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Research Article

AN ANALYSIS OF POTENTIAL DRUG-DRUG INTERACTIONS IN PATIENTS ADMITTED IN MEDICINE WARDS OF A TERTIARY CARE HOSPITAL

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ABSTRACT

Drug- Drug Interactions (DDIs) are one of the most significant problems with drug prescribing. The present study was conducted to analyse potential DDIs in inpatients of medicine wards of a tertiary care hospital, based on severity, mechanisms etc. and to create awareness about the implications of such potential DDIs among treating physicians. Data from patient's prescriptions admitted to the medicine department was collected over a period of 3 months and prescriptions were analysed for potential DDIs using medscape online drug interaction checker software. In this study, out of 200 prescriptions reviewed, 177(88.5%) prescriptions had potential DDIs. The total number of potential DDIs was 1135. Pharmacodynamic DDIs (58.23%) were most common as compared to pharmacokinetic DDIs (38.50%). Based on severity, 0.08% were contraindicated, 6% were serious, 72% to be monitor closely and 22% were minor DDIs. The most common drug class involved in DDIs were antibiotics(234). It was observed that polypharmacy played a crucial role for such a rise in number of DDIs. The study revealed that a large number of DDIs were clinically significant and seen with routinely used drugs in clinical practice. Hence, it is the need of the hour to create awareness among treating physicians the implications of DDIs and to prescribe carefully to minimise such DDIs in future.

INTRODUCTION

Clinically relevant and prominent drug interactions started unfolding in literature in the early 1960's. The first clinically relevant drug interaction was hypertensive crises found in patients with concomitant use of cheese and monoamine oxidase inhibitors. Due to such a milestone in late 1960's drug interaction monographs came into existence for proper prescription and dispensing practices[1,2].

A drug interaction results when pharmacologic effects of a drug are modified by concomitant use of another drug or food[3]. The drug effects may either be unchanged, antagonised or potentiated by its interaction with other drugs. Consequences of such interactions can cause no effect at all to drug related mortality and morbidity like treatment failure to severe adverse drug events[4].

DDIs are one of the most significant problems with drug prescribing[5]. DDIs account for about 3% of hospital admissions[6,7]. Studies show that up to 3-30% of patients experience symptoms associated with DDIs[8,9].

DDIs are caused by many factors, important ones being[10,11]

- Age of patient
- Number of drugs prescribed
- Duration of therapy
- Disease status
- Comorbid conditions and illness: cirrhosis, renal failure, shock
- Polypharmacy
- Prolonged periods of drug therapy
- Physiological aging

About 20-40% of DDIs are seen in geriatric patients. This is primarily due to polypharmacy and administration of various products to elderly which lead to adverse drug reactions[12,13]. Physicians are either not fully aware of all major and clinically important drug interactions or underestimate the risk of co administration of multiple drugs[14,15]. Thus, our study was carried out to identify potentially significant DDIs to the common drug groups involved. This study tends to improve our existing knowledge on potential DDIs with common drugs so

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that physicians can prescribe rationally and indulge in close monitoring of patients in whom these interactions are possible.
The study was conducted with the following aims and objectives in mind:

- To analyse the potential DDIs in patients admitted in medicine wards
- To classify the potential DDIs into contraindicated, serious, those needing close monitoring and minor
- To create awareness among the physicians about the implications of the potential DDIs

MATERIALS AND METHODS

This prospective observational study was conducted in the medicine wards of a tertiary care Hospital in Goa over a period of 3 months After obtaining approval from the Institutional Ethics Committee, data was gathered from the case record sheets and nurse's registers of 200 patients who were admitted in medicine wards during the study period and exposed to at least 3 concomitant drugs.

Data Evaluation and Analysis

Data was analysed using Microsoft Excel 2010. All data was tabulated according to the combinations of drugs in treatment charts. Potential DDIs were identified using medscape online drug interactions checker software, textbooks and reference books. Medscape drug interaction checker software classifies interactions into various categories like contraindicated, serious, monitor closely and minor.The severity and occurrence of potential DDIs was evaluated by cross checking each patients prescription profile. Collected data was analysed for the following:

- Age and Gender distribution of potential DDIs
- Average number of drugs per prescriptions
- Classification of drug interactions
- Mechanisms of potential DDIs
- Severity of DDIs
- Major therapeutic classes of drugs involved in DDIs

RESULTS

Demographics

The prescriptions evaluated in this study comprised more female (54%) than male (46%) patients.
The age distribution and number of prescriptions in each age group are as follows:

Table 1 Showing number of prescriptions in the corresponding age groups

Age Group (years)	Number of Prescriptions
18-25	13
26-39	26
40-49	34
50 and above	127

Out of 200 patients, 94 were males, of which 82 had DDIs and 12 were without DDIs. Similarly, out of 106 females, 95 had DDIs and 11 were without DDIs.

