Academic Sciences Asian Journal of Pharmaceutical and Clinical Research
Vol 4, Suppl 2, 2011 ISSN - 0974-2441

Research Article

INCIDENCE AND PATTERN OF POTENTIAL DRUG INTERACTIONS OF ANTIMICROBIAL AGENTS IN THE DEPARTMENT OF MEDICINE IN A TERTIARY CARE TEACHING HOSPITAL: A PROSPECTIVE STUDY

MAHENDRA KUMAR BJ *, KUMARASWAMY M, MAHADEVAMMA L

Department of Pharmacy Practice, SAC College of Pharmacy, B.G. Nagara-571448, E mail: bjmahendra2003@yahoo.co.in

Received: 6 may 2011, Revised and Accepted: 30 may 2011

ABSTRACT

Objective: To estimate and assess of nature, extent and drug class involved in potential drug interaction, the pattern of drug class involved, to evaluate the possible outcome and to evaluate the interactions of individual drug based on patient and characteristics of interactions
Methodology: This was a prospective and observational study carried out for a period of nine months in a tertiary care hospital. All patients admitted to medicine ward and satisfied inclusion criteria were taken consent. Case records of the patients were checked for drug interactions caused by antimicrobials based on the onset, severity and documentation was done.
Result: Among 226 enrolled patients males 134 (59.3%) and females 92(40.7%) were found. In this, 32(14.2%) potential drug interactions were found. Drug laboratory interactions 19(50.00%) and drug-drug interactions 15(39.5%), drug-disease interactions 3(79%) and drug-food interactions 1(2.6%) were found. The class of drug most commonly involved in potential drug interactions was primarily Fluoroquinolines, Cephalosporin 3rd generations, Antiamoebics and Macrolide antibiotics constituting 18(47.4%), 7(18.4%), 4(10.5%) and 4(10.5%) respectively. Descriptive statistical analysis has been carried out in the present study.
Conclusion: This study observed that common outcomes of PDIs such as increased Theophylline toxicity and Digoxin toxicity, increased laboratory values and also reduced effectiveness of some drugs.

Keywords; Antimicrobials, Potential Drug interactions (PDIs), drug interactions (DIs).

INTRODUCTION

Infective agents treat infection by suppressing or destroying the causative microorganisms' bacteria, mycobacteria, fungi, protozoa, or viruses. Anti-infective agents derived from natural substances are called antibiotics; those produced from synthetic substance are called antimicrobial agents.[1]

It is difficult to have an accurate estimate of the incidence of drug interactions mainly because published studies have frequently used different criteria for defining a drug interaction, particularly in distinguishing between clinically significant and non-significant interactions.[2]

Drug- Drug interactions (DDIs) are changes in a drug's effects caused by another drug taken during the same time period.[3]

Potential drug interactions (PDIs) may include, drug contraindications, drug combinations that require monitoring and possible dosage adjustment when given concomitantly. It is important not only to identify PDIs that are clinically meaningful, but also to understand options to approaching the potential loss efficacy or toxicity that may result when combinations of drugs are administered together.[4]

Most interactions involving antibiotics are pharmacokinetic ones and occur when one drug alters the absorption, distribution or elimination of another. Antibiotics may be the targets of such interactions, especially when their absorption from the gastrointestinal tract is affected. The potential for interaction between antibiotics and other drugs needs to be continually borne in mind, especially with the increasing trend towards polypharmacy such that many patients are taking four or five different agents. In these circumstances even short courses of antibiotics may have serious consequences.[5]

Potential drug interaction not only presents a danger to the patients 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 drugs.[4]

The incidence of drug interactions is a controversial issue. Study result varies greatly because of population type and methodology. Apart from this complexity, we must distinguish between PDIs and DDIs that actually occur.[6]

There are various patterns (categories) of interaction with drugs,

Drug- drug interactions: Reflect the modulation of the pharmacological activity of the object drug by concomitantly administering the precipitant drug resulting in a severe decrease or increase in the pharmacological properties of either drug.

