Original Article

ID: JCDR/2012/4118:2424

Pharmacology Section

Surveillance of the Potential Drug-Drug Interactions in the Medicine Department of a Tertiary Care Hospital

SHAHABUDIN SOHERWARDI, BHARTI CHOGTU, FAIZAL P.

ABSTRACT

Introduction: Drug-Drug Interactions (DDIs) account for 6-30% of the adverse drug events, pose a significant risk to the patient's health outcome and they put an economic burden on the health care system. Polypharmacy significantly contributes to these interactions. This study was aimed at assessing the drug-drug interactions in the in-patients in the medicine department in a tertiary care hospital.

Materials and Methods: The case records of 250 patients who were admitted in the medicine ward were analyzed regarding the demography of the patient, the prescription and the interaction details like the object drug, severity, management and the outcome.

Results: The patients received drugs which ranged from 5 to 18. 66% of the patients had DDIs, with a majority being moderate in severity and occurring in the patients who received cardiovascular drugs. Age and gender did not have a significant effect on the drug- drug interactions.

Conclusion: Most of the DDIs are preventable. The frequently occurring DDIs are seen between fluoroquinolones and oral anti-diabetics, iron and pantoprazole, aspirin and clopidogrel.

Key Words: Drug- drug interactions, Mild, Moderate and Severe interactions

INTRODUCTION

A drug interaction is defined as a modification of the effect of a drug when it is administered with another drug. The effect may be an increase or a decrease in the action of either substance, or it may be an adverse effect that is not normally associated with either drug. This definition applies to the interactions of drugs with other drugs (drug-drug interactions), as well as of drugs with food (drug-food interactions) and other substances.

Whenever 2 or more drugs are taken concurrently, there is a chance that there will be an interaction between the drugs. The likelihood of the drug interactions increases as the number of drugs which are taken by a patient increases. The factors which are significantly associated with having 1 or more potential interactions include: taking 5 or more medicines, patient age of 60 years or older and those suffering from cardiovascular diseases [1].

Drug-Drug Interactions (DDIs) are estimated to account for 6%-30% of all the adverse drug events, and they continue to pose a significant risk to the patient's health outcomes and a considerable economic burden on the health care system [2]. Hence, as they are an important hazard to the health of millions of patients, drug- drug interactions have to be tackled and it is the need of the hour.

In order to take preventable measures, we need to have a database which can be used as a reference to the known interactions like that of the drug reax system (micromedex). Then, there is a need to know and to understand what the most commonly occurring preventable interactions are. So, it is prudent to monitor the DDIs in patients who are on polypharmacy and to collect the data regarding the various commonly occuring drug interactions. With this background, the aim of this study was to monitor the drug -drug interactions in the patients of the medicine ward in a tertiary care hospital in south India.

MATERIAL AND METHODS

This prospective study was performed on the inpatients of the medicine ward of a tertiary care teaching hospital. This study was started after obtaining ethical clearance from the institutional ethical committee. The study period was two months, during which the data was collected.

Inclusion criteria

1. The patients who were admitted to the medicine department and treated for a minimum period of three days with a minimum of four drugs.
2. Patients of both the sexes.
3. The patients who were aged 12 years or more.

The investigator visited the medicine wards daily and the patients were included as per the inclusion criteria. The data was collected from the patient's case records. Only one prescription from each patient during his/her hospitalization in the ward during the study period was included. The Information was collected on the drug drug interactions and montoring from which included demography of the patient, the prescription and interaction details like the object drug, the severity, management and the outcome. The data was analyzed by using the online data base-micromedex [3] and standard references. A severity rating scale with categories of minor interaction if the risk of the adverse outcome appeared small, moderate interaction if the administration of the drug was avoided unless it was determined that the benefit of the administration outweighed the risk and major interaction if the administration of the drug was avoided if a combination was used to describe the potential DDIs, was used.

Statistical analysis

Statistical analysis was performed by using the SPSS, version 14.0. A p-value of <0.05 was considered as statistically significant.

RESULTS

The prescriptions of total 250 patients were analyzed. Of these, 165 prescriptions i.e., 66% had drug -drug interactions.

