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Research Article

Prospective study on identification and assessment of potential drug-drug interactions in emergency medicine department at KIMS hospital and research centre

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ABSTRACT

In the emergency department, medications may be added to complex treatment regimens without the benefit of screening for drug interaction. There are numerous potential drug-drug interactions that can result in toxicity, an alteration of the desired therapeutic end point or at the very extreme in life threatening situations. The objectives of this study were to identify the potential drug-drug interactions in patients admitted to Emergency Department in KIMS Hospital & Research Centre, and to categorize the potential drug-drug interactions based on their severity.A total of 215 (70.49%) patient prescriptions out of 305 showed 1676 pDDIs and the remaining 90 (29.50%) had no pDDIs. Out of 215 patients who showed pDDIs 126 (41.31%) were males and 89 (29.18%) were females.In present study, 177 (10.56%), 1021 (60.91%), 478 (28.52%) patients showed serious, significant and minor pDDIs respectively.On correlating between patient`s age group and pDDIs it has been found that most number of recorded pDDIs, 683 patients (40.8%) were belong to age group between 61-75 years and in relationship between polypharmacy and pDDIs the highest number of patients, 639 (38.1%) have been received 10-13 medications. Furosemide caused largest number of pDDIs (7.9%). The drug pair clarithromycin and budesonide has resulted in 3.9% of the pDDIs, followed by the drugs albuterol and furosemide at 3.1%, ceftriaxone and furosemide at 1.4% respectively.Constant vigilance by the prescriber and careful monitoring of patients' medication charts by clinical pharmacists can avoid DDIs and ensuring improvement in quality of patient health care.

Key words: *Potential Drug-Drug Interaction, Emergency Department.*

INTRODUCTION

Drug-drug interactions occur when a drug interacts or interferes with another drug which can alter the way one or both the drugs act in the body, or cause unexpected side effects. There are several mechanisms by which drugs may interact, but most can be categorized as pharmacokinetic, pharmacodynamic, or combined interactions. An adverse effect depends on both patient- and drug-specific factors. Patient factors can include intrinsic drug clearance, genetics, gender, concurrent diseases, and diet. Drug-specific factors include dose, route of administration, drug formulation, and the sequence of drug administration. The gastrointestinal absorption of drugs may be affected by concurrent use of other agents that have a large surface area upon which the drug can be adsorbed, bind or chelate, alter gastric pH, alter gastrointestinal motility, or affect transport proteins such as P-glycoprotein and organic anion transporters. The metabolism of drugs can be stimulated or inhibited by concurrent therapy, and the importance of the effect varies from negligible to dramatic. Induction of cytochrome P450 isoenzymes in the liver and small intestine can be caused by drugs such as barbiturates, carbamazepine, phenytoin, primidone, and rifampin. Drugs that may inhibit the cytochrome P450 metabolism of other drugs include amiodarone, androgens, chloramphenicol, cimetidine, ciprofloxacin, clarithromycin, cyclosporine, diltiazem.[1-5] When drugs with similar pharmacologic effects are administered concurrently, an additive or synergistic response is usually seen. Conversely, drugs with opposing pharmacologic effects may reduce the response to one or both drugs. Pharmacodynamic drug

interactions are relatively common in clinical practice, but adverse effects can usually be minimized if one understands the pharmacology of the drugs involved. In this way, the interactions can be anticipated and appropriate countermeasures taken.[2]There are numerous potential drug-drug interactions that can result in toxicity, in an alteration of the desired therapeutic end point or at the very extreme in life threatening situations. Drug-drug interactions pose significant harm to the patient and simultaneously increase health care costs.[4]The department of emergency medicine is a medical specialty which requires health care providers including physicians, nurses and pharmacists to be working at an exhaustive pace and is often prone to the increased possibilities of many adverse drug interactions owing to the complexity and diverse nature of the cases presenting to the emergency department (ED). ED is known to be a particularly high-risk environment with frequent medication errors.[5]The use of multiple medications or Polypharmacy has been attributed as one of the major risk factors in precipitating drug-drug interactions.[4] There is always an increased use of multiple medications and higher risk medications in emergency situations. Also, multiple patients will have to be treated at once by the physicians and nursing staff, with frequent interruptions. The ED lacks the ability for direct follow up, and thus, adverse interactions between medications prescribed in the ED may go unnoticed by the providers.[5]The task of recognizing drug interactions is somewhat more difficult in the emergency department, where every patient is new and unknown to the staff. Thus, the incidence of potential drug interactions in this patient population is high.[6]The patients in the emergency department are at a greater risk for drug interactions because they are elders, and/or they have chronic illnesses requiring treatment with multiple medications.[7]The examples for most dangerous drug combinations include warfarin interactions with nonsteroidal anti-inflammatory drugs (NSAIDs), sulfonamides, macrolides, or quinolones; angiotensin-converting enzyme (ACE) inhibitor interactions with potassium supplements or spironolactone; digoxin interactions with amiodarone; and theophylline interactions with quinolones. Previous studies conducted to evaluate drug interactions have mostly been retrospective in nature.[8-10]

MATERIALS AND METHODS

Study design

The Hospital based prospective, observational study has been conducted for a period of 6 months in the Emergency Medicine Department of Kempegowda Institute of Medical Science (KIMS) Hospital and Research Center which is a 1200 bed tertiary care teaching hospital providing both inpatient and ambulatory services to people in and around Bengaluru.

