heart disease	0	33	0.34
Non-IHD	7	116	
COPD	0	11	1
Non-COPD	7	138	

*Using Fischer's exact test *P* value significant for gender, age and number of drugs prescribed, IHD: Ischemic heart disease, COPD: Chronic obstructive pulmonary disease, DDI: Drug-drug interactions

DISCUSSION

Drug-related adverse events have been identified as a major source of morbidity and mortality in the United States, and DDIs are significant source of these events. Frequency of potential DDIs and the risk factors has widely been investigated in the hospital of modern countries,[18,19] but it has not been considered a lot in developing countries. In the present study, we calculated the frequency with which potential DDIs would be highlighted by computer-based online Medscape DI checker software.

In our study, the mean age was 53.38±16.84 years with the majority of male patients (M:F - 1.9:1). The average number of medications/patient administered in the study population was 9.99 ± 2.55 indicating polypharmacy which was a major risk factor for DDI. A study by Glintborg *et al*, reported median number of drugs 8 (1-24).[20] These patients were likely to have more medical complications and at a higher risk of drug-related interactions.[11,21,22] In our study, average potential DDI was 7.63 ± 3.53 per prescription

Table 3: Serious and significant potential pharmacodynamics DDIs

Potential effect	Effect of DDI	Drugs	Number
Serious			
↑ Bleeding tendency	Anticoagulant effect enhanced	Heparin+Streptokinase	17
Additive cardiotoxicity	QTc interval prolonged	Azithromycin+Ondansetron	10
		Levofloxacin+Ondansetron	10
↑ Bleeding tendency	Anticoagulant effect enhanced	Ceftriaxone+Heparin	9
Arrhythmia	Hypomagnesemia+digoxin toxicity	Pantoprazole+Digoxin	8
Significant			
↑Bleeding tendency	Hemorrhage	Aspirin+Clopidogrel	53
		Heparin+Clopidogrel	39
		Heparin+Aspirin	36
↓ Therapeutic effect, renal function deterioration	Antihypertensive	Ramipril+Aspirin	30
Altered S. K+	Fluctuation of K+	Aspirin+Furosemide	29

DDI: Drug-drug interactions

Table 4: Serious and significant potential pharmacokinetic DDIs

Mechanism	Potential effect	Drugs	Number
Serious			
Absorption	↑ Digoxin	Omeprazole+Digoxin	3
	↑ Digoxin	Ranitidine+Digoxin	2
Metabolism	↑ Heparin	Azithromycin+Heparin	2
	↓ Clopidogrel	Omeprazole+Clopidogrel	2
	↑ Theophylline	Ciprofloxacin+Theophylline	1
Significant			
Metabolism	↑ Midazolam	Metronidazole+Midazolam	9
	↓ Midazolam	Budesonide+Midazolam	8
Absorption, renal clearance	↑ Digoxin	Carvedilol+Digoxin	5
Metabolism, renal clearance	↑ Digoxin	Spironolactone+Digoxin	5

DDI: Drug-drug interactions

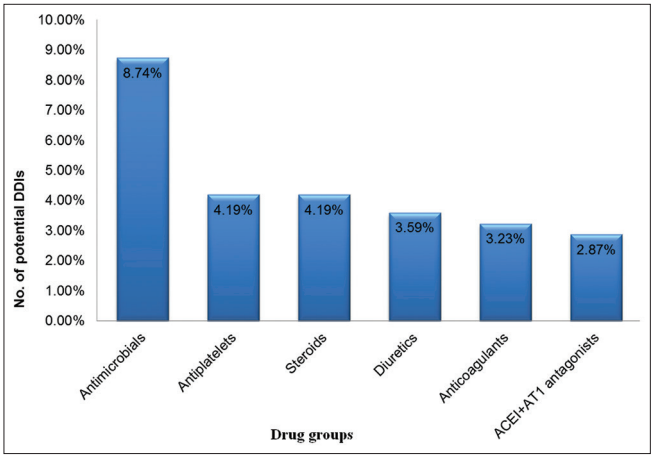

Figure 1: Drug groups involved in potential drug-drug interactions

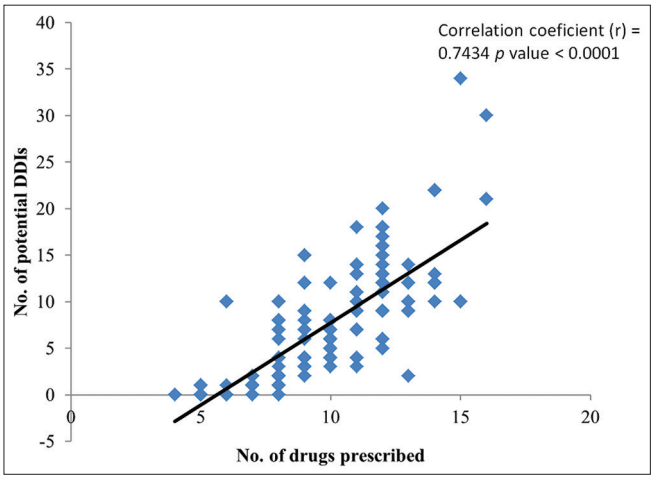

Figure 2: Potential drug-drug interactions with number of drugs prescribed

which was higher than that reported by Zwart-van Rijkom *et al.* with the average of 3.4 DDIs.[23]