Prescription Analysis

Out of 200 prescriptions analysed, a total of 177 prescriptions were involved in DDIs. The total number of potential DDIs evaluated in this study were 1135 with female and male distribution of 584 and 551 respectively. There were no DDIs in 23 prescriptions, 143 prescriptions had 1-10 DDIs, 32 prescriptions had 11-20 DDIs and only 2 prescriptions had DDIs in range of 21-30.

Drugs use Pattern

Total 200 patients received 1571 drugs with average number of drugs prescribed per patient being 7.84. The highest number of drugs per prescription was 18 and this prescription had maximum number of DDIs i.e.22. The lowest number of drugs per prescription was 3, which had DDIs ranging from 0-4.

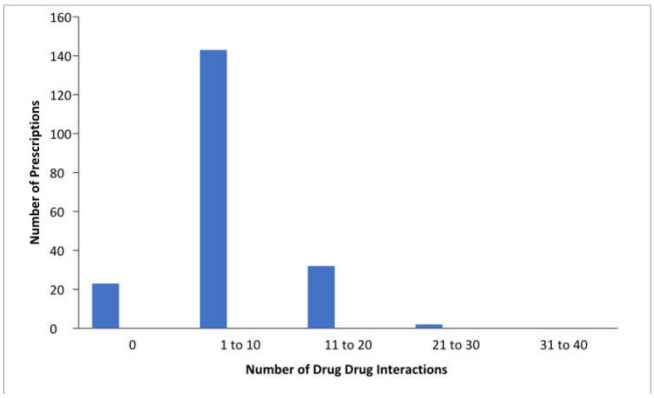

Figure 1 Correlation between potential DDIs and number of drugs prescribed

Classification of DDIs Based on Severity

Out of identified DDIs, only one DDI(0.08%) was in the contraindicated category, 69(6%) were serious (Use alternate) DDIs, 811(72%) were to be closely monitored DDIs; remaining 254(22%) were minor interactions.

Mechanism of Interactions

Pharmacodynamic DDIs were the most common, comprising of 58.23%, followed by pharmacokinetic DDIs which were 38.50%. 3.17% were interactions due to unspecified or unknown mechanisms.

Major Therapeutic Classes of Drugs

In our study, the major drug classes involved in DDIs were antibiotics (234), followed by antiplatelet and anticoagulants (148), antihypertensives (145) and antiulcer drugs (142).

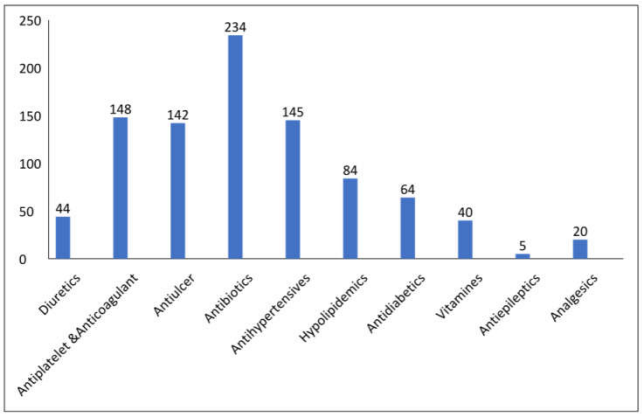

Figure 2 Major Drug Classes involved in Drug-Drug Interactions

DISCUSSION

When effects of a drug are altered by another drug(s), food , drink or an environmental chemical a drug interaction occurs[16]. The modifications of pharmacologic effects of one drug by the prior or concomitant use of another drug results into a DDI[17]. DDIs are under-recognised contributors to medication errors and their risk increases with an increase in number of drugs prescribed. Drug interactions are of different types which includes Drug- Drug interactions, Drug –Food interactions, Drug-Disease interactions and Drug herb interactions. Of these, DDIs are most crucial in terms of frequency and severity[17]. A review of 9 studies reported that the incidence of hospitalisations due to DDIs was 0-2.8% ; it has also been shown that nearly 1% of all hospitalized patients suffer an adverse drug event during hospitalization[18]. DDIs account for nearly 17% of adverse drug events in hospitalized patients[10]. For treating drug related problems in US the cost has increased from $76.6 billion in 1994 to $ 177.4 billion by the year 2000 [19,20]. In Indian settings data regarding types and frequency of potential DDIs is limited. The prescribing pattern for most diseases differs in India from one institution to another and also vis a vis the Western countries[17]. Hence the present study was conducted to analyse the potential DDIs in inpatients of medicine wards with regards to their demographics, severity, clinical significance, mechanisms and common drugs involved. We analysed 200 prescriptions in the patients admitted to medicine wards of Goa Medical College. The prevalence of potential DDIs in our study was very high (88.5%). This figure is higher than prevalence values reported by studies conducted in different settings in Iran (20.3%)[21]. The differences in prevalence rates are due to variability in prescribing habits, availability of alternative drugs and existence of drug prescription policies in hospitals.