Study Criteria:

Inclusion Criteria

- Patients admitted to and who are on drug therapy in the emergency medicine department

Exclusion Criteria

- Patients transferred and admitted to other departments in the hospital from the emergency department
- Patients discharged against medical advice
- Patients on herbal medications
- Patients treated on outpatient basis

Data collection and Documentation

A total 305 patients who fulfilled the study criteria were included in present study. Potential drug-drug interactions (pDDIs) were detected during the ward rounds from the inpatient case records on a daily basis. The medication data included all the drugs with both brand and generic names, their dose and frequency, route of administration, date of drug started and stopped. The details regarding the potential drug-drug interaction, a brief description of the reaction and its severity were documented. The number of drugs prescribed for the patients were analyzed. The interactions were classified based on their severity. The potential drug-drug interactions were categorized according to their level of severity using the drug interaction checker Medscape.

Drug-Drug Interaction Categories

1. **Minor:** Minor drug reaction would be something very small which is definitely bearable but maybe a bit bothersome.
2. **Significant:** Significant drug reaction would be something that is bearable to an extent but can also cause the patient`s clinical status to deteriorate and require extension of hospital stay.
3. **Serious:** A senior drug reaction would be something that is unbearable, could be life threatening and can cause permanent damage or can even be fatal.

The severity of the potential drug-drug interaction is important in assessing the risk vs. benefit of the treatment and that of the therapeutic alternatives. With appropriate dosage adjustments or modification of the administration schedule, the undesirable effects of several interactions can be avoided.

RESULT

The prescriptions of 305 patients who admitted to the department of emergency medicine were analyzed during the study period to determine potential drug-drug interactions (pDDIs). Among all included patients, 180 (59.2%) male and 125 (40.98%) were female. A total 305 patients, 215 (70.49%) patients showed 1676 pDDIs and the remaining 90 (29.50%) had no pDDIs. Out of 215 patients who showed pDDIs 126 (41.31%) were males and 89 (29.18%) were females (Table No.1).

Table No.1: Sex Distribution, Relation between Sex and pDDIs

Sex Distribution (n=305)		
Sex	**Number**	**Percentage (%)**
Male	180	59.02
Female	125	40.98
Relation between Sex and pDDIs		
Male	126	41.31
Female	89	29.18

In present study 177 (10.56%), 1021 (60.91%), 478 (28.52%) patients showed serious, significant and minor pDDIs respectively (Table No.2).

Table No.2: Classification of pDDIs Based on Severity

Severity	Number of pDDIs	Percentage (%)
Serious	177	10.56
Significant	1021	60.91
Minor	478	28.52

On correlating between patient`s age group and pDDIs it has been found that most number of recorded pDDIs, 683 patients (40.8%) were belong to age group between 61-75 years and in relationship between polypharmacy and pDDIs the highest number of patients, 639 (38.1%) have been received 10-13 medications. Furosemide was found to be number one medicine with highest number of pDDIs (Table No.3). List of drug pairs which have caused highest number of pDDIs was observed which showed that drug pair clarithromycin and budesonide has resulted in 3.9% of the pDDIs, followed by the drugs albuterol and furosemide at 3.1%, ceftriaxone and furosemide at 1.4%, aspirin and clopidogrel, clarithromycin and hydrocortisone both pairs at 1.3% respectively (Table No.4).

Table No.3. Correlation between Age Group, Polypharmacy with pDDIs and Drugs Causing Highest Number of pDDIs

Correlation between Age Group and pDDIs		
Age Group (years)	**Number of pDDIs**	**Percentage (%)**
15-30	181	10.8
31-45	258	15.4
46-60	420	25.1
61-75	683	40.8
76-99	134	8
Correlation between Polypharmacy and pDDIs		
Number of Prescribed Drug	**Number of pDDIs**	**Percentage (%)**
2 to 5	66	3.9
6 to 9	410	24.5
10 to 13	639	38.1
14 to 17	410	24.5
18 to 21	151	9
Drugs Causing Highest Number of pDDIs		
Name of Drug	**Number of pDDIs**	**Percentage (%)**
Furosemide	267	7.9
Budesonide	235	6.9
Clarithromycin	225	6.7
Aspirin	223	6.6
Albuterol	181	5.4
Hydrocortisone	118	3.5
Pantoprazole	85	2.5
Theophylline	79	2.3
Clopidogrel	69	2
Ondansetron	47	1.4

