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RESEARCH ARTICLE

To Identify and Analyse Potential Drug- Drug Interactions from the Medication Charts of Medicine Units of a Tertiary Care Teaching Hospital, Davangere

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ABSTRACT

Drug-drug interactions have become an important issue in health care and may often lead to preventable adverse drug events and health damage. The objective of this prospective study is to identify and analyse the potential drug-drug interactions from the medication charts of medicine units of a tertiary care teaching hospital, Davangere. This prospective study was conducted for a period of 6 months. Data of all patients who were prescribed with more than three drugs were included in the study. The collected cases were analysed by using the commercially available software Micromedex®- 2.0. The results of the identified pDDIs were notified to the physicians. Among 90 case collected, 33 (36.67%) patients were female and 57 (63.33%) patients were male. Out of 90 cases collected 74 (82.2%) cases were identified with 263 pDDIs. Maximum number of patients had shown moderate pDDIs 149 (56.7%). Antiplatelets (n=112) were the most frequently observed drugs with pDDIs. The most interacting drug pairs were Aspirin- clopidogrel, Atorvastatin- Clopidogrel (n=12). The patients who were prescribed with 12-15 drugs had the majority of pDDIs per person. Out of 143 drug combinations, 12 pDDIs were identified as beneficial with respect to that particular case. Results of this study indicated that pDDI is associated with increased number of drugs prescribed and increasing age of the patients. Drug combination involving antiplatelets were associated with greater risk of pDDIs. Physicians should be aware of these risks to better assess their patient's therapeutic risk- benefit profiles.

KEYWORDS

Adverse Drug Events, Potential Drug- Drug Interactions, Therapeutic Risk- Benefit Profiles

INTRODUCTION

Drugs are used in the prevention and treatment of symptoms and diseases, but if used improperly, they can produce harmful effects and can show new symptoms or even produce subtherapeutic effects[1]. The optimal choice of pharmacotherapy also depends on the possibility of a drug influencing the safety or efficacy of another drug[2]. A drug interaction occurs when a patient's response to a drug is modified by food, nutritional supplements, formulation excipients, environmental factors, other drugs or disease[3].

There are various patterns of interaction with drugs. They are drug – disease interactions (eg: verapamil with heart failure), drug – food interactions (eg: Chelation occurs with components in food like milk and drugs like tetracycline), environment induced interactions

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(smoking with drugs like caffeine, olanzapine causes pharmacokinetic interactions), drug – drug interactions (eg: Levofloxacin increases theophylline toxicity)[4].

Drug – drug interactions (DDIs) are defined as drug combinations resulting in a pharmacological or clinical response, which differs from response to the agents when either is given alone[5]. The risk and severity of drug interactions varies under the influence of factors such as number of medications received, duration of treatment, patient's age, the number of prescribing physicians and stage of disorder[7]. The elderly patients are at increased risk, as they are with the diseases that alter drug metabolism (eg: renal or liver disease)[1]. With the increasing burden of patients with multiple disease states, the drug therapy has grown more complex[8].

DDIs are an important target for improving patient safety since they can be considered as a preventable medical error.[5] such interactions may lead to increase risk of hospitalization and higher health care costs[6,9,10]. Drug interactions may produce beneficial, desirable, undesirable or harmful effects. The beneficial effects are those whose purpose is to treat concomitant diseases, enhancing the effectiveness, reducing adverse effects and allowing to reduce the dose, while the undesirable effects may reduce the drug effectiveness and may produce adverse and even toxic effects in the body, besides increased treatment cost[11].

According to severity pDDI were classified as:

1. Major- the effects are potentially life threatening or capable of causing permanent damage.

   Ex: Aspirin- Clopidogrel: Concurrent use may result in increased risk of bleeding.

2. Moderate – The effects may cause deterioration in patient's clinical status and additional treatment or extension of hospital stay.

   Ex : Atorvastatin- Phenytoin : Concurrent use may result in decreased atorvastatin plasma concentration.

3. Minor- These are mild interactions. Consequences may be bothersome or unnoticeable but should not significantly affect the therapeutic outcome[11].

   Ex: Ranitidine- Theophylline: Concurrent use may result in theophylline toxicity.

