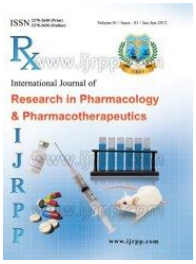
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 ***IJRPP |Vol.6 | Issue 2 | Apr - Jun - 2017***
ISSN Online: 2278-2656 ***Journal Home page: www.ijrpp.com***

Review article ***Open Access***

A review on essentials of drug interactions

Dr. G. RamyaBalaprabha[1], Sai Mahitha[1], Aparna[1], Vikas Patnaiak[1], Sikha Singh[1], Dr.Sharadha. R[2], Dr. K. Abbulu[2]

Department of Pharm.D, CMR College of Pharmacy, Kandlakoya, Medchal, Telangana – 501401.
***Corresponding author:Dr. G. RamyaBalaprabha**

ABSTRACT

Drug interactions are widely an important source of medication errors. Recently, potentially serious drug-drug interactions among medication errors has achieved significant clinical importance. An interaction is said to occur when the effect of one drug is changed by the presence of another drug, food or environmental chemical changes. Many of the drug interactions can be predictable; if the prescriber updates the knowledge with clinical pharmacology they can be avoided. Monitoring safety and effectiveness and evaluating the patient's response to therapy. To identify and prevent drug related problems like adverse drug events by conducting a comprehensive medication review. Warfarin with Antimicrobials (Amoxycillin, Ampicillin, Ciprofloxacin, Nitrofurantoin) - may have risk for upper Gastrointestinal bleeding and the interaction occurs prior to 14 days of administration.

Drug interactions are considered as one of the major important factor for the occurrence of negative outcomes like adverse drug events. So, drug interactions cannot be neglected and should be considered seriously. Patient should be monitored closely for adverse drug reactions.

Keywords: *Drug interactions, Drugs, Food.*

INTRODUCTION

Drug interactions are widely an important source of medication errors.[1]Recently, potentially serious drug-drug interactions among medication errors has achieved significant clinical importance.[2] As the number of drugs in the prescription increases, the chance of occurrence of drug interactions also get increased.[3] Prescription containing 5 drugs has 40% and prescription with 7 or more than 7 drugs exceeding to 80% has incidence of potential drug-drug interactions.[4][5] Drug interactions vary depending on population type and environmental factors so, incidence of drug interactions is a controversial issue.[6] Drug-drug interactions are more likely to develop in hospital inpatients because of severe illness, comorbid conditions, polypharmacy, chronic drug regimen, frequent alterations in therapy.[7] Failure to follow up the therapy of patients are more prone to develop drug related problems like drug-drug interactions.[8]Sometimes drug interactions are intentional causing synergistic effect and they may be unintentional leading to therapeutic failure by antagonistic effect.[9] The physiology of a patient changes as the age increases affecting the

pharmacokinetics and pharmacodynamics features of many drugs leading to increased susceptibility of drug interactions in elderly people.[10] Possible way to prevent drug interactions includes viewing past medical history, pharmacological principles and by computerised screening systems for prescriptions which detects potential drug interactions.[11] Drug interactions affects the quality and socio-economic status of the patient.[12]

Definition

An interaction is said to occur when the effect of one drug is changed by the presence of another drug, food or environmental chemical changes.[13] Potential drug interactions are identified on the basis of retrospective data and Actual drug interactions on the basis of clinical evidence (laboratory investigations and clinical symptoms).[14]

TYPES OF DRUG INTERACTIONS

Actual drug interactions

These are rare type of drug interactions which leads to Adverse Drug Reactions (ADR) [15] [16]

Potential drug interactions

These interactions occur when two or more drugs, which are known to interact, are prescribed regardless of the outcome. [17]

CLASSIFICATION OF DRUG INTERACTIONS

There are many factors, leading to occurrence of drug interactions which include:

