Drug Interaction Management in Critically Ill Patient

Hemraj Singh Rajput1* and Nirmal V. Shah1

1Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i43B32570

Editor(s):
(1) Dr. Thomas F. George, University of Missouri- St. Louis, USA.

Reviewers:
(1) Subbarao Jampani, Acharya Nagarjuna University, India.
(2) Dhirajsingh Sumersingh Rajput, India.

Complete Peer review History: https://www.sdiarticle4.com/review-history/73643

Received 29 June 2021
Accepted 09 September 2021
Published 14 September 2021

ABSTRACT

Drug interaction in critically ill patient is very common and affecting patients Physically, Mentally and Financially. There are various measures which has been taken to minimize this burden on patient, such as books being prepared which include various drug interaction, maintain websites and database that provides information regarding drug interactions. With the use of these website and databases the drug interaction can be managed. It is common practice that side effects of drug interaction are being managed by additional drugs, the main reason behind it could be non-availability of alternative drugs or costlier alternative. These factors remain the main cause of treatment failure in majority of patients leading to prolong. The current study was performed for the duration of 12 months, from this study it was identified that 113 types of major drug interactions commonly found in total 250 prescriptions which were evaluated and managed accordingly. Suggestions being prescribed by various sites were, avoid concomitant use of drug, use alternative therapy, and monitor closely for any adverse effect. During suggestion made by the Clinical Pharmacist, for the same drug interactions it was identified that more of drug therapy adjustment can be done then provided by the online database. The parameter on which the drug interactions management are being suggested were focused on just type of drug interaction and its effect, it does not include the actual pharmacodynamic and pharmacokinetic changes in therapy. The suggestion made by the clinical pharmacist were includes drug removal, drug dosage changes, alternative therapy, alternative route of administration, change in time interval etc. From this study it

*Corresponding author: E-mail: hemrajs119@gmail.com;
was concluded that the drug interaction management can be done at various stages of treatment with proper therapy modification by the clinical pharmacist, and if done properly it will improve the overall outcome of patient health care.

Keywords: Drug interaction; antagonism; adverse drug reaction; critical ill patients.

1. INTRODUCTION

The treatment of critically ill patient is never been simple, these patients require special arrangements at hospital and expensive drug therapy. It becomes more difficult for a health care system to provide a good and satisfactory treatment to these patients as there are increase chance of Drug Interactions (DIs) with addition of every drug in the patient drug therapy. It is a known fact symptom either as disease condition or as side effect of drug interaction being treated with additional drugs rather than any other means. The impact of drug interactions has been very well studied and documented in various research articles. These research articles have shown that how it is being affecting patients physically, Mentally and financially. Any effect from a drug interaction also affects the decision making in the drug therapy, causing additional burden on the doctors who certainly relay on the gold standards and guidelines provided by various health care statutory bodies [1-3]. The DIs can be divided in majorly two categories Pharmacokinetic drug interactions and Pharmacodynamic drug interactions. Both of which may lead to increase the toxicity of the drug or decrease its effectiveness. There are various mechanisms through which either of increase or decrease of drug effects can be achieved. By understanding Pharmacokinetic and Pharmacodynamic properties of the drug it is possible to predict the effect of drug on the patient. The Pharmacokinetic drug interactions can be elaborated more as, the changes in the concentration of drug in the various body masses such as body fluids and body tissues. These changes generally occur during the process of drug absorption, drug distribution and elimination of the drug. For Pharmacokinetic interaction to occur metabolism of drug is necessary and for this to occur the drug should undergo through two phase of metabolism which are Phase I and Phase II metabolism. The Phase I includes the oxidative transformation of the drug and the Phase II increases the polarity of the drug by the means of conjugation reaction with the endogenous groups like glucuronides or sulfates. When it comes to Pharmacodynamic drug interactions, it is usually associated with alteration in safety and efficacy of the drug. Which may or may not include alteration in the drug Pharmacokinetic profile. Generally, when two drugs of same objective in a treatment given together can produce additive or synergistic effects on patient body, such effects can be considered under Pharmacodynamic drug interactions. DIs can be managed by understanding mechanism through which the interaction is occurring. The understanding of pharmacokinetic and pharmacodynamic properties and applying same on the individual patient can help in reduction of drug interaction and related effects drastically. With the understanding of pk and pd properties of drugs which are interacting a clinical pharmacist can provide a proper drug therapy of prescribed drugs. The prepared drug therapy may include changes in drug dosage, route of administration, different salt formation, addition or removal of drug if necessary [4]. The availability of various drug interaction related information providing database has gain popularity in the recent decade. The provided drug interaction database does contain information for severity, possible effect of interaction on patient, mechanism of drug interaction and source of information form where it has been collected. The very crucial part of provided information on drug interaction is first its management and second its source of information with appropriate justification. The database does lacks in quality of these two parameters. This lacuna can be fulfilled with the help of clinical Pharmacist actively managing drug interaction at the bedside with constant monitoring of the drug chart at the hospital [5]. The practice of Evidence based medicine is a part of the evolutionary medical care. It is necessary to keep in check the type of evidence available for the drug interactions also and keep them updating. The updated version for classification of evidence as per by Centre for Evidence Based Medicine: Levels of Evidence (March 2009) can be used to classify the level of evidence provided in various online drug interaction database to provide necessary strength to the claim of drug interaction. The current study is an attempt of provide best possible management of drug interactions to the critically ill patient with the help of the online drug
interaction data bases and various research articles available online.

