Study of Drug-drug Interactions in the Medication Charts in Medicine Wards at a Tertiary Care Hospital, Bangalore

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ABSTRACT

Submitted: 02/12/2012 *Accepted: 16/12/2012*

Introduction: Drug-drug interactions (DDIs) can occur when two or more medications are simultaneously administered, where one medication increases or decreases the effectiveness of the other. There are three possible outcomes when drug-drug interactions occur; one drug may intensify the effects of the other, one drug may reduce the effects of the other and the combination may produce a new response which is not seen when either of the drugs is given alone. **Objective:** This prospective study aimed to evaluate drug-drug interactions in the medication charts of the patients. Data of all patients admitted to MICU and Female Medical Ward was collected and subjected to drug-drug interaction analysis using drug information resources such as "Thomson Reuters MICROMEDEX® 2.0 DRUGDEX anddrugs.com. **Results:** From among the 230 cases collected, 120 (52.17%)cases were identified with 330 DDIs out of which 10 (3.03%) were clinically observed and the rest 320 were potential DDIs. Majority (80.86%) of the potential DDIs were of pharmaco dynamic in nature. It was observed that out of 330 DDIs identified, 82 (24.85%) were major, 176 (53.33%) were moderate and 72 (21.82%) were minor in severity. Atleast one potential DDI was observed in 35% of the prescriptions. **Conclusion:** DDIs may not appear to cause a serious problem to the health of the patients and process of drug therapy but clinical investigations are required to know the actual consequence of the DDIs.

Keywords: Drug-drug interactions, medication charts, adverse drug reactions

INTRODUCTION

Concomitant use of several drugs for a patient is often necessary for achieving a set goal or in cases when the patient is suffering from more than one disease. Patients may also take OTC drug/s in addition to prescription medications. A multiplicity of outcomes is possible when people use drugs. In these cases the chance of encountering drug - drug interactions could increase. Drug-drug interactions (DDIs) in patients receiving multi-drug therapy are of wide concern. The term drug-drug interaction is used when the effect of one drug is altered by the concomitant use of another drug.[1]The clinical output of such interactions could appear as antagonism, synergism or idiosyncratism.

Drug interactions may happen by two or more mechanisms acting in concert. The mechanisms of interaction can be sub-divided pharmacokinetic andpharmacodynamic. Pharmacokinetic interactions are those which can affect the processes by which drugs are absorbed, distributed, metabolized and excreted. Pharmacodyanamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action. Sometimes, the drugs directly compete for particular receptors but often the reaction is more indirect and involves the interference with physiological mechanisms.[2]

Based on the profile of medications prescribed, the drug-drug interactions are identified and classified. According to severity, potential DDIs are classified as:

1) **Major:** The effects are potentially life threatening or capable of causing permanent damage.

2) **Moderate:** The effects may cause deterioration in patients' clinical status and additional treatment or extension of hospital stay.

3) **Minor:** The effects are usually mild.[3]

Drug interactions may lead to adverse drug reactions that can be severe enough to necessitate hospitalization and increased health care costs. About 5% of all the adverse drug reactions in the hospitals are caused by DDI, the majority of which are avoidable.[4] The contribution of various members of the healthcare team in improving the medication-related outcomes is less well explored in India. Drug therapy has become so difficult that no single professional is expected to optimize thedrug therapy and control drug related problems alone. Optimization of drug therapy may, by preventing drug

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related problems such as drug-drug interactions, potentially save lives and enhance patient's quality of life and reduces health expenses. In developed countries, pharmacists in hospitals frequently initiate changes to patient's therapy and management.

Hence, this project was proposed to identify potential drug-drug interactions in the drug therapy by the clinical pharmacist and report the same to the physician so that adverse drug reactions can be prevented and patient outcome can be improved.

METHODOLOGY

The study was conducted for a period of 9 months (June 2011–Feb 2012). Before starting the study Ethical Committee Clearance was obtained from the Institutional Review Board of St.Martha's Hospital. Data of all patientsviz. case history, diagnosis, co-morbid conditions, laboratory values and drugs prescribed with their doses and frequency of administration were collected and subjected to drug-drug inter actionanalysis using sophisticated drug information resources such as Thomson Reuter MICROMEDEX® 2.0-Drugdex, www.drugs.com.If any patient was experiencing an adverse drug reaction then the prescribed drugs were checked whether it was due to drug-drug interactions and the findings of the data analysis was reported to the physician in-charge.

