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Research Article

ASSESSMENT OF DRUG-DRUG INTERACTIONS IN HOSPITALISED PATIENTS IN INDIA

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ABSTRACT

This study was conducted to assess the frequency, factors affecting frequency and severity of PDDIs in hospitalised patients. This was a prospective study carried out in all the Medicine wards for a period of six months. Of the 240 patients reviewed, a total of 77 (32%) patients had PDDIs. The frequency of PDDIs found to be 44%. The number of drugs received by the patients ranged from 3-10 (Mean ± SD: 7 ± 2). Majority (60%) of the patients were exposed to PDDIs of moderate level of severity, 37.5% of patients were exposed to PDDIs of severe level of severity and only 2.5% patients experienced PDDIs of mild level of severity. It was observed that the frequency of PDDIs increased with an increase in the age of the patient and with the size of the prescription. A positive correlation was found between the age of the patients and PDDIs ($r = 0.338$, $P < 0.01$) and the prescription size and PDDIs ($r = 0.402$, $P < 0.01$). The more number of PDDIs were due to proton pump inhibitors (PPIs) followed by statins. The most of the PDDIs were between PPIs and paracetamol and PPIs and clopidogrel which are moderate in severity and of risk rating D. The study showed that regular monitoring of PDDIs will definitely help in better patient care.

Keywords: Potential drug, Drug interactions, Frequency, Severity, Risk rating.

INTRODUCTION

Potential drug- drug interactions (PDDIs) are the pharmacological or clinical responses to the administration of drug combinations different from that anticipated from the known effects of the two agents when given alone[1].

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 a life threatening situation. PDDIs may include, drug contraindications, drug combinations that require monitoring and possible dosage adjustments when given concomitantly or drugs which may be beneficial when administered together.

It is important not only to identify PDDIs that are clinically meaningful, but also to understand options to approaching the potential loss of efficacy or toxicity that may result when certain combinations of drugs are administered together[2].

Understanding the pharmacology of a drug and the mechanism by which a drug may interact can assist in prediction of early recognition of a drug interaction. In every potential drug-drug interaction, an index drug and an interacting drug is involved. The drug for which the pharmacological or clinical response is altered is called the index drug, and the drug that induces the interaction is the interacting drug[1].

Many studies have confirmed polypharmacy as one of the major risk factors in precipitation of PDDIs [1, 3]. The elderly populations are at increased risk because of decreased functioning of the systems, more number of medications due to co morbidities, and complicated drug regimens[4, 5].

The magnitude of potential drug-drug interactions increases significantly in certain patient populations and as the number of medications taken each day increases.

PDDIs not only present a danger to the patient but they can also greatly increase health care costs. The outcome can be harmful if the interaction causes an increase in the toxicity of the drug. It is well documented that drug interactions are a problem in hospitalised patients. Hence it is important to discuss the occurrence and management of PDDIs among the health care professionals.

Many PDDIs can be avoided or managed safely through careful monitoring. Since PDDIs are alarming problem for our society, it must be addressed by all health care providers and needs to play an important role in preventing a potentially adverse situation from occurring[3]. Hence the study is conducted to monitor and assess the frequency of PDDIs in a tertiary care teaching hospital.

MATERIALS AND METHODS

The present study was conducted at tertiary care teaching hospital, Mysore. It is a 1200 bedded multispecialty tertiary care teaching hospital. The hospital provides primary and specialized health care facilities to people in and around Mysore district.

This study was a prospective review of PDDIs and was carried out in all the Medicine wards for a period of six months. An approval from the Institutional Ethical Committee was obtained prior to the study. Patients who were admitted to in-patient wards of Medicine wards and the patients of either sex aged ≥18 years were all included in the study. The patients receiving less than 24 hours in-patient care and patients who themselves have enrolled in any other investigational studies were excluded from the study. Patients who met the study criteria were included in the study.

All the relevant and necessary data of the patient's including , demographic data such as age, gender, body weight, past medical history, reason for admission, co-morbidities, clinical data such as haematology, biochemistry, and therapeutic data including dose, duration, frequency, route, time of administration and concomitant medication were collected from patient's case notes, treatment charts, laboratory reports, interviewing patients or patients care takers, interviewing healthcare professionals. All the collected data were documented in the suitably designed data collection form.

All patients admitted to Medicine wards were reviewed every day and PDDIs were identified by using the standard text books and online resources. Also all the PDDIs were categorized according to the risk rating of PDDIs (Table 2), level of severity (Table 3) [6,7] .The PDDIs were notified to the respective health care professionals of the respective wards where these PDDIs were identified for the necessary change in the therapy. Evaluation of drug-drug interactions was performed for all PDDIs identified in patients. The patients were followed until their discharge to identify PDDIs and their effects.