2. METHODOLOGY

The Intensive Care Unit of Dhiraj General Hospital was the site of data collection for this study. The study was a retrospective observation study conducted for the duration of 12 months (November 2019 to October 2020). The objective of the study was to identify common drug interaction in critically ill patient, To identify the level of evidence references used by various drug interaction database, and to identify type of drug interaction categories in major and moderate type. Total 251 cases were analysed for the drug interactions. The drug interaction was identified with the help of various drug interaction data providing websites Micromedex and Medscape. The selection of Critically Ill patient was made on the basis of inclusion and exclusion criteria. Inclusion criteria: Patient admitted at Intensive care unit, only patient who were 18 year and above included in the study. The Patient admitted in ICU will be considered Critically Ill. Exclusion criteria: Those patient drug charts which does not containing drug interaction was not included. The identified drug interaction was assessed for its severity and interaction with Major and Severe type of drug interaction were selected for further analysis. Drug interaction found to be Major or Severe then provided with Management from either source of online drug interaction database and Clinical Pharmacist approach of information retrieval from research article and available medical books. The gathered information was then provided to treating doctor who will manage patient treatment accordingly. Descriptive statistics was applied for the analysis of data.

3. RESULTS

In this study total 345 drug interaction were identified from 251 prescription out of which 113 were Major and 232 were Moderate type of interaction (Fig 1). Total 24 type of Major drug interaction were found to be most frequent (Table 1).

Total number of drug interaction found was 345 out of which 113(32.75%) was Major or Severe, 232(67.24%) was Moderate.

Table 2 shows all major drug interactions, common types of disease conditions possible effect of drug interaction on the patient, management give as per the online database, frequency of drug interactions and level of evidence of the interactions.

This table shows Highest Level of Evidence provided for drug interaction in online data base. The level of Evidence has been provided on the basis of chart provided by Centre for Evidence Based Medicine: Levels of Evidence (March 2009). Majority of drug interaction provide in online database were having a poor level of evidence i.e., 71 drug interaction was having level 5 evidence followed by 15 drug interactions were having level 3b and only 10 drug interactions were having level 1b evidence.

4. DISCUSSION

In this study 251 prescriptions were included from which total 345 drug interactions was found. Out of those 345-drug interaction 113 were major drug interactions and 232 were moderate drug interactions. 1/3rd of total interaction was major drug interaction. In a similar study conducted at Cardiothoracic ICU has shown that 1/4th of the total interaction found were major drug interaction [6]. Another study conducted in ICU have shown that 15 percent of total drug interaction were highly significant [7]. Another similar study has shown that 54 percent of potential drug-drug interaction occurred in ICU patient and from those interaction 90 percent of interactions can be set in 20 set of potential drug interactions types [8]. The study also shows that the most common type of effect form drug interaction was QT interval prolongation, Increased risk of bleeding and cardiac arrhythmias. Majority of patients were suffering from Cardiovascular, Neurological and Nephrological disease conditions. The most frequent major drug interaction found were Aspirin with Furosemide, Aspirin with Clopidogrel, Aspirin with Heparin, Aspirin with Ramipril, Aspirin with Spironolactone and Aspirin with Heparin. Similar study has shown most common drug interaction were between antihypertensive, anticoagulants and antiplatelet agents [9]. In a study conducted at United Kingdom on combination therapy of clopidogrel and aspirin shows significant increase in bleeding time through synergistic antiplatelet action [10]. Similar study conducted titled antagonism of spironolactone induced natriuresis by aspirin has been observed. The study has shown that 1/3rd reduction in sodium excretion can affect the treatment of patient adversely for the patient treated with spironolactone for ascites.
or edema [11]. Another study shows that Dexamethasone, Ciprofloxacin, Tramadol, Moxifloxacin, Diclofenac, Pantoprazole and Theophylline [12]. The level of evidence provided by the online database for the given major drug interaction were majorly of poor level of evidence i.e., 71 drug interaction with level 5 evidence followed by 15 drug interactions of 3b, 10 drug interaction of 1b, 6 drug interaction of 4 and 5 drug interaction of 2b. Article reviewed for the identification of level of evidence of the drug interaction in Table 1 [13-51].