E.g.; Levofloxacin increases the Theophylline toxicity.[7]

Drug - disease interactions: Tend to occur when a medication has the potential to worsen a disease. The effect a drug has in certain patients may be unexpected not related to the drug per se but because of the patient's disease pattern. It is important for the physician to know the patients entire disease profile to plan a suitable therapeutic regimen to avoid drug interactions.

E.g.; Warfarin- Metronidazole interaction causes the intracerebral hemorrhage.[8]

Drug- Food interactions: The myth that natural products, not being drugs, are completely safe creates a need for responsible, public/physician education especially as they are widely used by our rural/semi-urban populace; the potential and true incidence of these interactions is largely unknown. A lack of standardization and contamination further contribute to these interactions. The majority of clinically relevant food-drug interactions are caused by food-induced changes in the bioavailability of the drug.[9]

E.g.; Are frequently caused by chelation with components in food like milk (as occurs with penicillamine and tetracycline) or dairy products (ciprofloxacin and norfloxacin).[10]

Environment induced interactions: Are chiefly due to smoking that entails both

Pharmacokinetic and pharmacodynamic reactions. Pharmacokinetic (PK) interactions with smoking occur with drugs like caffeine, clozapine, olanzapine, theophylline, haloperidol and imipramine that are substrates of CYP1A2. But in pharmacodynamic (PD) interaction with the carcinogenic polycyclic aromatic hydrocarbons in tobacco smoke are potent inducers of the CYP4501A1/1A2/and possibly 2E1 enzymes.[9]

Rational prescribing can be achieved by practicing evidence-based medicine. Since pharmacist is often the final link between prescribed

medication and the patient, better interaction between pharmacists and the patient can lead to better patient knowledge about drug use and compliance to therapy.[15]

Since potential drug- drug interactions are an alarming problem for our society, it must be addressed by all health care providers and pharmacists needs to play a major role in preventing a potentially adverse situation from occurring. Educating all group of prescribers and dispensers on the importance of appropriate antimicrobial use and contaminant of antimicrobial resistance.

METHODOLOGY

Study site

This study is conducted at Sri Adichunchanagiri Hospital and Research Center, B.G.Nagar. It is a 750 bed multispecialty tertiary care teaching hospital. This hospital provides primary and specialized health care facilities to people in and around Nagamangala taluk.

Study design

This was a prospective and observational study.

Study period

The period of nine months from June 2010 to January 2011.

Study criteria

Inclusion Criteria

- Inpatients of department of medicine with length of stay more than 24 hours
- Patients on multiple drug therapy; with minimum of two drugs out of which one is an antimicrobial agent

Exclusion Criteria

- Pregnant and pediatrics
- Patients on single drug therapy with an antimicrobial agent
- Outpatients of department of medicine
- Patients whose length of stay in hospital is less than 24hrs

Source of data

All the necessary data were collected from the inpatients of all the four units of medicine department. The main source of data collection included,

- Patient case notes
- Treatment charts
- Laboratory reports
- Patient interview

STUDY PROCEDURE

Method of data collection

An approval from the Institutional Ethical Committee of Sri Adichunchanagiri Hospital and Research Center, B.G.Nagara, was obtained prior to the study. All patients admitted to medicine wards during the study period were screened for use of any antimicrobial agents. Those who met the inclusion criteria were included for the study purpose. Follow up was carried out till the day of discharge from the hospital. After the patients were included in the study, the data including, demographic data such as the age, gender, past medical history, reason for admission, co-morbidities, clinical data such as hematology, biochemistry and therapeutic data including dose, duration, frequency, route, time of administration and concomitant medication were collected and documented in the suitably designed data collection form (Annexure-1). Probable DIs were identified by using the software MICROMEDEX and the standard text books (Stockly). The potential outcome of the interaction was assessed based on literature patient interview and discussion with clinician. Those interactions which were assumed to have happened in the patients were evaluated for various parameters. Nature of interaction were evaluated with regard to onset, severity, documentation was evaluated. Data was assessed to evaluate the individual drug and drug class involved in interactions. Data on interactions of the individual drugs were evaluated based on patient demographics (age and gender) and characteristics of interactions (onset and severity). Data was evaluated using suitable statistical tools.