Assessment of frequency of PDDIs

The frequency of the PDDIs was estimated by using the formula[8] (Table 1).

The factors such as, age of the patients and polypharmacy which affect the frequency of PDDIs were determined and correlation analysis was performed to assess the statistical significance between the number of drugs prescribed and the number of potential drug-drug interactions. Also correlation analysis was performed to assess the statistical significance between age of the patients and the number of potential drug-drug interactions.

Criteria of evaluation of severity

The criteria of risk rating (Table 2) and criteria for severity were used for evaluation of PDDIs [6, 7] (Table 3).

RESULTS AND DISCUSSION

A total of 240 patient's case sheets were reviewed in all the Medicine wards during the six months study period. The mean age of the patients was (55±15.5) ranging from 18 to 84 years. Out of which 124(52%) were males and 116(48%) were females. Among the 240 patients 103 (43%) patients were with prior medical problems and 137(57%) patients were without prior medical problems. Of the 240 patients case sheets reviewed, 105 (44%) PDDIs were identified in 77 (32%) patients. The frequency of PDDIs was found to be 44%.

The mean age of the 77 patients who have experienced PDDIs were (60±14.62) ranging from 18 to 84 years. Out of which 59(77%) were males and 18(23%) were females. Among 77 patients who have developed PDDIs 40(52%) patients were with prior co-morbidities. The numbers of drugs received from 77 patients were ranging from 2 to 10 drugs (Mean± SD: 7±3).The relationship between patient characteristics and PDDIs were given in Table 4.

Comparing the patient characteristics with the PDDIs, the patients with PDDIs had a mean age of 60±14.62 years when compared to 49±15.6 years for the patients without PDDIs. There was more number of male patients having PDDIs when compared to female patients.

The numbers of drugs prescribed to the patients with PDDIs were 7±3 drugs when compared to 5±2 drugs for patients without PDDIs. Of the 240 patients, 103 patients had co-morbidities, out of which, in 40 patients PDDIs were identified and in 63 patients there were no PDDIs (Table 4).Two factors affecting the frequency of PDDIs, evaluated through correlation analysis were age of the patients and prescription size of the patients. The number of PDDIs experienced by the patients was directly proportionate to their age ($r = 0.338$, $P < 0.01$).The number of PDDIs experienced by the patients was directly proportionate to the number of medications received by the patients ($r = 0.402$, $P < 0.01$).

Among the 105 PDDIs, 35 (33%) PDDIs were of major severity, 33(32%) PDDIs were of moderate severity and 37 (35%) PDDIs were of minor severity. Among the 105 PDDIs, 67% of the PDDIs were of the risk rating D, 30% of the PDDIs were of the risk rating C, 8% of the PDDIs were of the risk rating B and 1% of the PDDIs were of risk rating A.

The details of PDDIs and the risk rating are given in (Table 5). Among 77 patients majority 46 (60%) of the patients were exposed to PDDIs of moderate level of severity, 29(37.5%) of patients were exposed to PDDIs of severe level of severity and only 2(2.5%) patients experienced mild level of severity of PDDIs.

Of the 105 potential drug-drug interactions, 54%, 12% and 7% were attributed to proton pump inhibitors (PPIs), steroids and statins respectively. Involvement of other class of drugs in developing PDDIs was shown in Figure 1. The most of the PDDIs were between PPIs and paracetamol and PPIs and clopidogrel, which are moderate in severity and of risk rating D (Table 5). The distribution of PDDIs in each patient was also assessed, it was found that 73% patients experienced single PDDI. The details of distribution of PDDIs/patient are shown in Figure 2.

In the present study, out of 240 Patients case sheets reviewed, 32% (n=77) of the patients had PDDIs. The frequency of PDDIs was found to be 44%. There was a considerable variation found between the males and females with PDDIs. The males had more PDDIs when compared to females.

Elderly individuals were exposed to more multiple drug regimens than younger individuals. Majority (93%) of patients who experienced PDDIs were aged more than 40 years. A direct correlation was also observed between the age of the patients and the number of potential drug-drug interactions ($r = 0.338$, $P < 0.01$).These findings are similar to the study conducted by Leif Bergendal et.al. and many others which state that the elderly patients are at increased risk of PDDIs[4, 5, 9, 10].

The average number of drugs taken by patients with PDDIs and those without PDDIs varied widely. Comparing the mean number of drugs taken by the patients with PDDIs was found to be more (7±3) when compared to the patients without PDDIs (5±2) (Table 4). A direct correlation was observed between the number of drugs prescribed and the number of PDDIs ($r = 0.402$, $P < 0.01$).