Harmful drug- drug interactions are important as they cause 10-20% of the adverse drug reactions requiring hospitalization and they can be avoided[3]. In the Harvard Medical Practice Study of Adverse events, 20% of events in an acute hospital in- patient setting were drug related. Of these 8% were considered to be due to Drug-Drug Interactions (DDI)[12]. Since potential drug-drug interactions are an alarming problem for our society, it must be addressed by all health care providers including pharmacists to play a major role in preventing a potentially adverse situation from occurring[4].

Objectives

Primary Objectives

- To collect, identify and analyze potential drug – drug interactions in the medication charts of the patients admitted in the medicine unit of a tertiary care teaching hospital, Davangere.

Secondary Objectives

- To categorize and classify the pDDIs as major, moderate and minor.
- To identify the effect of age and gender in pDDI.
- To identify the relation between number of drugs prescribed and number of pDDI.
- To classify the drugs involved in pDDI and to find out the most frequently involved class of drugs in pDDI.
- To measure the frequency of most commonly occurred pDDIs among the inpatients.
- To classify the identified pDDIs as harmful or beneficial.
- To notify the physicians about the results of the identified pDDIs.

MATERIAL AND METHODS

Study Site

The study was conducted in the medicine wards of a tertiary care teaching hospital in Davangere.

Study Period

The study was conducted for a period of six months.

Study Design

This is a prospective study.

Study Criteria

The patients were selected and assessed for pDDIs by the following inclusion and exclusion criteria.

Inclusion Criteria

- All Patients who were prescribed with more than 3 drugs in the medicine department of a tertiary care teaching hospital.

Exclusion Criteria

- Paediatrics and Pregnant patients.
- Patients who were not prescribed with more than 3 drugs.

Sources of Data

Data were collected from prospective series of in-patients who were prescribed with more than 3 drugs in the medicine unit.

Ethical Approval

The Institutional Ethical Committee of Bapuji Pharmacy College, Davangere has approved the study.

Study Procedure

- The students attended ward rounds every day in medicine unit of a tertiary care teaching hospital and collected data of all the patients who were prescribed with more than 3 drugs.
- Students collected patient details, diagnosis, co-morbidities and drugs prescribed with their doses and frequency of administration from the medication charts of the patients.
- The collected data was analyzed for potential drug- drug interaction using commercially available software Micromedex® 2.0 and other tertiary resources, eg: Stockley's Drug Interaction.
- The identified pDDIs were classified as major, moderate, minor according to Micromedex® 2.0.
- Drugs involved in the potential DDIs were categorized based on the pharmacological classifications and the most frequently involved class of drugs were identified.
- Differences in number of potential DDIs in males and females as well as between age groups were identified.
- The relation between the number of drugs prescribed and number of potential DDIs were identified.
- The frequency of most commonly occurred pDDIs were measured.
- The identified potential DDIs were classified as harmful or beneficial.
- The results of the identified pDDIs were notified to the physicians.

Development of Data Collection Form

Patient Data Collection Form

A suitably designed patient data collection form was developed. The information includes patient demographic details, diagnosis, co-morbidities, drugs prescribed with their doses, frequency and route of administration. Identified pDDIs were mentioned in this form.

RESULTS

A total of 90 prescriptions were analyzed during the study period out of which 33(36.67%) and 57(63.33%) were females and males respectively.

Out of 90 cases, 74(82.2%) cases were identified with pDDIs and 16(17.8%) were without DDIs**.** Table 1 below shows the result.

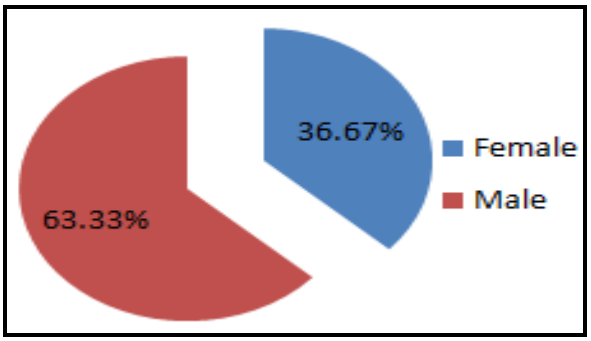

Figure 1: Distribution of patients according to gender

Table 1: Distribution of cases with respect to pDDIs

Type of case	No. of cases	Percentage (%)
No. of cases with pDDI	74	82.2
No. of cases without pDDI	16	17.8
Total No. of cases	90	100

According to age group, the numbers of pDDIs were distributed. Among which the majority of pDDIs were found in the age group of 56-60 yrs (18.63%).