**Fig. 1. Type of Drug interaction Identified**

Table 1. The common major drug interactions were found to be between following drugs

| S. No | Interacting Drugs       | No. of Interaction Found (Percentage) |
|-------|-------------------------|--------------------------------------|
| 1.    | Aspirin & Furosemide    | 24 (9.6%)                            |
| 2.    | Aspirin & Clopidogrel   | 22 (8.8%)                            |
| 3.    | Aspirin & Heparin       | 17 (6.8%)                            |
| 4.    | Aspirin & Ramipril      | 17 (6.8%)                            |
| 5.    | Aspirin & Spironolactone| 15 (6%)                              |
| 6.    | Clopidogrel & Heparin   | 15 (6%)                              |
| 7.    | Atorvastatin & Budesonide| 10 (4%)                       |
| 8.    | Ramipril & Spironolactone| 10 (4%)                        |
| 9.    | Ceftriaxone & Heparin   | 08 (3.2%)                            |
| 10.   | Metronidazole & Ondansetron| 06 (2.4%)                 |
| 11.   | Metronidazole & Phenytion| 06 (2.4%)                       |
| 12.   | Ondansetron & Tramadol  | 06 (2.4%)                            |
| 13.   | Ofloxacin & Ondansetron | 05 (2%)                             |
| 14.   | Aspirin & Torsemide     | 04 (1.6%)                            |
| 15.   | Digoxin & Spironolactone| 04 (1.6%)                        |
| 16.   | Heparin & Warfarin      | 04 (1.6%)                            |
| 17.   | Piperacillin & Heparin  | 04 (1.6%)                            |
| 18.   | Aspirin & Enalapril     | 03 (1.2%)                            |
| 19.   | Aspirin & Prasugrel     | 03 (1.2%)                            |
| 20.   | Atropine & Glycopyrrolate| 03 (1.2%)                   |
| 21.   | Ceftriaxone & Warfarin  | 03 (1.2%)                            |
| 22.   | Digoxin & Metoprolol   | 03 (1.2%)                            |
| 23.   | Domperidone & Ondansetron| 03 (1.2%)                     |
| 24.   | Heparin & Nitroglycerine| 03 (1.2%)                        |

The frequent drug interactions were between, Aspirin & Furosemide, Aspirin & Clopidogrel, Aspirin & Heparin 17, Aspirin & Ramipril 17, Aspirin & Spironolactone
Table 2. Identified drug interaction along with management as per online database and Pharmacist management