Drug-food interaction

For certain drugs, the absorption and bioavailability is altered in the presence of food. For example, the effect of statins, antihypertensives and anti-histamines is decreased by stimulating the P-gp transporter by grape fruit juice. Iron absorption is increased by enhancing dissolution and converting ferrous to ferric form in the presence of citrus fruits and juices, cranberry juice containing vitamin C. [18]

Drug-herbal interaction

Interactions occur due to the lack of standardization of ingredients, variations in the dose of the Active Pharmaceutical Ingredient (API), contamination by microbes and adulterations with other dangerous natural ingredients of the herbal drugs. [19]

For example, when kava kava (Piper methysticum) is used with alprazolam, they show synergistic effect in CNS depression. [18]When ginger (Zingibarofficinale) is used along with anticoagulants, the risk bleeding gets increased. [20]

Drug-disease interaction

Drug interactions occur mostly in patients suffering with various diseases like renal and hepatic dysfunction and other conditions like epilepsy, aplastic anemia, asthma, cardiac arrhythmia, diabetes, hypothyroidism and intensive care patients. Alteration in doses is essential in the conditions listed. [9]

Drug-drug interaction

Alterations in effect of one drug in the presence of another drug.[21] For example, acetaminophen when concurrently administered with phenytoin causes alterations in effect of acetaminophen and produce serious affect that may lead to liver toxicity.[22] When methotrexate and ibuprofen are administered concurrently, it causes increase in the risk of methotrexate toxicity (leukopenia, thrombocytopenia, anaemia and nephrotoxicity) [23]

CLASSIFICATION BASED ON SEVERITY

Major

These are life threatening type of interactions which may lead to serious clinical consequences, so close monitoring is required to prevent serious adverse effects.

Moderate

This interaction occurs when one drug alters the effect of another drug that may result in exacerbation of patient's condition and requires changes in drug therapy (Individual Dose Adjustment).

Minor

These interactions probably has no clinical significance and would not require changes in drug therapy. [24]

Examples of Drug Interactions and their Adverse outcomes (Based on Severity)[25]

Interaction	Causative Drugs	Adverse outcomes
Major	Rifampicin + Pyrazinamide	May cause Liver damage.
	Warfarin + Heparin	May cause bleeding easily.
Moderate	Ceftriaxone + Furosemide	May increase the risk of Kidney damage.
	Sulfadiazine + Pyrimethamine	May increase the risk of Anaemia.
Minor	Furosemide + Doxycycline	May decrease renal function by increasing clotting factor.
	Digoxin + Spironolactone	May reduce tubular secretion of digoxin.

CAUSES OF DRUG INTERACTIONS

Narrow therapeutic index drugs (Eg:-Digoxin), patients with chronic diseases (Diabetes Mellitus, Hypertension),[26] usage of OTC drugs,[27] alterations in physiology of elderly patients, [28] Administration of multiple drugs,drug abuse, disease state (Hepatic and Renal dysfunction), genetic factors, alcohol consumption, smoking, diet, environmental factors.[29]Many of the drug interactions can be predictable, if the prescriber updates the knowledge with clinical pharmacology they can be avoided. [30]

Mechanism of Drug Interactions

Mechanisms by which drug interactions occur are:

Pharmacokinetic interaction

These interactions occurs when absorption, distribution, metabolism, elimination are altered by the presence of the another drug. [31]

Drug Interactions caused by Alterations in Absorption

Alterations in absorption cause sub-therapeutic drug concentration leading to therapeutic failure. Various factors alter the gastrointestinal absorption of drug by another drug(s). That includes gastrointestinal motility, changes in pH, binding, chelation, inhibition of efflux transporter, and inhibition of microbial flora.

Binding

The absorption of warfarin, statins was interfered by binding with bile acid sequestrants. So, 4 hours time interval should be maintained between administrations of these drugs to prevent interactions.