The Number of Drugs which were Administered and the Frequency of Interactions

The number of drugs which were prescribed to the study population ranged from 5 to 18, with an average of 7.8 drugs. The number of drugs which were prescribed and the change in the percentage of the interactions is shown in [Table/Fig-1].

Age

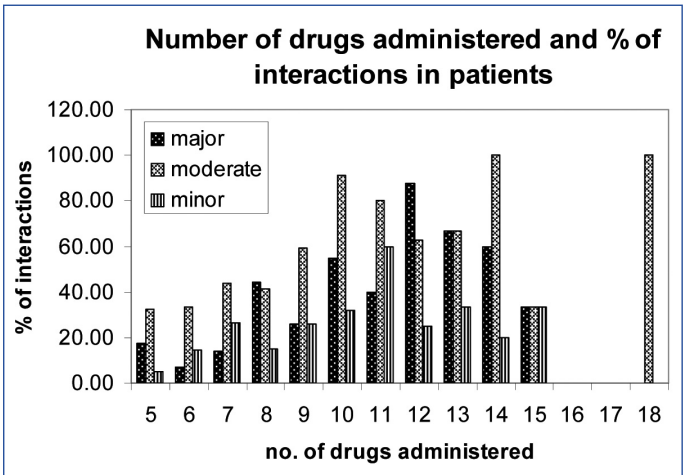
The patients in the age group of 56-65 years constituted the highest number of the patients i.e., 26% of the total patients. This age group showed the highest number of major drug interactions [Table/Fig-2].

Gender

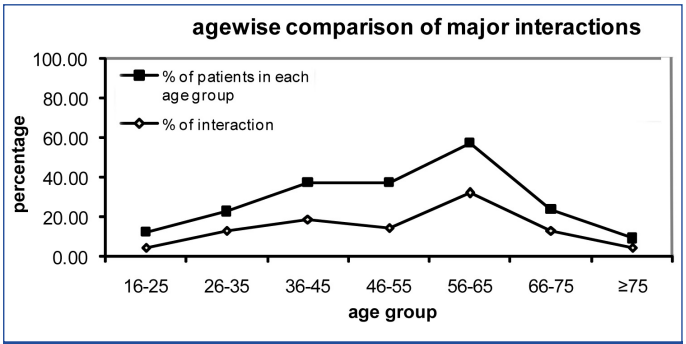
On comparing the drug interactions in the two sexes, it was found that males had 61% and that the females had 64% major interactions.

Diseasewise Distribution of the DDIs

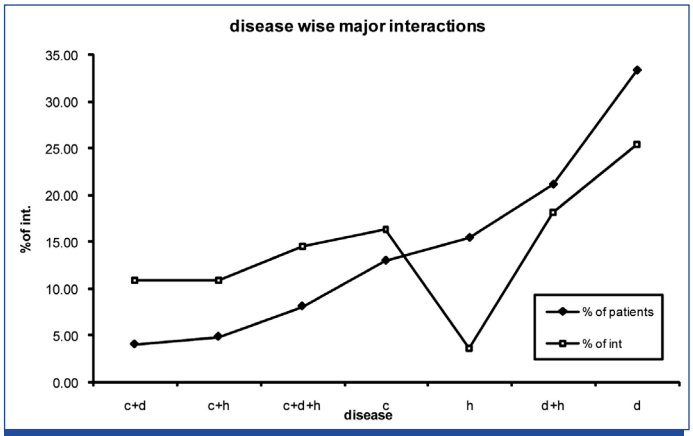
The DDIs were maximum in the patients with isolated diabetes (d)-33%, followed by those with diabetes and hypertension (d+h) -21.1%, those with isolated hypertension (h)- 15.4%, those with isolated cardiac diseases (c)- 13%, those with cardiac diseases with diabetes and hypertension (c+d+h) -8.1%, those with cardiac diseases and hypertension (c+h) -4.9% and those with cardiac diseases and diabetes (c+d) -4%.[Table/Fig-3]



[Table/Fig-1]: Number of Drugs administered and % of interactions in patients



[Table/Fig-2]: Agewise comparison of major interactions



[Table/Fig-3]: Disease wise major interactions

Frequency of the interactions

The first 5 commonly observed major, moderate and minor interactions and their frequencies are shown in [Table/Fig-4,5 & 6] respectively.