Table No.4.Drugs Pairs which have Resulted in Highest Number of pDDIs and the Underlying Mechanisms of pDDIs

Number of pDDIs	Percentage (%)	Mechanism
66	3.9	Clarithromycin will increase the level or effect of budesonide by affecting hepatic/intestinal enzyme CYP*3A4 metabolism and by P-glycoprotein (MDR1)** efflux transporter
52	3.1	Albuterol and furosemide both decrease serum potassium and can cause hypokalemia by pharmacodynamics synergism
23	1.4	Ceftriaxone increases toxicity of furosemide by pharmacodynamic synergism and there will be increased risk of nephrotoxicity
22	1.3	Either increases toxicity of the other by pharmacodynamic synergism
22	1.3	Clarithromycin will increase the level or effect of hydrocortisone by affecting hepatic/intestinal enzyme CYP3A4 metabolism and by P-glycoprotein (MDR1) efflux transporter

***Cytochrome**

****Multidrug Resistance Protein 1***

DISCUSSION

A hospital based prospective, observational study was conducted to identify and determine the potential drug-drug interactions and to categorize them based on their severity in patients admitted to Emergency Medicine Department in KIMS Hospital & Research Centre, Bengaluru. The patients who fulfilled the inclusion and exclusion criteria were enrolled for the study. The prescriptions of 305 patients were analyzed during the study period and a total of 215 (70.49%) patient prescriptions showed 1676 pDDIs and the remaining 90 (29.50%) had no pDDIs. Among 215 patients who had pDDIs 41.31% were males and 29.18% were females.Classification of pDDIs based on their severity as serious, significant and minor showed that 1021 (60.91%) of the pDDIs were significant, 478 (28.52%) of the pDDIs were minor and 177 (10.56%) of the pDDIs were serious. Similar study conducted to assess DDIs and their severity showed that majority of the DDIs were of moderate (significant) intensity followed by minor.[11] The results in this study also show that pDDIs of significant severity are highest in number.On correlating between patient`s age group and pDDIs it has been found that most number of recorded pDDIs, 683 patients (40.8%) were belong to age group between 61-75 years and in relationship between polypharmacy and pDDIs the highest number of patients, 639 (38.1%) have been received 10-13 medications. Furosemide was found number one medicine with highest number of pDDIs. Richard M. Goldberg et al undertook a study to determine the potential for adverse drug interactions in a high-risk population of ED patients and to characterize drug-drug interactions and obtained results which concluded that patients taking three or more medications are at substantial risk for adverse drug-drug interactions.[10] PuneetDhamija et al conducted a cross-sectional observational study describing the patterns of prescription of drug use and incidence of drug-drug interactions in patients reporting to medical emergency and concluded that polypharmacy was a factor associated significantly with DDI.[12] The results observed in this study also support the fact that polypharmacy is one of the important factors for drug-drug interactions. List of drugs which have been the reason for the highest number of pDDIs in this study was determined which revealed that furosemide is the reason for the highest number of pDDIs (7.9%) and ondansetron has caused least number of pDDIs (1.4%). A study to assess pDDIs also showed that

furosemide is a drug with high probability of causing DDIs.[13] Clarithromycin will increase the level or effect of budesonide by affecting hepatic/intestinal enzyme CYP3A4 metabolism and by P-glycoprotein (MDR1) efflux transporter. Drug-drug interactions may explain an important part of the systemic adverse effects of inhaled corticosteroids. A case of Cushing's syndrome attribute to an interaction between budesonide and clarithromycin has also been reported. [14] When the administration of an inhaled corticosteroid with a CYP3A4 inhibitor is needed, patients should be strictly monitored for any sign of adrenal insufficiently or Cushing`s syndrome. [15] Albuterol and furosemide both decrease serum potassium and can cause hypokalemia by pharmacodynamics synergism. Ceftriaxone increases toxicity of furosemide by pharmacodynamic synergism and there will be increased risk of nephrotoxicity. Aspirin and clopidogrel both increase toxicity of the other by pharmacodynamic synergism. Clarithromycin will increase the level or effect of hydrocortisone by affecting hepatic/intestinal enzyme CYP3A4 metabolism and by P-glycoprotein (MDR1) efflux transporter.[9, 10]

LIMITATION

Although the study has reached its aims, there were some limitations. First the study requires follow up of pDDIs in the patients to look for incidence of actual DDIs and second the number of patient prescriptions analyzed in the study could have been of a higher number.

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