Inhibition of Microbial Flora

Contraception failure occurs by concurrent administration of broad spectrum antibiotics like Amoxicillin, Ampicillin, Tetracyclines, Fluoroquinolones, Sulfonamides, Macrolides or Cotrimoxazole with Oral Contraceptives. The mechanism involved is reducing the enterohepatic circulation of oral contraceptives caused by the inhibition of intestinal flora by broad spectrum antibiotics. [32]

Inhibition of Efflux Transporter

Concurrent administration of Grape fruit juice with drugs like calcium channel blocker (Amlodipine, Nifedipine), Atrovastatin, Carbamazepine, Alprazolam, Midazolam, cisaprideand Estrogen the absorption of these drugs get increased by blocking P-gp by Grape juice. [33]

Changes in ph

Gastric pH is increased by antacids and H_2 blockers. Co administration of Sucralfate with Phenytoin decreases the absorption of Phenytoin. Coadministration of Ketoconazole with H_2 blockers and proton pump inhibitors decreases the absorption of Ketoconazole due to decrease in gastric acid.

Gastrointestinal motility

Gastrointestinal motility is altered by certain drugs like atropinic drugs, tricyclic anti-depressants, prokinetic drugs (metoclopramide or cisapride), opoids by affecting the absorption of drugs. Gastric emptying time of many drugs is decreased by atropinics causing slower absorption and greater degradation (Eg: Levodopa). [33]

Chelation

Milk and milk products absorption is interfered by chelating ions, by forming insoluble complex with tetracyclines and calcium. [16]

Drugs Interactions caused by Alterations in Drug Distribution

Plasma protein binding and displacement from plasma protein binding sites, Tissue binding and displacement from tissue binding site.

Plasma protein binding

Free form of drug is distributed to tissues for pharmacological action rather than bound form of a drug.Acidic and Neutral drugs (NSAIDS, Warfarin, Barbiturates, Phenytoin, Sulfonamides, Penicillin and Steroids) have more affinity towards Albumin. Basic drugs like Metaprolol, Quinidine, Tricyclic antidepressants and Verapamil shows more affinity towards alpha-1 acid glycoprotein. [33]

To Albumin at site 1 the drugs like Salicylates, Diclofenac, Warfarin gets bind whereas at site 2 Ibuprofen gets bind, so there is less chances of interaction between the site 1 and site 2 drugs.[34]

Plasma protein displacement

When two drugs get compete for one plasma protein binding site leading to displacement of one drug to another drug from binding site. These results in concentration increased in plasma that may lead to enhanced effect or toxicity of the displaced drug.

Methotrexate toxicity is caused by displacing the methotrexate with other drugs like Naproxen, Diclofenac and Salicylates. [35**]**

Tissue Binding and Displacement

Digoxin concentration can be increased by Nifedipine and Amiodarone by binding at tissue binding site. [16]

Drug Interactions caused by Alterations in Metabolism

Enzyme induction and Enzyme inhibition are the important factors in drug interactions.

Enzyme induction

Common inducers include Rifampicin, Barbiturates, Griseofulvin, Phenytion, Carbamazepine, Nevirapine and Dichlorodiphenyltrichloroethane (DDT).Antibiotics (Doxycycline) when given to the patients who are receiving enzyme inducers may lead to therapeutic failure. [36]

Enzyme inhibition

It is a direct phenomenon in which drugs causes inhibition of certain enzymes. [32] Classification of Enzyme inhibitors are based upon their effect on the substrate that includes strong, moderate or weak. Strong inhibitors include fluconazole, fluvoxamine, ciprofloxacin, bupropion, paroxetine, fluoxetine, quinidine, indinavir, retonavir, clarithromycin, itraconazole and ketoconazole. Moderate inhibitors includesamiodarone, terbinafine, erthyromycin, fluconazole, grape fruit juice, verapamil and diltiazem. [36]

When drugs like terfenadine are administered concurrently with the inhibitors like fluoxetine, the terfenadine gets precipitated and it may results in fatal cardiac arrhythmia. [33]