Interaction	Frequency
Ciprofloxacin + Insulin	17
Digoxin + Spironolactone	11
Spironolactone + Ramipiril	7
Atorvastatin + Niacin	6
Ciprofloxacin + Theophylline	4

[Table/Fig-4]: Major Interactions

Interaction	Frequency
Iron + Pantoprazole	40
Ciprofloxacin + Iron	12
Digoxin + Furosemide	11
Iron + Zinc	11
Ciprofloxacin + Zinc	11

[Table/Fig-5]: Moderate Interactions

Interaction	Frequency
Aspirin + Clopidogrel	13
Vitamin C + Cyanacobalamin	9
Gentamicin + Penicillin	7
Terbutaline + Theophylline	4
Cotrimoxazole + Lamivudine	4

[Table/Fig-6]: Minor Interactions

CONCLUSION

This study has put forth the common interactions which we come across in a tertiary care hospital. A thorough knowledge of these can decrease the incidence of DDIs, particularly during the prescription of multiple medications.

Discussion/Further Prospectives:

Drug-Drug interactions are associated with potential severe events and even death. These can be prevented with rational prescribing and the knowledge of the untoward effects which occur secondary to these.

The drug-drug interactions are classified as mild, moderate and severe according to their severity and undesirable effects [4]. Mild drug-drug interactions limit the clinical effects. The manifestations include an increase in the frequency or the severity of the adverse

effects, but these usually do not require a change in the therapy. Moderate drug-drug interactions may result in exacerbation of the disease of the patient and/or a change in the therapy. The severe drug-drug interactions are life threatening and/or they require medical treatment or an intervention to minimize or to prevent the severe adverse effects.

Drug-Drug interactions cause 4.8% of the hospitalizations in the elderly [5]. They are attributed to polypharmacy, non-compliance of the patients, and deterioration because of illnesses or secondary infections [6]. An increased number of drugs enhances the risk of the potential drug- drug interactions. This article has revealed as to how common this problem is in the medicine units in patients. An awareness on the most prevalent potential DDIs can help the practitioners in preventing the concomitant use of these dangerous medication combinations.

The incidence of the drug-drug interactions in our study patient population was 66%, which included the major, moderate and the minor interactions. Of these, over one fourth of the interactions were major. This was less in comparison with the findings of a study which was conducted in Costa, Mexico, in which the incidence of the interactions was 80% [7]. The average number of drugs which were prescribed in this study was 7.8 per patient, which was more than that which was found in a study which was conducted in Mexico, in family medicine clinics in ambulatory patients, which was 5.9 per patient [2]. This increased number of drugs which were prescribed can be explained on the basis that all our patients were hospitalized and that the comparative study was done on ambulatory patients.

On dividing the patients into different age groups, it was found that the maximum number of patients were in the age group of 56- 65 years. But the incidence of the interactions in the different age groups was as per the percentage of the patients which constituted that group and there was no significant difference between the different age groups. This was in contradiction to the findings of previous studies which showed that elderly patients were at a high risk of having drug interactions [8]. This may probably be due to polypharmacy, but in our study, all the patients were inpatients and they were thereby on polypharmacy. So, in our study, it was not the age but the number of the drugs which were prescribed, that determined the incidence of the drug interactions. No influence of gender on the incidence of the drug interactions was observed.

The patients with isolated diabetes showed the highest number of major severity interactions. This was because the number of medications used in the management of diabetes had dramatically increased in the past few years. The risk for possible drug interactions that may cause hyperglycaemia, hypoglycaemia, or other deleterious effects increases exponentially, as the number of medications in a patient's regimen increases [9]. In addition to the risk for adverse interactions which are caused by prescription medications, the potential exists for interactions with over the counter medications [9].The most common major interaction in our study was between insulin and the fluoroquinolones.

The patients with isolated cardiac diseases had the largest number of moderate interactions, followed by the patients with cardiac diseases in addition to diabetes and hypertension. This can be attributed to the large number of drugs which are prescribed to the patients with cardiac diseases, like hypolipidaemics, antiplatelets and anticoagulants, to decrease the risk of various complications.