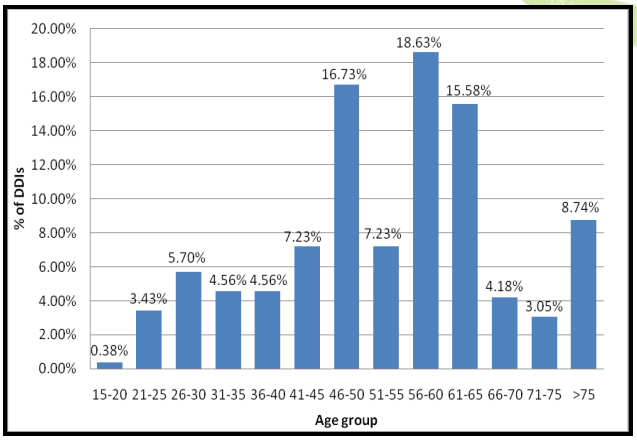

Figure 2: Distribution of patients with respect to age

The identified potential DDIs were analysed as major, moderate and minor. A total of 263 potential DDIs were obtained from 74 cases. From these 87 (33.1%) were of major severity, 149 (56.7%) were of moderate severity and 27(10.2%) of minor severity. Majority of the identified pDDIs were of moderate severity.

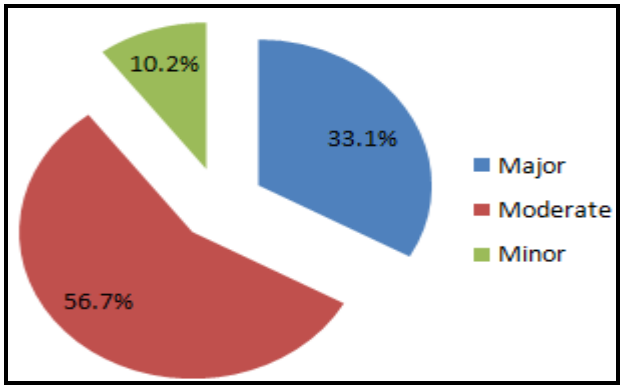

Figure 3: Distribution of potential DDIs according to degree of severity

In the present study conducted, antiplatelets were the most frequently implicated drugs with 112 of all potential DDIs identified, followed by diuretics and beta blockers (n=35), antiemetics (n= 29). Table 2 summarizes the most frequent DDI.

Table 2: Categorization of pDDIs based on Drug Classification

Sl. No.	Drug Classification	No. of frequency involved in pDDIs
1	Anti platelets	112
2	Diuretics	35
3	Beta adrenergic blockers	35
4	Anti emetics	29
5	Anti diabetic agents	27
6	Fluoroquinolones	27
7	Hypolipidemic agents	25
8	Antiepileptics	22
9	Anti tubercular agents	22
10	Calcium channel blockers	18

The most prevalent potential DDIs were identified. The most frequent interacting drug pairs were Aspirin + Clopidogrel (n=12), Atorvastatin + Clopidogrel (n=12), Aspirin + Insulin(n=8), Furosemide + Aspirin(n=7) which is shown in the table 3.