Non-microsomal enzyme inhibition

Significant drug interactions can be produced by inhibition of non-microsomal enzymes with certain drugs. Xanthine oxidase inhibitor like allopurinol (used in gout) and anti cancer drugs like mercaptopurine or azathioprine when administered concurrently, as this drugs are metabolised by the same enzyme leading to inhibition of breakdown of these anti cancer drugs. That results in potential therapeutic effect. So the doses of these anti cancerdrugs should be reduced when they are concurrently administered with allopurinol. [37]

Drug Interactions caused by Alterations in Elimination

The mechanism in which a drug can alter the rate of renal excretion of other drugs includes: alteration in protein binding and filteration, inhibition of tubular secretion, binding to active transporters in

proximal tubules or altering the urine flow or urine pH. [38]

P-gp, OATP and OCT are the transporters involved in tubular secretion of drugs. Serum drug concentration is increased by inhibiting these transporters by decreasing renal clearance. The drugs transmitted through OATP are probenecid and penicillin. Probenecid and penicillin complete with each other and finally probenecid binds to OATP and gets excreted, increasing the duration of action of penicillin by inhibiting its elimination. [33]

Interactions produced at the level of elimination are due to alterations in urine flow or urine Ph. The urinary excretion of many drugs can be increased by administrating diuretics as they increase the urine flow. When thiazide diuretics and lithium are administered concurrently, depletion of sodium occurs due to thiazide diuretic so, lithium gets reabsorbed from proximal tubule and shows its toxicity. [38]

Pharmacodynamic interaction

These interactions occur when activity of drug at its site of action is altered by another drug.

Additive or Synergistic Interactions

When two drugs having, similar effects are concurrently administered, and then they show synergistic effect. Generally trimethoprim and sulfamethoxazole are bacteriostatic drugs but when given in combination (Cotrimoxazole) they shows bactericidal effect by blocking the steps in folic acid synthesis in microorganism.

Antagonistic interaction

Antagonistic effect may be competitive antagonism or non-competitive antagonism. [33]

Competitive receptor antagonism

These interactions are mostly used in the treatment of over dose of a drug or poisoning conditions. When two drugs are competing for the same receptor site, the drug which has more affinity for the receptor site gets bind and displaces the other drug from it. Some of the examples are flumazenil in benzodiazepines overdose, atropine in organophosphorous and naloxane in opioid overdose. [18]

Non-competitive receptor antagonism

Norepinephrine-phenoxybenzamine or diazepam-bicuffineare some examples of non-competitive antagonism.

Pharmaceutical interactions

When any two drugs are mixed in infusion or syringe, they react with each other and become inactive resulting in loss of drug affect. The drugs which should not be mixed with beta-lactams like cephalosporin's includes tetracyclines, aminoglycosides, macrolides and chloramphenicol because they are physically and chemically incompatible causing inactivation of antibiotic activity by beta-lactams. Phenytoin should not be mixed with 5% dextrose solution because it gets precipitated in the presence of 5% dextrose. [16][33]

Examples for Mechanism of Drug Interactions

Types of Interaction	Type of mechanism	Examples
Pharmacokinetic Interactions	Absorption gets affected	Concurrent use of metoclopramide and digoxin may result in decreased absorption of digoxin[18]
	Distribution gets affected	Concurrent use of Valproic acid and phenytoin, may lead to displacement of phenytoin that results in phenytoin toxicity[18]
	Metabolism gets affected	Concurrent administration of macrolides and theophylline may result in inhibition of theophylline metabolism leading to risk of toxicity[33]

		Concurrent administration of salicylates and methotrexate resulting in reduction of tubular secretion resulting in methotrexate toxicity.[32]
	Elimination gets affected	
	Synergistic Interactions	Concurrent administration of Epinephrine and lidocaine results in potentiating the action of lidocaine, thus resulting in vasoconstriction and prolong the duration of local anaesthesia[33]
Pharmacodynamic Interaction	Antagonistic Interactions	Nitrates when used along with cyanide, they react chemically and forms methemoglobine and antagonises cyanide[18]
Pharmaceutical Interaction	Thiopental when mixed with succinylcholine in a syringe then the thiopental gets precipitated.[33]	