These findings are similar to the study conducted by Kristina J and Inga K which states that the elderly patients receiving more medications are at higher risk of PDDIs[5]. This shows that as the number of drugs administered increases, the risk of PDDIs also increases. Van Dijk et.al. in his study, states that more drugs the patients were prescribed, the higher became their risk of having a PDDI[1]. Out of a total patient population of 240 there were 103 patients with prior co-morbidities and out of this 40 (52%) patients were identified with PDDIs (Table 4).

This shows that co-morbidities do have significant relationship with the occurrence of PDDIs. Therefore, it is necessary to monitor PDDIs especially in elderly patients, who are having co-morbidities and who are receiving more number of drugs.

There was 33% of PDDIs were of major severity and 32% were of moderate severity. There were 67% of the PDDIs were of the risk rating D and 30% of the PDDIs were of the risk rating C, which suggests that monitor the therapy and consider the therapy for modification. Majority (60%) of the patients were exposed to PDDIs of moderate level of severity and (37.5%) of patients were exposed to PDDIs of severe level of severity.

The criteria of assessing potential severity of the interaction are particularly important in assessing the risks vs. benefits of therapeutic alternatives. With appropriate dosage adjustments or modification of the administration schedule, the negative effects of most interactions can be avoided[7]. All these findings indicate that it is very much essential for the PDDIs to be assessed and monitored regularly.

Considering the distribution of PDDIs, 56 (73%) patients had only a single PDDI (Figure 2). Even though there was a reduction in the number of patients with increasing number of interactions, a direct relation was observed with the number of drugs prescribed and the PDDIs ($r = 0.402$, $P < 0.01$).

The commonly involved drug classes in the occurrence of PDDIs are Proton pump inhibitors (PPIs) followed by steroids, non steroidal anti inflammatory drugs (NSAIDs), statins, antibiotics and anti-tubercular drugs (Figure 1). The major drugs and the drug classes involved in the PDDIs identified in this study will help the practicing clinical pharmacists and other health care professionals for further monitoring and evaluating the PDDIs in the future.

CONCLUSION

The study concludes that there were 32% of PDDIs with a frequency of 44%. The PDDIs were found more in males, the elderly patients and in patients with co-morbidities and with polypharmacy. The considerable numbers of PDDIs identified were major in severity and of risk rating D.

There is a significant increase in PDDIs with the increase in age of the patient and the number of drugs prescribed to a patient. The more number of PDDIs were due to proton pump inhibitors followed by statins. The most of the PDDIs were between PPIs and paracetamol and PPIs and clopidogrel, which are moderate in severity and of risk rating D. The study concludes that the regular monitoring of PDDIs helps in better patient care.

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Table 1: Formula to calculate the frequency of PDDIs[8]

Frequency of PDDIs = Total number of PDDIs ÷ Total number of patients× 100

Table 2: Criteria for Risk rating[6]

Risk Rating	Action	Description
A	No known interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents
B	No action needed	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use
C	Monitor Therapy	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	Consider therapy modification	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents.
X	Avoid combination	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

Table 3: Criteria for severity[7]

Criteria	Description
Minor	The effects are usually mild, consequences may be bothersome or unnoticeable but should not significantly affect the therapeutic outcome. Additional treatment is usually not required.
Moderate	The effects may cause deterioration in a patient's clinical status. Additional treatment, hospitalization, or extension of hospital stay may be necessary.
Major	The effects are potentially life threatening or capable of causing permanent damage.

Table 4: Relationship between patient characteristics and PDDIs

Characteristics	Number (%)		
	Total (n=240)	Patients with PDDIs (n=77)	Patients without PDDIs (n=163)
Age (Mean± SD)	55±15.5	60±14.62	49±15.6
Males [N (%)]	124(52)	59(77)	65(40)
Females [N (%)]	116(48)	18(23)	98(60)
Number of drugs (Mean± SD)	6±3	7±3	5±2
Presence of co-morbidities N (%)	103(43)	40(52)	63(39)
Absence of co-morbidities N (%)	137(57)	37(48)	100(61)