Criteria for evaluation

Criteria for Severity

The potential severity of the interaction is important in assessing the risks versus benefits of therapeutic alternatives. With appropriate dosage adjustments or modification of the administration schedule. The negative effects of most interactions can be avoided.

(i) Major interactions may be life-threatening, or intoxication or permanent damage may be induced. Normally, these drugs should not be administered together.

(ii) Moderate interactions frequently cause therapeutic difficulties, but the combinations may be administered if the patient is carefully monitored (laboratory parameters, for example quick value, or clinical symptoms).

(iii) Minor interactions may cause increased or reduced effects or interactions only concerning a certain subgroup (for example patients with renal or hepatic failure, slow acetylizers).

Criteria for Onset

How rapidly the clinical effects of an interactions can occur determines the urgency with which preventive measure should be instituted to avoid the consequences of the interaction.

Two levels of onset are used

Rapid: The effects will be evident within 24 hours of administrations of the interacting drug. Immediate action is necessary to avoid the effects of interactions

Delayed: The effect will not be evident until the interacting drug is administered for a period of days or weeks. Immediate action is not required.

Criteria for frequency

Frequency of PDIs was calculated as the total number of potential dug-drug interactions per total number of patients.

STATISTICAL ANALYSIS

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%)... 95% Confidence Interval has been computed to find the significant features. Confidence Interval with lower limit more than 50% is associated with statistical significance. Student t test has been used to find the homogeneity of parameters on continuous scale.

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

Total of 75 potential drug interactions out of which upon evaluation it was observed 38 interactions happened in the patients and 37 are assumed to happen. The result of a study is represented based on these 38 drug interactions.

Patient demographic data: A total of 226 patient case sheets were reviewed in all the four medicine units during nine months study period. The mean age of the patients were 52.19 ±16.5 ranging between 18 to >80 years. Of case sheets reviewed 32(14.2%) patients had potential drug interactions (PDIs). Out of which 19 (59.4%) and 13 (46.6%) patients were males and females respectively. Majority (50%) of the patients presented with drug lab

interactions. Less number of PDIs were found in drug food interaction1 (2.6%).

Table 1: Pattern of potential drug interactions

Potential Drug interactions	Number of patients with drug interactions (n=38)	%
Drug-lab-interactions	19	50.0
Drug-drug interaction	15	39.5
Drug-disease-interactions	3	7.9
Drug-food-interactions	1	2.6

Table 1 shows that out of 38 potential drug interactions, more number of drug – lab interactions were found 19(50%) and least Number of drug food interaction were found 1(2.6%). Total numbers of drugs were 38, 6 patients were given multiple drugs

However, it should be remembered that the clinical outcomes of most interactions is highly situational and depends on several factors including the sequence of administration, duration of therapy, dose of each drug and even the influence of other drugs. In this study showed more potential drug interaction outcomes, potential drug- laboratory interactions, increased theophylline toxicity.

Table 2: Severity of Potential Drug Interactions

Severity	Number of patients with drug interactions (n=38)	%
Minor	10	27.0
Moderate	10	27.0
Major	18	46.0

Table 2 shows that both minor and moderate severity of potential drug interactions were less number of patients 10(27.0%) and major severity of potential drug interactions were more number of patients 18(46.0%). Total numbers of drugs were 38, 6 patients were given multiple drugs

Table 3: Onset of potential drug interactions

Onset	Number of patients with drug interactions (n=38)	%
Delayed	13	34.2
Rapid	14	36.8
Unspecified	11	29.0

In table 3 shows that rapid 14(36.8%), delayed 13(34.2%) and unspecified 11(29.0%) onset of potential drug interactions were identified.