EXPERIMENTAL METHODS TO DETECT DRUG INTERACTIONS

Invitro methods

Drug interactions are studied under various invitro methods like sub-cellular fractions of human liver tissue, whole cell models, heterologous expressed and purified human drug metabolising enzymes, pharmacological probes and immunochemical probes.[39] Drug interactions are detected in pre-clinical trials of drug development by using invitro methods and results may vary from one phase to another phase.[40]

Sub-cellular fractions of human liver tissue

By differential high speed centrifugation of homogenised liver, hepatic microsomes are produced.[41] In this method microsomes from different donors are to be used. Enzymes like CYP450, Flavin mono-oxygenases, transferases and epoxide hydrolases are used in this method.

Whole cell models

Whole cell method uses harvested liver with is not used for liver biopsy and liver transplantation. Age, diet, health, alcohol and tobacco use, medication use and genotype of the donor vary the characteristics of whole cell model.

Heterologous expressed and purified human drug metabolising enzymes

Cloning of complementary DNA is done by recombinant human enzymatic protein which is present in various cells with low intrinsic CYP450 enzyme activity for the common CYP450 enzyme. Bacteria, yeast, mammalian cells, insect cells and lymphoblastoid cells are the different types of cells present in it.

Pharmacological probes

With the help of pharmacological probes by the use of selective chemical inhibitors of specific CYP enzymes, metabolic pathways for the test drug is demonstrated.

Immunochemical probes

For selective inhibition of microsomal preparations, polyclonal or monoclonal antibodies for specific isoform of CYP enzymes the immunochemical probes are used. [39][41]

Invivo methods

Invivo methods are employed to study drug interactions in clinical trials. Drugs having long elimination half-life, parallel group studies are mostly preferred. The population for this study generally includes healthy individual with restrictive eligibility criteria, for metabolic polymorphisms individuals selected based on phenotype or genotype, for heterogenicity the individuals are selected from general population. To increase the possibility of recognizing the interaction, the highly approved doses of test drugs and shortest dosing intervals are preferred. Directions for sample collection (blood) from patient suffering with serious, severe or unexpected adverse events are included in the protocol of clinical trials. [18]

Recognization and Prevention of Drug Interactions

Recognization of drug interaction has a great impact on patient care. Chance of occurrence of drug

interactions is more in elderly patients, patients with renal and hepatic dysfunction. Patients receiving narrow therapeutic index drugs along with other two or more drugs are more prone to produce drug interactions. Complete medication history of the patient should be maintained and regular monitoring of prescription should be needed.

To prevent drug interactions physician should have awareness regarding interactions and should be able to detect them. Occurrence of drug interactions can be reduced by identifying the risk factors and maintaining complete history of the patient, initiating alternative drug therapy whenever needed, individualise the therapy and patient should be educated. [29]

Preventive measures for drug interactions are optimisation of number of drugs in the prescription should be needed as the occurrence of interactions increases by increasing the number of drugs in prescription. Physician should have thorough knowledge in detection and recognization of clinical symptoms of drug interactions. Patients with narrow therapeutic index drugs should be closely monitored with therapeutic drug monitoring system. [42]

Monitoring Program for Drug Interaction

Drug interaction monitoring program is essential for early detection and prevention of interactions. The program should perform important activities like identifying the interactions, generating interventions and evaluating the significance of interactions. The composition of monitoring program includes physician, pharmacologist, pharmacist and nurses and their role is to analysing patient's condition and medications prescribed. From the patient prescriptions, the drug interactions are detected and are analysed according to the literatures and interactions are categorised based on their severity. An alteration in the drug therapy is needed to prevent the occurrence of interactions (mainly serious interactions). Creating awareness to medical studies, pharmacist and nurses regarding drug interactions. [42]