MINOR

Aspirin and Clopidogrel

The most common minor interaction in our study was between aspirin and clopidogrel. Clopidogrel, in addition to aspirin, increases the risk of the minor and the major bleeding episodes. For every 1000 patients who are treated with clopidogrel, 6 will require a transfusion. However, there was no excess in the bleeding that caused strokes, that required a surgical intervention or inotropic agents, or that caused a permanent disability [10]. The risk of a life-threatening or major bleeding is increased by the addition of aspirin to clopidogrel as compared to that which is caused by clopidogrel alone [11].

MODERATE

Iron and Pantoprazole

Pantoprazole lowers the gastric acidity. A chronic treatment with Pantoprazole leads to loss of the gastric acidity, leading to a decreased bioavailability of the iron salts [12].

MAJOR

Ciprofloxacin and insulin

The pharmacokinetics of the insulin products are difficult to evaluate, owing to many confounding factors such as the injection site, the insulin source, and the ambient temperature, which affect the exogenous insulin [9]. Therefore, the knowledge of the interaction between the exogenously administered insulin and other drugs becomes important. In a study which was done on perfused mouse β-cell islets, it was found that ciprofloxacin enhanced the insulin secretion at high glucose concentrations [13]. The enhancement of the insulin secretion is a group effect of the fluoroquinolones. It depends on their ability to block the K_{ATP} channels in the pancreatic β-cells. In patients with non-insulin dependent diabetes mellitus who were maintained on diet and exercise, ciprofloxacin produced a sustained increase in the insulin release and production [14].

Digoxin and spironolactone

Spironolactone substantially reduces the risk of both morbidity and death among the patients with severe heart failure [15]. When spironolactone and digoxin are prescribed concomitantly, spironolactone reduces the digoxin clearance and prolongs the digoxin elimination half life [16]. As digoxin has a narrow therapeutic range, this combination can lead to digoxin toxicity.

Spironolactone and Ramipril

The combination of spironolactone and an ACE inhibitor can lead to hyperkalaemia, arrhythmia and death [17]. In patients with heart failure who take spironolactone and ACE inhibitors, undetected hyperkalaemia can lead to sudden death [18]. The authors recommend that a combination of ACE inhibitors and spironolactone should be considered with caution and that it should be monitored closely in patients with renal insufficiency, diabetes, older age, worsening heart failure and a risk for dehydration, and in combination with other medications that may cause hyperkalaemia [19].

To conclude, in this study, we tried to put forth the common interactions which we come across in tertiary care hospitals. An awareness on the most prevalent potential DDIs can help the practitioners in preventing the concomitant use of dangerous medication combinations [20]. A careful and continuous monitoring

of the patients will also help in identifying the adverse events and thereby in preventing the morbidity and the mortality. A recent study has shown that Italian general practitioners were aware of the potential risk of the drug interactions which were caused by digoxin and other drugs and that this had led to relatively few drug interactions [21].

An awareness on the common interactions which occur in our set up will make it possible to decrease the risk of such interactions.

ACKNOWLEDGEMENTS

Indian Council of Medical Research (ICMR) for supporting this study.