Table 4: Outcome of potential drug interactions

Sl.no	Drugs	Drug number	Interacting drug	Outcome
1	AZITHRO	1	AZITHRO+DIGOXIN	digoxin toxicity (vomiting)
2	AZITHRO	2	AZITHRO+ATORVA	symptoms of rhabdomyolysis (dark urine(red) and muscle pain)
3	OFLOXACIN	1	OFLOX + LAB VALUES	false positive urine opiate immuno assay results (increased urine values)
4	AZITHRO	1	AZITHRO+ATORVA	symtoms of rhabdomyolysis (dark urine(red) and muscle pain)
5	LEVO	1	LEVO+THEO	theophlline toxicity(nausea, vomitting)
6	CEFO	1	CEFO+LAB VALUES	false positive urine glucose test (increased fbs, ppbs values)
7	CEFO	1	CEFO+LAB VALUES	false positive urine glucose test (increased uria and rbs values)
8	CIPRO	1	CIPRO+LAB VALUES	theophlline toxicity(increased palpitation)
9	OFLOXACIN	1	OFLOX + LAB VALUES	false positive urine opiate immuno assay results (increased urine value)
10	CAFO	1	CEFO+LAB VALUES	a false positive urine glucose test (increased urine value)
11	CIPRO	1	CIPRO+LAB VALUES	false positive urine opiate immuno assay result (increased serum creatinine ,urine values)
12	METRO	1	METRO+LAB VALUES	intereferes in serum alanin measurment (increased alt value)
13	METRO	2	METRO+LAB VALUES	intereferes in serum aspartate measurment (increased ast value)
14	CEFEXIME	1	CEFEXIME+LAB VALUE	a false positive urine glucose test (increased serum creatinin,urine values)
15	LEVO	1	LEVO+THEO	theophylline toxicity (increased palpitation and vomiting)
16	AMOXI	1	AMOXI+LAB VALUES	a false positive urine glucose test (increased serum creatinine and urine value)
17	METRO	2	METRO+AMIODERON	increased risk of cardio toxicity(ventricular tachycardia)
18	CEFEXIME	1	CEFEXIME+LAB VALUE	a false positive urine glucose test(increased serum creatinin,urine values)
19	AZITHRO	1	AZITHRO+DIGOXIN	digoxin toxicity(headache,vomiting)

20	CIPRO	1	CIPRO+LAB VALUES	false positive urine opiate immuno assay results (increased serum createnine, rbs,and urine values
21	LEVO	1	LEVO+THEO	theophylline toxicity(increased palpitation and nausea)
22	CIPRO	1	CIPRO+SUCRALFATE	decreased ciprofloxacin effectiveness
23	CIPRO	1	CIPRO+INSULINE	a false positive urine glucose test(increased fbs and ppbs values)
24	CIPRO	2	CIPRO+GLIMI	changes in blood glucose and increased risk of hypoglycemia or hyperglycemia(increased fbs and ppbs values)
25	ITRA	1	ITRA+RIFA	reduced itraconazole efficacy
26	ITRA	2	ITRA+INH	loss of itraconozole efficacy
27	LEVO	1	LEVO+THEO	theophylline toxicity(increased palpitation)
28	LEVO	1	LEVO+THEO	theophylline toxicity(increased palpitation)
29	ALBEND	1	ALBEND+THEO	theophylline toxicity(increased palpitation)
30	CIPRO	1	CIPRO+GLIMI	changes in blood glucose and increased risk of hypoglycemia or hyperglycemia(increased urine and fibs values)
31	METRO	1	METRO+ETHANOL	disulfuram reaction like increased respiratory rate,tachycardia
32	CIPRO	1	CIPRO+CAFFINE	increased caffeine concentration and enhanced cns stimulation(increased back pain)
33	CIPRO	1	CIPRO+INSULINE	changes in blood glucose and increased risk of hypoglycemia or hyperglycemia(increased fbs and ppbs values)
34	LEVO	1	LEVO+INSULIN	changes in blood glucose and increased risk of hypoglycemia or hyperglycemia(increased fbs, ppbs and urine values)
35	LEVO	2	LEVO+GLIMI	changes in blood glucose and increased risk of hypoglycemia or hyperglycemia(increased fbs, ppbs and urine values)
36	CEFTRIO	1	CEFTRIO+LAB VALUES	hematological disorder like neutrophilia
37	GENTA	1	GENTA+FURO	additive ototoxicity or nephrotoxicity(tinnitus)
38	CEFTRIO	1	NO	hematological disorder