Management of Drug Interactions

- Monitoring safety and effectiveness and evaluating the patient's response to therapy.
- To identify and prevent drug related problems like adverse drug events by conducting a comprehensive medication review.
- Monitor patient's condition when there is a change in the medication (Added or Discontinued).[43]
- When two possible interacting drugs are prescribed which are necessary, then adjustments in the dosage and close clinical monitoring is necessary.[44]
- When one drug has high interacting properties then other drug from the same class, then the drug with low interacting properties should be prescribed to avoid interaction.[45]

Common Drug-Drug Interactions and their Adverse Outcomes

- Warfarin with Antimicrobials (Amoxycillin, Ampicillin, Ciprofloxacin, Nitrofurantoin) - may have risk for upper Gastrointestinal bleeding and the interaction occurs prior to 14 days of administration.[46]
- Theophylline with Ciprofloxacin - may have for risk for developing theophylline toxicity prior to 14 days of administration.[47]
- Glipizide with Antimicrobials (Fluconazole, Ciprofloxacin) - may have risk for developing hypoglycaemia prior to 20 days of administration.[48]
- Digoxin with Clarithromycin or Cephalexin - may have risk for developing digoxin toxicity prior to 7 days of administration.[49]
- Tamoxifen with SSRI`s (Citalopram, Fluoxetine, Venlafaxine) - may have risk for developing breast cancer in woman's.[50]
- ACE inhibitors with Potassium sparing diuretics - may have risk for developing hyperkalaemia prior to 7 days of administration.[51]
- CCB's (Verapamil, Diltiazem, Amlodipine) with Macrolide antibiotics (Clarithromycin, Erythromycin) - may have risk for developing hypotension or shock prior to 7 days of administration.[52]

CONCLUSION

Drug interactions are considered as one of the major important factor for the occurrence of negative outcomes like adverse drug events. So, drug interactions cannot be neglected and should be considered seriously. Patient should be monitored closely for adverse drug reactions. Detailed reviewing of patient medication chart along with comorbidity conditions, adjustments in dose if

necessary, appropriate drug selection by adhering to the policies of writing prescriptions, regular follow up of patient therapy may reduce the occurrence of adverse drug events. Education of physicians and health care professionals for updating knowledge and providing computerised systems for prescription and drug information, pharmaceutical care may significantly increase in providing better patient care.

REFERENCE(S)

[1]. Sandson N. Drug-drug interaction: the silent epidemic. Psychiatric Services 56(1), 2005, 22-4.

[2]. Jankel CA and Speedie SM. Detecting drug interactions: a review of the literature. DICP. 24, 1990, 982-89.

[3]. Merlo J, Liedholm H, Lindblad U, Bjorck-Linne A, Falt J, Lindberg G, Melander A. Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study. BMJ. 323(7310), 2001, 427-428.

[4]. Kappa PA, Klop AC, Jenkins LS, Drug interactions in primary health care in the George subdistrict, South Africa: a cross-sectional study. South AfrFamPract 55(1), 2013, 78-84.

[5]. Grattagliano I, Portineasa P, D'Ambrosio G, Palmieri VO, Palaseiano G. Avoiding drug interactions; here's help. J FamPract 59, 2010, 322-329.

[6]. Peng CC, Glassman PA, Marks IR, Powler C, Castigliene B, Good CB, Retrospective drug utilization review: incidence of clinically relevant potential drug-drug interactions in a large ambulatory population, J Manag Care Pharm. 9(6), 2003, 513-522.

[7]. Zwart-Van-Rijkom JEF. Uijtendaal EV, Ten Berg MJ, VanSolinge WW, Erberts ACG, Frequency and nature of drug-drug interactions in a Dutch university hospital. Br J ClinPharmacol 68, 2009, 187-193.

[8]. Wiesner C, Hersberger KE, Surber C, Haefeli WE. Drug safety after hospital discharge. Pharm World Sci. 22, 1999, A18.

[9]. Lee A, Stockley IH. Drug interactions In Walker R, Edwards C. Clinical pharmacy and Therapeutic, 3rd edition. Churchill Livingstone, Philadelphia 2003, 21-31.