| Sr. No. | Drug Interaction                  | Disease Condition                  | Effect of Drug Interaction                  | Management as per Drug Interaction Database | Frequency of Interactions (in 250 Prescriptions) | Highest level of Evidence |
|---------|-----------------------------------|------------------------------------|---------------------------------------------|---------------------------------------------|------------------------------------------------|--------------------------|
| 1.      | Acetaminophen + Isoniazid         | Tuberculosis, Diabetes II          | Increase risk of Hepatotoxicity             | Acetaminophen use should be avoided or limited in patients taking isoniazid. | 01                                              | 05                       |
| 2.      | Amikacin + Mannitol               | Acute left sided subdural hemorrhage | Increase risk of Renal toxicity             | Avoid concomitant use of amikacin and mannitol | 01                                              | 05                       |
| 3.      | Amiodaron + Ondansetron           | Diabetes Mellitus, Hypothyroidism  | QT Interval Prolongation                    | Avoid Concomitant administration of Amiodarone | 01                                              | 05                       |
| 4.      | Amiodaron + Warfarin              | Rheumatic Heart Disease            | Increase risk of bleeding                   | Avoid or Use Alternative Drug               | 02                                              | 2b                       |
| 5.      | Amlodipine + Clarithromycin       | Peptic Ulcer, Hypertension         | Increase risk of Hypotension                | Dosage adjustments should be done if coadministration is clinically warranted | 01                                              | 1b                       |
| 6.      | Amlodipine + Digoxin              | Rheumatic Heart Disease            | Increase risk of bradycardia or complete heart block | Avoid or use Alternative Drug               | 01                                              | 05                       |
| 7.      | Amlodipine + Domperidone          | Cerebrovascular Accident           | Increase risk of QT interval Prolongation, Ventricular Arrhythmias | Domperidone Should be initiated at lowest possible dose and titrated with caution. Discontinue Domperidone if the patient experiences dizziness, Palpitations, Syncope. | 01                                              | 05                       |
| 8.      | Augmentin + Warfarin              | Rheumatic Heart Disease            | Increased risk of bleeding                  | Frequent Monitoring of INR is recommended   | 02                                              | 1b                       |
| Sr. No. | Drug Interaction        | Disease Condition                                                                 | Effect of Drug Interaction                          | Management as per Drug Interaction Database          | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|---------|-------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|-------------------------------------------------|---------------------------|
| 9.      | Aspirin + Clopidogrel   | Ischemic heart disease                                                            | Increased risk of Bleeding                          | Use low dose of aspirin                             | 22                                              | 05                        |
| 10.     | Aspirin + Digoxin       | Heart Failure, Ischemic Heart Disease, Hypertension                               | Increase serum potassium                           | Monitoring Serum Digoxin level                      | 02                                              | 05                        |
| 11.     | Aspirin + Duloxetine    | Cerebrovascular Accident, Hemiparesis                                             | Increase Risk of Bleeding                           | Monitor Signs of Increased Bleeding                 | 01                                              | 05                        |
| 12.     | Aspirin + Enalapril     | Cerebrovascular Disease, Diabetes Mellitus                                        | Significant decrease renal function                 | Avoid or Use Alternative Drug.                     | 03                                              | 1b                        |
| 13.     | Aspirin + Furosemide    | Congestive Heart Failure, Hypertension, IHD                                       | Reduced Diuretic Effectiveness and Possible Nephrotoxicity | Monitor for signs of worsening renal function, assure diuretic efficacy. | 24                                              | 1b                        |
| 14.     | Aspirin + Glimepiride   | Congestive Cardiac Failure, Diabetes Mellitus                                     | Increase risk of hypoglycemia                       | Use Caution, Monitoring                             | 02                                              | 05                        |
| 15.     | Aspirin + Heparin       | Congestive Cardiac Failure, Acute Myocardial Infarction, Ischemic Heart Disease    | Increase risk of Bleeding                           | Monitor patients closely for any signs of bleeding  | 17                                              | 2a                        |
| 16.     | Aspirin + Metformin     | Congestive Cardiac Failure, Diabetes Mellitus                                     | Increase risk of hypoglycemia                       | Monitor blood sugar carefully                      | 02                                              | 5                         |
| 17.     | Aspirin + Prasugrel     | Cerebrovascular Accident, Hemiparesis                                             | Increase risk of Bleeding                           | If coadministration is required, Monitor for bleeding | 03                                              | 5                         |