RESULTS& DISCUSSION

During the study period, a total of 230 patients were enrolled out of whom, 130 patients were female (56.52%) and 100 were male (43.48%). The age of patients ranged from 11 to 90yrs and majority of the patients were in the age group of 61-70 yrs (18.7%). The average age of patients was found to be 50.5 years.

Out of230 cases, 120 cases (52.17%) had 330 potential DDIs in which 10 drug-drug interactions were clinically observed as adverse drug reactions and 320 interactions were reported in the literature. The number of clinically relevant drug interactions (3.03%) is very low.

The DDIs could be classified as pharmacokinetic (e.g. altered plasma concentration of drug) and pharmacodynamic outcomes (e.g. Blunting of diuretic effect of furosemide, hypoglycemia, etc.). The pharmacokinetic outcome was identified in 67 DDIs (19.14%) and pharmacodynamic outcome was identified in 283 DDIs (80.86%) which is similar to the study conducted by Virendra K.P et al.[5]

From among the 330 DDIs identified, 82 were major (24.85%), 176 were moderate (53.33%) and 72 (21.82%) were minor interactions (Table 1) which can be compared with the results obtained by Jacqueline M et al.[6] where the major, moderate and minor DDIs were 17%, 56% and 27% respectively and also similar to the results of Satish A et al.[7] where major was 25.82%.

The number of potential DDI ranged from 1 to 10; 42 cases (35%) showed one potential DDI and 2 cases showed 10 potential DDIs(Table 2). Atleast one drug-drug interaction was seen in 35%, which is much higher than those seen by Jeannette E F et al.[8] where they found in 28% and Reimche L et al.[9] where it was only 19.3%, but it is less than the result obtained by Cruciol-Souza JM et al.[10] i.e. 73.6%.

The most common interactions reported were with furosemide and theophylline (16), followed by paracetamol and furosemide (15), and azithromycin with ondansetron (13). The effects reported were altered theophylline concentration, blunting of diuretic effect of furosemide and increased risk of QT interval prolongation respectively (Table 3).

The documentation of 165 identified DDIs were fair (50%), 134 (40.61%) DDIs were good and 31(9.39%) DDIs were excellent (Table 4) which is comparable to the study conducted by Joice MCS et al.[11] The DDIs were documented by referring to the literature for the combination of drugs prescribed. In 10 cases (3.03%) the clinical effect was actually seen. In the studies carried out by Rajesh R et al.[12], Reimche L et al.[9], Margro L et al.[13], they dealt with only potential interactions rather than genuine one as they did not determine the clinical relevance of the interactions.

Ten patients experienced ADRs such as nausea, vomiting, palpitation, etc. Upon consulting drug information resources, it was found that nausea and vomiting are well documented due to interaction of furosemide and alprazolam with digoxin. Nausea and palpitation are also documented to be due to

Table 1: Distribution of DDIsaccording to the degree of severity

Severity of DDIs	No. of DDIs	Percentage of DDIs
Major	82	24.85
Moderate	176	53.33
Minor	72	21.82
Total no. of DDIs	330	100

Table 2: Distribution of cases with number of DDIs

No. of DDIs	No. of cases	Percentage of Cases
One	42	35
Two	26	21.66
Three	16	13.33
Four	16	13.33
Five	11	9.17
Six	2	1.67
Seven	2	1.67
Eight	2	1.67
Nine	1	0.83
Ten	2	1.67