The most frequent classes of medications implicated in potential DDIs were antimicrobials (8.74%), steroids (4.19%), antiplatelets (4.19%) diuretics (3.59%) anticoagulants (3.23%), ACE inhibitors + AT_1 antagonists (2.87%) and β blockers (2.75%). This was comparable to study by Goldstein *et al.* in which the most frequent classes of medications implicated in potential DDIs were NSAIDs, beta-blockers, steroids, ACE inhibitors, and anticoagulants.[7] A study by Hohl *et al.* reported that the most frequent implicated drugs were nonsteroidal anti-inflammatory drugs, antibiotics, and anticoagulants.[24] Goldberg *et al.* expressed medication-related DIs by relative risk, and found the greatest relative risk with digoxin, ranitidine, and furosemide.[19] Beers *et al.* reported in 1990 that 89% of DDIs were accounted for by opioid analgesics, nonsteroidal anti-inflammatory agents, benzodiazepines, antacids, and diuretics.[25] Gaddis *et al.* reported most common drugs associated with a DI digoxin, warfarin and aspirin.[11] These differences in causes of DDIs may be due to institution-specific bias in prescribing habits, patient population and screening systems utilized or changes in prescribing habits.[26,27]

Many of these DIs can be monitored and avoided, by means of serum dosage adjustments or by means of clinical or laboratory control. The easiest way to reduce the frequency of DDI is to decrease the number of medicines prescribed. Nevertheless, sometimes it's difficult to reduce the number of drugs prescribed for patients with multiple chronic conditions; therefore, to lower the frequency of potential interactions it would be necessary to make a careful selection of therapeutic alternatives, and in cases without other options, patients should be continuously monitored to identify adverse events.[28]

The association between patients with DDI and male gender was considered to be statistically significant ($P = 0.04$) by Fischer exact test. The association between patients with DDIs and number of drugs prescribed more than 5 was considered to be statistically extremely significant ($P < 0.0001$) by Fischer exact test. The number of drugs prescribed were in correlation with increasing age of the patient ($r = 0.85$, $P = 0.05$). The number of potential DDIs were correlated with the number of drugs prescribed ($r = 0.74$, $P < 0.0001$). So, old age and polypharmacy were important risk factors for causing DDIs in our study. This was comparable to the study by Gaddis *et al.* where DDIs were higher in older age (>60 years) and in patients with more than 6 drugs per prescription.[11] A study by Goldberg *et al.* reported that emergency department patients taking three or more medications and patients older than 50 years of age taking two or more medications are at substantial risk for adverse DDIs and drug-disease interactions.[19]

The most frequent serious pharmacodynamic DDIs were heparin + streptokinase (17). Both increases anticoagulation and can lead to hemorrhage. The most frequent significant pharmacodynamic DDIs were aspirin + clopidogrel (53). Both increases anticoagulation and can lead to hemorrhage. The contraindicated DDIs were linezolid and dopamine/norepinephrine (5). Linezolid increases effects of dopamine/norepinephrine by pharmacodynamics synergism leading to acute hypertensive episode.

Numbers of authors have suggested that computer-aided order entry and prescription writing can reduce the number of medication errors.[29,30] Use of computerized order entry for inpatients, in which all medications are entered and cross-checked for interactions, has been shown to decrease medication errors and adverse drug-related events and to generate cost savings as well.[29] Our data suggest there may be a great deal of added value in translating a similar system to the ED. While a number of potential interactions have been identified, not all are clinically relevant. Patient safety may be improved by decreasing the frequency of preventable adverse drug events.[23]

Limitation

In this study, we did not gather the information to assess the actual relevance of the potential DDI; this may be the topic of our further research.

CONCLUSION

More than 95% patients had potential for DDIs. Close monitoring of patients with drugs groups involved in potential DDIs is required. Safeguards need to be introduced to prevent patients from receiving medications that have the potential to cause adverse DIs (antimicrobials, steroids, antiplatelets, diuretics, anticoagulants, ACE inhibitors + AT_1 antagonists, and β blockers) in the ED. Actual interactions are relatively few. Physicians should be vigilant for potential DDIs, especially among the most high-risk patients taking multiple medications. Further research is needed to investigate the clinical relevance of these DDIs.

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