Table 3: Most prevalent DDIs

Sl. No.	Drug Combinations		No. of cases	Severity	Consequences of DDI
1	Clopidogrel	Aspirin	12	Major	Increased risk of bleeding
2	Clopidogrel	Atorvastatin	12	Moderate	Decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet activity
3	Aspirin	Insulin	8	Moderate	Hypoglycemia
4	Furosemide	Aspirin	7	Moderate	Blunting of the diuretic effect of furosemide
5	Telmisartan	Aspirin	6	Moderate	Decreased anti hypertensive effects and an increased risk of renal impairment
6	Vitamin B_{12}	Vitamin C	6	Minor	Reduced amount of cyanocobalamin (vitamin B_{12}) available for serum and body stores
7	Azithromycin	Ondansetron	6	Major	Increased risk of QT interval prolongation
8	Pantoprazole	Iron supplements	5	Moderate	Reduced iron bioavailability
9	Aspirin	Heparin	5	Major	Increased risk of bleeding
10	Aspirin	Hydrochlorothiazide	5	Moderate	Decreased diuretic and anti hypertensive efficacy
11	Ranitidine	Aspirin	5	Minor	Reduced salicylates plasma levels and decreased antiplatelet effect of aspirin
12	Amlodipine	Aspirin	5	Moderate	Increased risk of gastrointestinal haemorrhage and/or antagonism of hypotensive effect

Figure 4 below summarizes the distribution of potential DDIs with the number of drugs prescribed. 50 patients who were prescribed with 8 to 11 drugs were identified with majority of the potential DDIs (58.93%), whereas on average, patients prescribed with 12-15 drugs were found to have maximum pDDIs i.e., 3.2 pDDI per person.

The identified potential DDIs were analyzed and classified as harmful, beneficial and non-assessable. Out of 143 drug combinations 12 pDDIs were beneficial with respect to that particular disease condition, 127 were harmful and 4 were non-assessable. Some of the beneficial and harmful DDIs are summarized in the table 4 given below.

Table 4: Categorization of pDDIs as harmful and beneficial

Sl. No	Drug combinations	Disease & co-morbid condition	Harmful /Beneficial	Summary
01	Aspirin + Clopidogrel	CVA-IHD,MI,HTN, DM	Beneficial	Increased bleeding will be beneficial in case of cerebro vascular accident
02	Aspirin + Valproate sodium	Epilepsy- HTN, CVA	Beneficial	Increased free valproic acid concentration will be beneficial in epileptic patients.
03	Clopidogrel + Vitamin A	MI- CVA, ALD,HTN	Beneficial	increased bleeding will be beneficial in case of MI
04	Clopidogrel + Enoxaparin	Acute coronary syndrome- HTN, DM	Beneficial	Beneficial in case of acute coronary syndrome.
05	Pyrazinamide + Rifampicin	Koch- PAH	Harmful	Severe hepatic injury
06	Atorvastatin + Fenofibrate	HTN- DM, UTI	Harmful	Increased risk of myopathy or rhabdomyolysis.
07	Ondansetron + Ofloxacin	Acute GE- ARF,HTN	Harmful	Increased risk of QT interval prolongation.

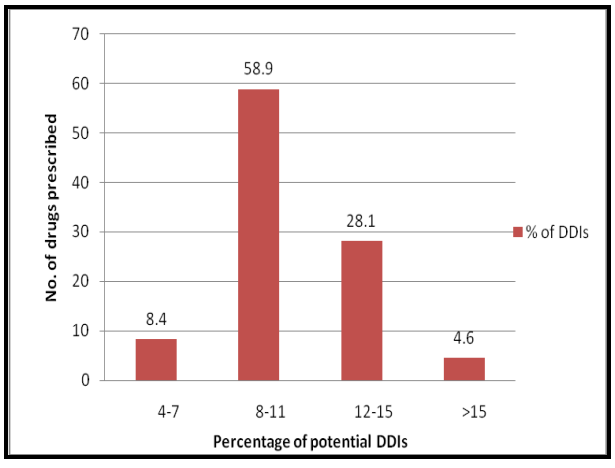

Figure 4: Distribution of potential DDIs with no. of drugs prescribed

DISCUSSION

Drug interactions have become more complex because of the increased use of multiple prescription drugs.[14] The present prospective study was conducted to identify and analyse pDDI from the medication charts of medicine units of a tertiary care teaching hospital, Davangere. The study was conducted for a period of 6 months and data was collected in prospective series of in-patients who were prescribed with more than 3 drugs. A total of 90 patients met the inclusion criteria.