Table 3: Most prevalent drug-drug interactions

Sl. No	Drug Combinations		No. of cases	Severity	Consequences of DDI
1	Furosemide	Theophylline	16	Minor	Altered theophylline concentration
2	Paracetamol	Furosemide	15	Moderate	Blunting of diuretic effect of furosemide
3	Aspirin	Furosemide	11	Moderate	Blunting of diuretic effect of furosemide
4	Levothyroxine	Furosemide	3	Moderate	Decreased effectiveness of furosemide
5	Hydrocortisone	Furosemide	9	Moderate	Hypokalemia
6	Levofloxacin	Theophylline	6	Major	Theophylline toxicity (nausea, palpitation)
7	Azithromycin	Theophylline	13	Moderate	Increased theophylline serum concentration
8	Aspirin	Insulin	13	Moderate	Hypoglycemia
9	Paracetamol	Clopidogrel	7	Major	Increased risk of bleeding
10	Levothyroxine	Insulin	6	Moderate	Decreased effectiveness of diabetic agent
11	Ranitidine	Theophylline	6	Minor	Theophylline toxicity (nausea, palpitation)
12	Aspirin	Clopidogrel	12	Minor	Increased risk of bleeding
13	Paracetamol	Amlodipine	8	Minor	Increased risk of GI hemorrhage and/or hypotensive effect
14	Azithromycin	Ondansetron	13	Major	Increased risk of QT interval prolongation
15	Ofloxacin	Hydrocortisone	1	Moderate	Increased risk for tendon rupture
16	Ofloxacin,	Paracetamol, aspirin	2	Moderate	Increased risk of seizure
17	Levofloxacin	Hydrocortisone	6	Moderate	Increased risk for tendon rupture
18	Levofloxacin	Paracetamol, aspirin	7	Moderate	Increased risk of seizure

Table 4: Distribution of DDIs depending upon their documentation

Type of Documentation	No. of DDIs	Percentage of DDIs
Fair	165	50%
Good	134	40.61%
Excellent	31	9.39%

interaction of levofloxacin with theophylline.The dose of digoxin was reduced in the above 4 cases and theophylline was stopped in all the 6 cases (Table 5).

Causality assessment was carried out for the same using WHO Probability Scale and Naranjo's Algorithm. As no de-challenge was carried out for digoxin, they can be classified as "possible" as per WHO Probability Scale and "probable" as per Naranjo Algorithm. For theophylline, as de-challenge was done, the adverse reaction can be classified as "probable" as per WHO Probability Scale and "possible" as per Naranjo Algorithm (Table 6).

Majority of the interactions were moderate and did not cause any significant clinical effects in the patients. In certain cases, it was difficult to assess the clinical effect of DDI. There were drug combinations, where the interaction of one drug combination was nullified by the other. As in the case of the combination of ranitidine, phenytoin and aspirin. Ranitidine is reported to interact with phenytoin leading increased phenytoin concentration whereas aspirin is reported to decrease the phenytoin concentration. Similarly, there were cases with drug combinations indicating the risk of GI bleeding, but the patients also received pantoprazole and therefore the effect was not clinically significant.

There are many drug-drug interactions which were potential but they may not be seen in the patient clinically such as pharmacokinetic outcomes where the interaction may not precipitate to show the outcomes by visual appearance. As stated by Janchawee Bet al[14], drug-drug interactions often need not always have clinically important adverse consequences but however, it is important to identify the DDIs in patients in order to prevent any possible harm in them.

LIMITATIONS

In some of the cases, where there were reports of increased or decreased serum concentration of drugs, we could not measure the same. Also, we did not have opportunity to observe some of the interactions such as ECG changes, etc.

To enable monitoring the interactions in a systematic way, patients should be encouraged to disclose all of their medications to the pharmacist and physician.By doing so, many drug interactions can be avoided or managed safely.

Table 5: Adverse drug reactions observed in patients due to DDIs

Drug combinations		No. of cases	Severity of DDIs	Adverse reactions
Furosemide	Digoxin	3	Moderate	Nausea, vomiting (digoxin toxicity)
Alprazolam	Digoxin	1	Major	Vomiting(digoxin toxicity)
Theophylline	Levofloxacin	6	Major	Nausea, palpitation (theophylline toxicity)

Table 6: Causality assessment of the ADRs

ADRs	WHO Probability Scale	Naranjo Algorithm
Nausea, Vomiting (Furosemide + Digoxin*)	Possible	Probable
Vomiting (Alprazolam+Digoxin*)	Possible	Probable
Nausea, Palpitation (levofloxacin+theophylline*)	Probable	Possible

* Causative agent

CONCLUSION

Overall, the potential DDIs did not cause any serious problem to the patients. However,a close monitoring of the medication chart is necessary to identify the potential DDIs which may lead to serious clinical problems in the patients.

SCOPE OF THE STUDY

We wish to continue the present research further and design another study in which these drug-drug interactions can be used as patient safety indicators which can avoid the occurrence of adverse drug reactions thereby contributing to the present knowledge of adverse drug reaction monitoring.

ACKNOWLEDGMENTS

We wish to acknowledgethe management of Al-Ameen College of Pharmacy and St. Martha's Hospital for giving an opportunityto carry out this project and the support provided in the successful completion of this project.

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