Table 5: Drugs involved in causing PDDIs

Index Drug	Interacting Drug	Risk Rating	No. of PDDIs	Total N (%)
Paracetamol	Pantoprazole	D	32	
Clopidogrel	Pantoprazole	D	28	
Atorvastatin	Fluconazole	D	7	68 (67%)
Amikacin	Ceftriaxone	D	1	
Insulin	Corticosteroids	C	7	
Atorvatstatin	Pantoprazole	C	7	
Isoniazid	Rifampcin	C	4	
Alcohol	Cefoperazone	C	1	
Diclofenac	Propranolol	C	1	28(30%)
Ranitidine	Cefpodoxime	C	1	
Diclofenac	ceftriaxone	C	2	
Salbutamol	Prednisolone	C	5	
Amlodipine	Atenolol	B	1	
Diclofenac	Amlodipine	B	1	
Ipratropium	Salbutamol	B	2	8(%)
Diazepam	Paracetamol	B	1	
Diclofenac	Pantoprazole	B	3	
Ranitidine	Diclofenac	A	1	1(%)
Total				**105(100%)**

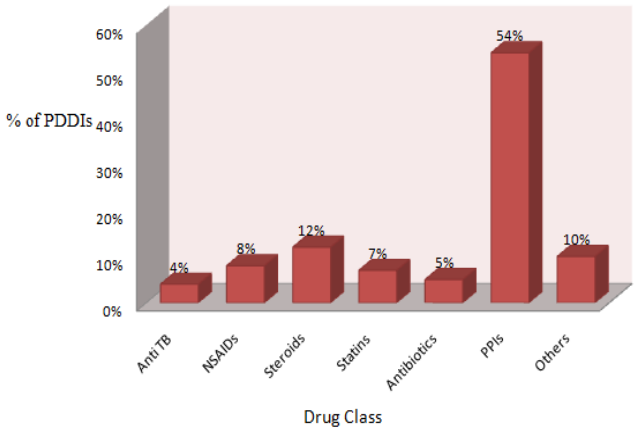

Fig. 1: Commonly Involved Drug Classes In Pddis

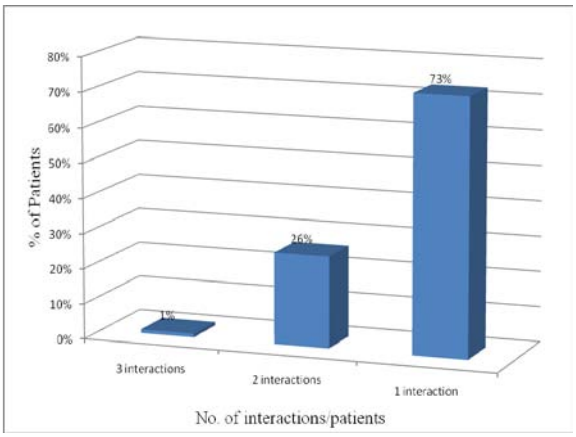

Fig. 2: Distribution of potential drug-drug interactions/patient

REFERENCES

1. Ivan Dijk. N, De Vries C S, Van Den Berg P B, Brouwers J R B J, De Jong-Van Den Berg. Occurrence of potential drug-drug interactions in nursing home residents. Int. J. Pharm. Pract. 2001; 3:45-51.
2. Daniel A. Hussa. Drug Interactions. Remington the science and practice of pharmacy 21st ed. Alfonso R Geunaro, editor. Lippincott Williams & Wilkins. 2006; 1:1889-1902.
3. Weideman RA, McKinney WP, Bernstein IH. Predictors of potential drug interactions. Hosp Pharm 1998:33(7); 835-40.
4. Leif Bergendal, Arne Friberg and Ann Marie Scheffrath. Potential drug-drug interactions in 5125 mostly elderly out-patients in Gothenberg, Sweden. Pharmacy world sci. 1995; 17:152-157.
5. Kristina J, Inga K. The relationship between number of Drugs and Potential Drug-Drug Interactions in the Elderly. Drug Safety 2007; 30(10):911-918.
6. William Alvarez Jr., Joseph F. Alexander, Jr., editors. Lexi-Interact Monograph Description [Internet]. Ohio: Lexi-comp Inc. Available from: http://online.lexi.com/crlsql/servlet/crlonline?a=in
7. Drug interaction facts. St. Louis, Mo.: Facts and Comparisons; 2001.
8. Arul Prakasam K C, Senthil Kumar N, Ramesh. J A study of drug-drug interactions in prescriptions received at selected community pharmacies in Tamil Nadu. Int. J. Res. Pharm. Sci. 2010; 1 (4): 490-492.
9. Richard M Goldberg, John Mabee, Linda Chan, Sandra Wong. Drug-Drug and Drug-Disease interactions in the Elderly. Analysis of a high-risk population. Am J Emerg Med. 1996; 14:44-47.
10. Matthijs L B, L E Visser, Teun V G, Albert H, Burno H S. Increasing exposure to Drug-Drug Interactions Between 1992 and 2005 in people aged ≥55 years. Drugs & aging. 2008; 25(2):145-152.