Where, CIPRO-Ciprofloxacin, LEVO-Levofloxacin, GLIMI-Glimepride, THEO-Theophylline, AZITHRO-Azithromycin, ATORVA-Atorvastatin, METRO-Metronidazole, CEFO-Cefotaxime, CEFTRIO-Ceftriaxone, ITRA-Itraconazole, INH-Isoniazide, RIFA-Rifampicin, OFLOX-Ofloxacin, ALBEND-Albendazole, AMOXI-Amoxicillin, GENTA-Gentamycin.

Evaluation of individual drugs involved in relation to patient and interaction characteristics and table 23, shows that Ciprofloxacin 9 (23.7%) incidence were more than Albendazole 1(2.6%), Gentamycin 1(2.6%), Ceftriaxone 1(2.6%), and Penicillin 1(2.6%).

DISCUSSION

Clinical pharmacists get an opportunity to work in a team and utilize the professional skills, knowledge and expertise for better patient care.

It would be worth assessing the incidence and patterns of drug interactions for antimicrobials among these patients. Very few studies have been reported in literature to study the nature of drug interactions specifically among antimicrobial agents. Such data can be helpful in understanding opportunities for improving drug use.

Total of 75 potential drug interactions out of which upon evaluation it was observed 38 interactions happened in the patients and 37 are assumed to happen. The discussion of the study is represented based on these 38 drug interactions.

In our study the adults are exposed to more single and multiple regimens than Youngers. Majority 9 (28.1%) of patients with PDIs more in 51-60 years. More than one potential drug – laboratory interaction was present in majority 19(50%) of patients. Similar findings are found in a study conducted by Hovastadivs BO et al.[12]

Potential drug interactions were categorized based on the gender. In that compared to 13(40.6) females, males 19 (59.4%) were found to have more potential drug interactions. Our study more potential drug interactions in adult patients due to lack of nutrition and in elderly patients multiple prescribers, multiple drugs and multiple diseases as in a study conducted by Hersh EV.[13]

Incidences were calculated, among 226 patients 32(14.2%) were found potential drug interactions. Incidence evaluation study were conducted by Bista D et al.[14]

Pattern of potential drug interactions were found, drug - lab interactions were observed in more potential drug interactions as compared to drug-drug interactions 15(39.5%), drug-disease interactions 3(7.9%) and drug - food interactions 1(2.6%). Drug- lab interactions 19(50%) were more because of unavailability of therapeutic drug monitoring process and one more thing may due to chemicals or laboratory instruments and also potential drug-drug interactions as in the studies conducted by Ray WA et al.[15] and Peng CC et al.[16]

Estimation of potential drug and drug-disease interactions were found, 15(39.5%) Potential drug interactions were more observed than potential drug-disease interactions 3(1.32%) because of patient medication inadherence, polypharmacy and multiple drug

Table 5: Evaluation of individual drugs involved in relation to patient and interaction characteristics