Based on severity only 1(0.08%) DDI belonged to ‘ Contraindicated ’ category , whereas maximum 811(72%) fell in the ‘ To be monitored closely ’ category, 69(6%) belonged to ‘ Serious ’ category . Thus, 78% DDIs were clinically significant. These trends are consistent with findings of Tesfaye *et al* [21]and Kapadia *et al*[17]. Polypharmacy (3-5drugs) and high end polypharmacy (>5drugs) was frequent in all the prescriptions. Average number of drugs per prescription was 7.4. Our findings were in concurrence with the results of Barot *et al*[22] and Glintborg *et al*[23]. An average of 5.67 potential DDIs were detected per prescription in our study. This was higher than that reported by Zwart –van Rijkom *et al*[10] with an average of 3.4 DDIs and lower than that reported by Barot *et al*[22] which averages to 7.63 DDIs per prescription. Polypharmacy increases the risk of DDIs and should be implemented to patients with utmost care[24]. However, in admitted patients with multiple comorbidities this is often difficult. Our study findings also suggested that higher number of potential DDIs were attributed to higher number of drugs per prescription, these results are similar to studies by Birader *et al*[25] and Kohler *et al*[26].

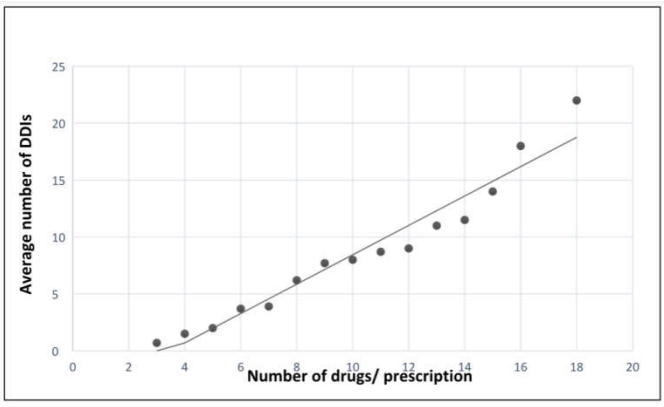

Figure 3 Correlation between number of drugs versus average number of DDIs per prescription

Based on mechanisms, 661(58.3%) belonged to pharmacodynamic category, 437(38.5%) were of pharmacokinetic type and rest 37(3.17%) of unspecified category. This finding is in par with studies by Kapadia *et al* where most of the DDIs were of pharmacodynamic type. These interactions have the potential to increase or decrease the therapeutic effect[17].

According to a Brazilian study, DDIs are more prevalent in patients aged more than 55 years[27]. A Swedish study reported 31% incidence of DDIs in elderly patients with an average age of 78.2 years [28]. Similarly in a study on out patients at least 1 potential DDIs was detected in 46% of 1601 elderly people in six European countries[29]. In the present study also, it was noted that as the age of the patient increased, the average number of drugs prescribed and potential DDIs per prescription also showed an increment. Patients in the age group of 50 years and above were prescribed most number of drugs per prescription and also had maximum number of potential DDIs. It was observed that higher number of potential DDIs were attributed to higher number of drugs per prescription. Therefore caution must be exercised while selecting drug therapy in elderly patients to avoid the risks associated with potential DDIs, as to whether the higher number of drugs are genuinely necessary in these age groups.

Table 2 Most frequently encountered DDIs in each category among commonly used drugs

Contraindicated	Serious (use alternative)	Monitor closely	Minor
ceftriaxone + calcium carbonate	aspirin + ramipril	aspirin + clopidogrel	aspirin + furosemide
	clarithromycin + atorvastatin	aspirin + insulin	Pantoprazole + cyanocobalamine
	azithromycin + enoxaparin	aspirin + enoxaparin	calcium carbonate + aspirin
	clarithromycin + clopidogrel	enoxaparin + clopidogrel	metronidazole and pyridoxine
	pantoprazole + digoxin	aspirin + metoprolol	metronidazole + thiamine
	rabeprazole + clopidogrel	metoprolol + furosemide	aspirin +folic acid
	phenytoin + rabeprazole	metoprolol + amlodipine	furosemide + calcium carbonate

In our study concomitant use of ceftriaxone with calcium carbonate was the only DDI under 'contraindicated' category. Unabsorbable complexes formed due to this pharmacokinetic interaction decreases their therapeutic effect. If both are given simultaneously there is a potential for particulate precipitation in lungs and kidneys thus causing toxicity[30].