REFERENCES

[1] Costa AJ. Potential drug interactions in an ambulatory geriatric population. *Fam Pract.* 1991;8:234–36.
[2] Mahmood M, Malone DC, Skrepnek GH, Abarka J, Armstrong EP, Murphy JE, et al. Potential drug drug interactions within the veteran affairs medical centers. *Am J Health-Syst Pharm* 2007;64: 1500-05.
[3] Micromedex® Healthcare Series. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc., 2007. Available from URL: https://www.thomsonhc.com/hcs/librarian/ [Accessed 2011 Jul 5].
[4] Almeida SM, Gama CS, Akamine N. The prevalence and the classification of drug drug interactions in intensive care patients . *Einstein* 2007 ;5(4):347-51.
[5] Doucet J, Chassagne P, Trivalle C, Landrin I, Pauty MD, Kadri N, et al. Drug-Drug interactions which are related to hospital admissions in older adults: a prospective study on 1000 patients. *J Am Geriatr* Soc. 944-48.
[6] Seymour RM, Routledge PA. Important drug-drug interactions in the elderly. *Drugs Aging.* 1998;12:485–94.
[7] Johnson JA, Bootman JL. Drug related morbidity and mortality. A cost-of-illness model. *Arch Intern Med* 1995: 155:1949-56.
[8] Mallet L, Spinewine A, Huang A. The challenge of managing the drug interactions in elderly people. *Lancet* 2007;370: 185-91.
[9] White JR, Campbell RK. Dangerous and common drug interactions in patients with diabetes mellitus. *Endocrinology and Metabolism Clinics* 2000; 29:789-801.
[10] Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. The effect of Clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345: 494-502.
[11] Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. The aspirin and clopidogrel combination which was compared with clopidogrel alone after a recent ischemic stroke or a transient ischemic attack in high risk patients (MATCH): a randomized, double blind, placebo controlled trial. *Lancet* 2004;364: 331-37.
[12] Brunton LL, Chabner BA, Knollman BC, Eds., Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th ed., McGraw Hill, New York, USA, 2011;1312.
[13] Ghaly H, Kriet C, Sahin S, Pfloger A, Holzgrabe U, Zunkler BJ, et al. The insulinotropic effects of the fluoroquinolones. *Biochemical Pharmacology* 2009; 77: 1040-52.
[14] Gajjar DA, LaCretabFP, Kollia GD, Stolz RR, Berger S, Smith WB, et al. The effect of multidose gatifloxacin or ciprofloxacin in patients with non-insulin dependent diabetes mellitus which was maintained with diet and exercise. *Pharmacotherapy* 2000; 20: 76S-86S.
[15] Pitt B, Zannad F, Remme WJ, Cody R, Castargne A, Perez A.The effect of spironolactone on the morbidity and the mortality in patients with severe heart failure. *N Eng J Med* 1999; 341: 709-17.
[16] Fenester PE, Hager WD, Goodman MM. The Digoxin-quinidine-spironolactone interaction. *Clin Pharmacol Ther* 1984; 36: 70-73.
[17] Johnston RT, De Bono DP, Nyman CR. Preventable sudden death in patients who received angiotensin converting enzyme inhibitors and loop/potassium sparing diuretic combinations. *Int J Cardiol* 1992;34:213-15.
[18] Wregner E, Muller R, Moesenthin M, Welte T, Frolich JC, Neumann KH. Interaction of spironolactone with the ACE inhibitors or an angiotensin receptor blocker: an analysis of 44 cases. *BMJ* 2003; 327: 147-49.
[19] Schepkens H, Vanholder R, Billiouw JM, Lamiere N. Life-threatening hyperkalemia during a combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. *The American Journal of Medicine* 2001; 110: 438-41.
[20] Gagne JJ, Maio V, Rabinowitz C. The prevalence and the predictors of the potential drug- drug interactions in Regione Emilia-Romagna, Italy. *J Clin Pharm Ther.* 2008; 33: 141-51.
[21] Magro L, Conforti A, Del Zotti F, Leone R, Iorio ML, Meneghelli I, et al. Identification of the severe potential DDIs by using an Italian general-practitioner database. *Eur J Clin Pharmacol* 2008; 64: 303-09.

AUTHOR(S):
1. Dr. Shahabudin Soherwardi
2. Dr. Bharti Chogtu
3. Mr. Faizal P.

PARTICULARS OF CONTRIBUTORS:
1. MBBS, Kasturba Medical College, Manipal University, Manipal, India.
2. MBBS, MD, Pharmacology, Associate Professor, Department of Pharmacology Kasturba Medical College, Manipal University, Manipal, India.
3. M Pharm PhD, Scientist III, Manipal-Ecron-Acunova, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Bharti Chogtu
Associate Professor, Department of Pharmacology
Kasturba Medical College, Manipal University,
Manipal, India.
bhartimagazine@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS:
None.

Date of Submission: **Feb 08, 2012**
Date of Peer Review: **Apr 17, 2012**
Date of Acceptance: **Jul 13, 2012**
Date of Publishing: **Sep 30, 2012**