Out of the 90 cases 57 patients (63.33%) were males and 33 (36.67%) were female. This study also revealed a male predominance over female

as similar to a study conducted by Radhakrishnan R, et.al, Hosssein R, et.al. In contrast more prevalence of drug interactions in women has been found by Joice MC, et.al.[7,9,13]

The study focused on the patients who were aged more than 15 yrs and majority of the patients were in the age group of 56- 60 yrs. In many of the reported studies, age more than 60 was reported as an independent risk factor for potential DDIs. Since this age group usually has many intercurrent illnesses, they might be subject to polypharmacy which increases the chance for pDDIs.[12]

The collected data was analysed for potential DDIs by using commercially available software Micromedex®-2.0. A total of 263 potential DDIs were identified in 90 patients with total of 143 different drug combinations. Out of these 90 cases, 74(82.2%) cases were identified with pDDIs and 16(17.8%) were without pDDIs.

Identified DDIs were classified into major, moderate and minor using the software Micromedex® -2.0. In the 263 potential DDIs, 87 were of major severity (33.1%), 149 were of moderate severity (56.7%) and 27 were of minor severity (10.2%). Of the total potential DDIs majority were of moderate severity in our study which is similar to a study conducted by Virendra KP, et.al.[12]

In our study the commonly interacting drug pairs were Aspirin-Clopidogrel (n=12), Clopidogrel-Atorvastatin (n= 12), followed by Aspirin-Insulin (n=8) and Furosemide -Aspirin (n=7). The effects of these interactions are increased risk of bleeding, decreased formation of clopidogrel active metabolite, hypoglycemia and blunting effect of furosemide respectively.

In our study the majority of the patients were prescribed with 8 to 11 drugs, thus maximum pDDIs were found in this group. Whereas, patients prescribed with 12-15 drugs have maximum number of pDDIs i.e 3.2 per patients. In a previous study conducted by Virendra KP, et.al it was seen that there is a linear increase in the percentage incidence of drug interactions with an increase in the number of drugs prescribed to the patient.[12]

Some of the most common drug classes involved in DDIs were anti- platelets (n=112), followed by diuretics (n=35) and beta adrenergic blockers (n=35). The reports were almost similar to the studies conducted by Virendra KP, et.al and Mateti UV, et.al in which antiplatelets and anticoagulants were the most common drugs responsible for pDDIs. In fact some of these drug combinations were used for therapeutic benefit in clinical practice and others were harmful having an increased risk of DDIs. These drugs can be used together to treat cardiac conditions following a risk-benefit assessment. It is likely that many clinicians balance the risks of pDDIs against the benefits when prescribing patients with multidrug regimens.[12]

The identified pDDIs in the study were classified as harmful, beneficial and non-assessable. Out of 143 drug combinations, 12 pDDIs were beneficial with respect to that particular patient's condition, 127 were harmful and 4 were non-assessable. Some of the beneficial pDDIs are Aspirin and Clopidogrel, Aspirin and Valproate sodium which causes increased bleeding and increased free valproic acid concentration in cases of CVA and epilepsy respectively.

The identified pDDIs related problems were notified to the physicians and assured that they will take possible safety measures to minimize the DDIs in future. The recognition of DIs by General practioners will help to improve the patient safety and therapeutic outcome.

This study was concerned with potential drug-drug interactions on prescriptions, and no attempt was made to determine whether the patients actually ingested the medication or whether the interaction resulted in an adverse drug event. Thus, the study were only potential, no clinical outcomes or consequences were evaluated. Identification of pDDIs was based mainly on the information obtained from the Micromedex database.

The pharmacodynamic and pharmacokinetic interactions were not evaluated due to lack of

time and insufficient data collection. The clinical relevance of the identified DDIs was evaluated according to the criteria stated in the literature. But the clinical evaluations of the real effects of these interactions were not possible. However, the results emphasized the possibility of DDIs that could have led to severe problems. Intervention was not done on daily basis.

CONCLUSION

The pDDIs are frequent among the hospitalized patients who were prescribed with more than three drugs. Our study demonstrated that a total 263 pDDIs were identified from 74 cases. The majority of the pDDIs identified were of moderate severity. Antiplatelets were found to be as the most interacting drug class. The majority of the identified pDDIs were harmful. In order to prevent these pDDIs, health care providers should have adequate information about DDIs and thereby prevent drug therapy problems. From this study it is concluded that future studies are needed to assess drug interactions and other drug-related problems that may appear clinically.

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