Under 'serious' category, combination of aspirin and ramipril was most commonly prescribed. This combination can lead to renal function deterioration and decrease the antihypertensive effect of ramipril. Similarly, the next combination of clarithromycin and atorvastatin can cause increased toxicity of atorvastatin by affecting its metabolism by the former drug. Combination of azithromycin and enoxaparin can cause increased toxicity of enoxaparin due to its decreased metabolism. Combination of clarithromycin and clopidogrel can cause a decrease in the levels of clopidogrel by affecting its metabolism which in turn can cause a decrease in antiplatelet effect. Combination of pantoprazole and digoxin can cause hypomagnesaemia and digoxin toxicity which has a potential to cause arrhythmias[30].

Aspirin and clopidogrel is a very commonly used combination for cardiac patients which needs close monitoring. There is increased anticoagulation due to the combined effect that has the potential to cause bleeding. The clinicians ought to observe the patients during administration and follow up as the combination is often prescribed during a patient's lifetime. Similarly, the combination of aspirin and insulin can cause increased effects of insulin by aspirin especially when administered in high doses (3gm / day or more) which has a potential to cause hypoglycaemia, so insulin dose adjustments and close monitoring of blood glucose may be required. Combination of aspirin and enoxaparin can cause increased anticoagulant effect and has a potential to cause increased bleeding tendency. Hence monitoring of blood parameters are needed. Aspirin and metoprolol together can cause increased risk of hyperkalemia and potential to cause arrhythmias so close monitoring of serum potassium in needed. Similarly, the combination of metoprolol and furosemide can cause fluctuations in serum potassium levels which has a potential to cause arrhythmias[30].The most frequent classes of drugs implicated in potential DDIs in our study were antibiotics (14.89%), anticoagulants and antiplatelet (9.38%) and antiulcer drugs(9%). This was comparable to study by Barot *et al* in which most frequent classes of medications involved in DDIs were antimicrobials (8.74%), steroids (4.19%), antiplatelet drugs (4.19%), diuretics (3.59%), anticoagulants (3.23%), ACE inhibitors and AT1 antagonist (2.87%) and beta blockers (2.75%)[22]. In a study by Goldstein *et al* the most frequently implicated drugs in potential DDIs were NSAIDs, beta blockers , steroids, ACE inhibitors and anticoagulants[31]. A study by Hohl *et al* showed that most frequent classes of drugs involved in DDIs were NSAIDs, antibiotics and anticoagulants[32]. Beer *et al* reported that 89% of DDIs were accounted from opioid analgesics, NSAIDs, benzodiazepines, antacids and diuretics[33]. Gaddis *et al* reported most frequent drugs associated with DDIs were digoxin, warfarin and aspirin. These differences in drug classes causing DDIs varies considerably from one institution to the other due to variability in prescribing habits, patient population and screening systems[35,36].

These findings are alarming and need to be analysed with great apprehension about its future. We prescribe antibiotics recklessly without pharmacological rationale and often prescribe 3-5 antibiotics in a single patient. Often there are drug interactions leading to failure of therapy, which go unnoticed, thus increasing institutional financial burden and also the chances of resistance. We have to look into the wrong habit of co-prescribing ranitidine, pantoprazole and similar drugs with every prescription in an anticipation of a gastric adverse effect. This can lead to decreased absorption of its parent drug and failure of therapy.

CONCLUSION

Polypharmacy which is an important cause of DDIs was frequent in the present study. The number of drugs prescribed increased with age and also the number of potential DDIs. Our study revealed ignorance regarding the use of multiple drugs in clinical practice with fairly large number of DDIs being clinically significant. DDIs have potential to either alleviate or deteriorate the therapeutic effects and to accelerate risks of adverse drug reactions. Thus optimal number of drugs should be prescribed, careful selection of therapeutic alternative in case of potential DDIs should be done, continuous monitoring of adverse effects and use of computerised systems or free online drug interactions checker applications to see for drug interactions in inpatients, if possible, should be implemented in whom these drugs are prescribed.

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