Interactions of drugs	Number of patients (n=38)	%	Age in years	Gender		Severity			Onset			
				Male	Female	Minor	Mod	Major	Nil	Delayed	Rapid	Unspecified
CIPRO	9	23.7%	46	7	2	2	2	5	0	2	7	0
LEVO	7	18.4%	58	5	2	0	0	7	0	5	2	0
AZITHRO	4	10.4%	78	1	3	0	4	0	0	2	0	2
METRO	4	10.5%	51	2	2	2	0	2	0	1	1	2
CEFEXIME	2	5.3%	37	1	1	1	1	0	0	0	1	1
CEFO	3	7.9%	55	3	0	0	3	0	0	0	0	3
ITRA	2	5.3%	26	1	1	0	0	2	0	2	0	0
OFLOXACIN	2	5.3%	60	0	2	2	0	0	0	0	2	0
OTHERS	3	7.9%	49	1	2	2	0	1	2	1	1	1

Where, CIPRO- Ciprofloxacin, LEVO-Levofloxacin, GLIMI-Glimepride, THEO-Theophylline, AZITHRO-Azithromycin, ATORVA-Atorvastatin, METRO-Metronidazole, CEFO-Cefotaxime, CEFTRIO-Ceftriaxone, ITRA-Itraconazole, INH-Isoniazide, RIFA-Rifampicin, OFLOX-Ofloxacin, ALBEND-Albendazole, AMOXI-Amoxicillin, GENTA-Gentamycin.

Ten (27.00%) of interactions were considered to be moderate. Hence, it can be seen that for 28(73%) of the potential drug interactions were either moderate or major in terms of severity. Related studies are conducted Chatsisvili et al and Bjerrum L et al. [17] [18]

The potential drug interactions observed it was seen that 14(36.8%) of the interactions were rapid onset in nature. Hence the duration of concomitant drug use should also be taken into account. Only 13(34.2%) of the interaction had a delayed onset of effect, while for 11(29.0%) of the interactions the onset of action as unspecified in the literature. These finding are similar to the study conducted by Doubova SV et al.[19] and Jeannette E.[20]

The class of drug most commonly involved in potential drug interactions was primarily Fluoroquinolines,3rd generations Cephalosporin, Antiamoebics and Macrolide antibiotics constituting 18(47.4%), 7(18.4%), 4(10.5%) and 4(10.5%) respectively. These four classes together were involved in more than 80 % because in this hospital based patient condition and area physician were prescribed more numbers of Fluoroquinolones, cephalosporin, Antiamoebic and Macrolides least such as Cefexim 1(2.6%), Albendazole 1(2.6%), Amoxicillin 1(2.6%) and Gentamycin 1 (2.6%) were found of the potential interactions observed in the study.

Outcome of potential drug interactions however, it should be remembered that the clinical outcomes of most interactions is highly situational and depends on several factors including the sequence of administration, duration of therapy, dose of each drug and even the influence of other drugs. In our study, outcomes and potential drug- laboratory interactions due to lack of drug therapeutic monitoring, multiple prescribers, multiples drugs, chemicals and laboratory machines. Related studies are conducted by Cremaden J et al.[21] and Thompson AH et al.[22]

CONCLUSION

In our study, the incidences of PDIs are mainly observed in elderly male population. These PDIs have resulted due to improper monitoring of cases and improper services provided by the health care providers. PDIs in many patients can be prevented by explaining the details of the drug and its use in patients of the disease. To prevent the PDIs clinical pharmacist services can be extensively helpful.

It was observed that common outcomes of PDIs such as increased Theophylline toxicity and Digoxin toxicity, increased laboratory values and also reduce effectiveness of some drugs. Flouroquinolones have a tendency to cause a wide range of PDIs.

Drug interaction increases in an exponential manner with the number of drugs prescribed to a patient. Thus reduction in the number of drugs prescribed may limit the risk of potential drug interactions.

Acknowledgment

To thanks to Adichunchnagiri institute of medical science (AIMs) for their kind support, also thanks to Dr.B.Ramesh and Dr.MG Shivaramu, staff and students of clinical pharmacy department.