[10]. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lancet 370, 2007, 185-91

[11]. Horn JR, Hansten PD, Chan LN Proposal for a new tool to evaluate drug interaction cases. Annals of Pharmacotherapy, 41, 2007, 674-680.

[12]. Jha AK. Kuperman GJ, Rittenberg E, Teich JM and Bates DW. Identifying hospital admissions due to adverse drug events using a computer-based monitor. Pharmaoepidemiol Drug saf. 10, 2001, 113-119.

[13]. Stockley I H. Drug interaction: a source book of adverse interaction, their mechanisms, clinical importance and management. pharmaceutical press, London 5, 1999.

[14]. Gaeta TJ, Fiorini M, Ender K, Bove J, Diaz J. Potential drug-drug interactions in elderly patients presenting with syncope. J Emerg Med. 22, 2002, 159-62.

[15]. Quinn DI, Day RO. Clinically important drug interactions. In: Speight TM, Holford HG, editors, Avery's Drug treatment, Auckland (New Zealand): Adis International; 1997, 301-38.

[16]. May FE, Stewart RB, Cluff LE. Drug interactions and multiple drug administration. ClinPharmacolTher 22, 1977, 322-8

[17]. Oates JA. The science of drug therapy. In: Brunton LL, ed. Goodman and Gilman's The pharmacological Basis of Therapeutics. 11thed. New York: McGraw-Hill; 2006.

[18]. Madhav M, Sanghavi D, Review of drug interactions: A Comprehensive Update. British Journal of Pharmaceutical Research 4(8), 2014, 954-80.

[19]. Cupp MJ. Herbal Remedies: adverse effects and drug interactions.AmFam Physician 1999;59(5):1239-45.

[20]. Kruthi P, Brosi E, Fux R et al. Ginger-associated overanticoagulation by phenprocoumon. Ann Pharmacother 38, 2004, 257-60.

[21]. Segura-Bedmar I, Martinez P, de Pablo- Sanehez C. Extracting drug-drug interactions from biomedical texts. BMC Bioinformatics 1(5), 2010, 9.

[22]. Brackett CC, Bloch JD, Phenytoin as a possible cause of acetaminophen hepatotoxicity: case report and review of the literature. Pharmacotherapy 20, 2000, 229-33.