REFERENCE

1. Chambers HF. Antimicrobial agents General principles of antimicrobial therapy. The pharmacological basis of therapeutics, 10th ed, Hardman JG, Limbird LE, ed. New York: McGraw-Hill; 2001.
2. Bista D et al. Understanding the essential of drug interaction: A potential need for safe and effective use of drugs. Kathmandu University medical journal 2006; 1(3): 421-430.
3. Manual M. Medical information, 2nd home edn. America: Merch research laboratories; 2003.
4. Hussar DA, Drug Interactions. In: In: Beringer P, Gupta PK, Hoover JE, Marderosian AD, editor. Remington: The science & practice of pharmacy, editor. 21th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 46-61 and 1889-97.
5. Wood MJ. Interaction of antibiotic with other drugs. British society for antimicrobial chemotherapy 1987; 628-630.
6. Cremandes J et al. Relationship between drug interactions related negative clinical outcomes. Pharmacy practice 2009; 7: 34-39.
7. Baxter K. Stockley's drug interactions.8th edn. London: Pharmaceutical press; 2008.
8. Thompson AH et al. Intracerebral secondary to a warfarin-metronidzole interaction. Tennessee Health Science Center 2008: 1-7.
9. Lal HM, Lal U. Drug Interactions-Mechanisms and Clinical Implications. Medicine Update 2008; 18: 670-90.
10. Schmidt LE, Dalhoff K. Food-Drug Interactions. Adis International Limited Drugs 2002; 62(10): 1481-1502.
11. Khan NA et al. Antibiotic Prescribing Pattern in Department of Dermatology of a Teaching Hospital in Tamil Nadu. Indian Journal of Pharmacy Practice 2010; 3(3): 18-21.

12. Hovstadius BO et al. Dispensed drug and multiple medications in the Swedish Population. Biomedical central Clinical Pharmacology. 2009; 9(11)1-10.
13. Hersh EV. Adverse drug interactions in dental practice: Interactions involving antibiotics. *JADA* 1999; 130: 236-51.
14. Bista D et al. Impact of educational intervention on the pattern and incidence of potential drug-drug interactions in Nepal. Phramcy Practice 2009; 7(4): 242-247.
15. Ray WA, Katherine MT, Meredith S, Narasimhulu SS, Hall K, Stein M. Oral Erythromycin and the Risk of Sudden Death from Cardiac Causes. The New England Journal of Medicine 2004; 351: 1089-96.
16. Peng CC, Glassman A, Trill LE, Hunter JH, Good CB. Incidence and severity of potential drug-dietary supplement interactions in primary care patients. *Arch Intern Med* 2004; (164) 630-636.
17. Chatsisvili A, Sapounidis I, Pavlidou G, Zoumpouridou E, Karakousis, Spanakis VEM, et al. Potential drug-drug interaction in prescriptions dispensed in community Pharmacies in Thessaloniki. Indian journal of clinical pharmacy 2010; 32: 187-93.
18. Bjerrum L et al. Risk factors for potential drug interactions in general practice. Europe Journal of General Practice 2008; 14(1): 23-9.
19. Doubova SV et al. Potential drug-drug and Drug-disease interactions in prescriptions for ambulatory patients over 50 years of age in family medicine clinics in Mexico City. Biomedical centre Health Services Research 2007; 7: 147.
20. Jeanntte EF et al. Frequency and nature of drug-drug interactions in a Dutch university hospital. The British Pharmacology Society. British journal of clinical pharmacology 2009; 68(2):187-93.
21. Cremandes J, Gonzalo M, Arrebola I. Relationship between drug interactions related negative clinical outcomes. Pharmacy practice 2009; 7: 34-39.
22. Thompson AH, Hurdle AC, Arnold LB , Finch CK, Sands C, Self TM. Intracerebral hemorrhage secondary to a warfarin metronidazole interaction. University of Tennessee Health Science Center 2008: 1-4.