[23]. Cassano WF, Serious methotrexate toxicity caused by interaction with ibuprofen (letter). Am J PediatrHematolOncol 11, 1989, 481-2.
[24]. Cruciol-Souza JM, Thomson JC, A pharmacoepidemiologic study drug interactions in a Brazilian teaching hospital. Clinics 61(6), 2006, 515-20.
[25]. Akshaya SB et al. Prevalence of potential drug-drug interactions among internal medicine ward in university of Gondar teaching hospital. Asian pacific journal of tropical biomedicine 4(1), 2014, S204-8
[26]. Pratibha M, Drug Interactions-Causes and Implications. Research and Review: Journal of Pharmacy and Pharmaceutical Sciences 2(3), 2013, 101-5
[27]. Quintas LEM, Gram KRS, da Silveira GPE et al.Pharmacokinetic Modifications and Drug-Drug Interactions in Clinical Monitoring of the Elderly: A Short Review. Pharm Anal Acta 2, 2011, 141.
[28]. Ferdous S, Sultan MZ, Bashar T et al. Invitro and Invivo Studies of Drug-Drug interaction between Metformin and Cefepime. Pharm Anal Acta; 6, 2015, 348.
[29]. Hussar DA, Drug interaction, In: Gennaro, Marderosian AHD, Hanson GR et al. Remington The science and practice of pharmacy. Philadelphia: Lippincott Williams and Willinks 2000, 174-61.
[30]. Thomas A, Routledge PA. Drug interaction in clinical practice. Focus.Quarterly bulletin of pharmacovigilance. 2003.
[31]. Caterina P, Antonella DP, Chiara G et al. Pharmacokinetic drug-drug interaction and their implication in clinical management. J Res Med Sci 18, 2013, 600-9.
[32]. Katzung BG, Masters SB, Trevor AJ, editors. Basic and Clinical Pharmacology. New Delhi: McGraw Hill, Lange. Tata McGraw-Hill Edition; 12, 2012.
[33]. Tripati KD. Essentials of Medical Pharmacology. New Delhi: Jaypee Brothers Medical Publishers; 7, 2013.
[34]. Possi A, Gallelli L. Pain management for dentists: the role of ibuprofen. Ann Stomatol (Roma) 2(3-4), 2011, 3-24.
[35]. Patane M, Ciriaco M, Chimirri S et al. Interactions among low dose of methotrexate and drugs used in the treatment of rheumatoid arthritis. AdvPharmacolSci 2013.
[36]. Shimada T, Yamazaki H, Mimura M, et al.Interindividual variations in human liver cytochrome P-450 enzymes involved in oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians, J PharmacolExpTher.270(1), 1994, 414-23.
[37]. Forrester LM, Henderson CJ, Glancey MJ et al. Relative expression of cytochrome P450 isoenzymes in human liver and association with the metabolism of drugs and xenobiotics. Biochem J. 281(2), 1992, 359-68.
[38]. Caranasos GJ, Stewart RB, Cluff LE. Clinically Desirable Drug Interactions. Ann Rev PharmacolToxicol. 25, 1985, 67-95.
[39]. Brown HS, Galetin A, Hallifax D et al. Prediction of In vivo drug-drug interactions from In vitro data: factors affecting prototype drug-drug interactions involving CYP2C9, CYP2D6 and CYP3A4. Clin Pharmacokinetic. 45(10), 2006, 1035-50.
[40]. Von Moltke LL, Greenblatt DJ, Schmider J et al. In vitro approaches to predicting drug interactions in vivo. BiochemPharmacol. 55(2), 1998, 113-22.
[41]. Drug interactions studies- Study design, data analysis, implications for dosing and labelling recommendations. Draft guidance for industry. US Department of Health and Human Services Food and Drug Administration Centre for Drug Evaluation and Research. 2012, 1-75.
[42]. Bista D, Palaian S, Shankar PR et al. Understanding the essentials of drug interactions: A potential need for safe and effective use of drugs. Kathmandu University Medical Journal. 4(3), 2006, 421-30.
[43]. Ansari JA. Drug interaction and pharmacist. J Young Pharm 3, 2010, 326-31.
[44]. Kashif S, Syed YH, Faizan S, Ansari JA. Drug interaction: A brief of preventive approaches. IJUPLS 2(3), 2012, 422-7.
[45]. Pasternak RC et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am CollCardiol 40(3), 2002, 567-72.
[46]. Fischer HD, Juurlink DN, Mamdani MM et al. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: a population-based study. Arch Intern Med. 170, 2010, 617-21.

[47]. Antoniou T, Gomes T, Mamdani MM etal.Ciprofloxacin-induced theophylline toxicity: a population-based study. Eur J ClinPharmacol, 67, 2011, 521-26.
[48]. Schelleman H, Bilker WB, Brensinger CM et al. Anti-infectives and the risk of severe hypoglycaemia in users of glipizide or glyburide. ClinPharmacolTher. 88, 2010, 14-22.
[49]. Chan AL, Wang MT, Su CY et al. Risk of digoxin intoxication caused by clarithromycin-digoxin interactions in heart failure patients: a population-based study.Eur J ClinPharmacol. 65, 2009, 1237-43.
[50]. Kelly CM, Juurlink DN, Gomes T et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving ramoxifen: a population based cohort study. British Medical Journal. 340, 2010, c693.
[51]. Juurlink DN, Mamdani M, Kopp A et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. Journal of the American Medical Assocation. 289, 2003, 1652-58.
[52]. Wright AJ, Gomes T, Mamdani MM et al. The risk of hypotension following co-prescription of macrolides antibiotics and calcium-channel blockers. Canadian Medical Association Journal. 183, 2011, 303-7.