| 18.     | Aspirin + Prednisolone  | Recurrent Cerebrovascular Accident                                                | Increase risk of Gastro Intestinal Ulcer           | Use Caution, Monitoring                             | 01                                              | 3b                        |
| 19.     | Aspirin + Ramipril      | Congestive Cardiac Failure, Diabetes                                              | Significant Decrease in Renal Function              | The clinician should weigh the benefits            | 17                                              | 1b                        |
| Sr. No. | Drug Interaction | Disease Condition | Effect of Drug Interaction | Management as per Drug Interaction Database | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|---------|------------------|-------------------|---------------------------|---------------------------------------------|------------------------------------------------|-------------------------|
| 20.     | Aspirin + Spironolactone | Congestive Cardiac Failure, Diabetes Mellitus | Hyperkalemia, Possible Nephrotoxicity | Monitor Sign Symptoms of Hyperkalemia and Renal Toxicity | 15 | 1b |
| 21.     | Aspirin + Tirofiban | Anterior wall myocardial infarction, Diabetes, Coronary artery bypass grafting | Increase Risk of Bleeding | Patients should be closely monitored for signs and symptoms of active bleeding. | 01 | 05 |
| 22.     | Aspirin + Torsemide | Congestive Cardiac Failure, Diabetes | Nephrotoxicity | Monitor for signs of worsening renal function and assure diuretic efficacy, including appropriate effects on blood pressure. | 04 | 1b |
| 23.     | Atorvastatin + Budesonide | Acute Myocardial Infarction, Heart Failure, Ischemic Heart Disease | Increase effect of Budesonide | Use Caution and Monitor | 10 | 05 |
| 24.     | Atorvastatin + Digoxin | Dilated Cardio Myopathy | Tachycardia, Cardiac arrhythmias | Reduce digoxin dosage 15 to 30%, continue monitoring digoxin plasma concentration | 02 | 3b |
| 25.     | Atorvastatin + Fluconazole | Neuropathy with Cerebrovascular Accident | Increased risk of Myopathy or Rhabdomyolysis | If concomitant use is necessary, use the lowest atorvastatin dose necessary and closely monitor patients for signs or symptoms of muscle pain, tenderness, and weakness. | 01 | 05 |
| Sr. No. | Drug Interaction | Disease Condition | Effect of Drug interaction | Management as per Drug Interaction Database | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|---------|------------------|-------------------|---------------------------|---------------------------------------------|-----------------------------------------------|--------------------------|
| 26.     | Atropine + Glycopyrrolate | OP Poisoning | Increase the risk of additive anticholinergic effects, including worsening of narrow-angle glaucoma and urinary retention. | Avoid unnecessary use with other anticholinergic agents | 03 | 05 |
| 27.     | Atropine + Potassium Chloride | OP Poisoning | Retention of Potassium Chloride tablet in GI can cause lesions in GI tract. | Avoid solid dosage of Potassium Chloride | 01 | 05 |
| 28.     | Azithromycin + Levofloxacine | Iron Deficiency Anemia | Increased risk of QT Interval prolongation and arrhythmias | Avoid | 01 | 05 |
| 29.     | Azithromycin + Enoxaparin | Rheumatic Heart Disease | Increased risk of Bleeding | Avoid or Use Alternate drug | 01 | 05 |
| 30.     | Azithromycin + Warfarin | Rheumatic Heart Disease | Increased risk of Bleeding | Avoid or Use Alternate drug | 02 | 1b |
| 31.     | Azithromycin + Digoxin | Rheumatic Heart Disease | Increased Vomiting and Cardiac arrhythmias | Avoid or Use Alternate drug | 01 | 3b |
| 32.     | Azithromycin + Heparin | Heart Failure, COPD, Hypokinesis | Increased risk of Bleeding | Avoid or Use Alternate drug | 01 | 05 |
| 33.     | Azithromycin + Ivabradine | Balloon Mitral Valvotomy | Increased risk of QT Interval prolongation and arrhythmias | Use caution | 01 | 05 |
| 34.     | Azithromycin + Metronidazole | Acute Kidney Injury, Hypertension, Antepartum Hemorrhage | Increased risk of QT Interval prolongation and arrhythmias | Susceptible patients may require ECG monitoring | 01 | 05 |
| 35.     | Azithromycin + Norfloxacin | Upper respiratory tract infection, Kidney Stone | Increased risk of QT Interval prolongation and arrhythmias | If concomitant therapy is required, closely monitor ECG for QT interval prolongation. | 02 | 05 |
| Sr. No. | Drug Interaction            | Disease Condition                                      | Effect of Drug interaction                          | Management as per Drug Interaction Database          | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|--------|-----------------------------|-------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|-------------------------------------------------|----------------------------|
| 36     | Carvedilol + Diltiazem      | Alcoholic Cardiomyopathy, Heart Failure                | Increased risk of hypotension, bradycardia           | Modify therapy and Monitor Closely                  | 01                                              | 3b                         |
| 37     | Carvedilol + Metoprolol     | Decompensated cardiomyopathy                          | Increase risk of Hypotension                        | Avoid or Use Alternate drug                         | 01                                              | 05                         |
| 38     | Cefoperazone + Heparin      | Small Vessel Disease, PTCA                             | Increased risk of Bleeding                          | Monitor if required use alternative antimicrobial    | 02                                              | 05                         |
| 39     | Ceftriaxone + Heparin       | Myocardial Infarction, Rheumatic Heart Disease, Cerebrovascular Accident | Increased risk of Bleeding                          | Avoid or Use Alternate drug                         | 08                                              | 05                         |
| 40     | Ceftriaxone + Calcium Carbonate | Meningitis                                               | Ceftriaxone – Calcium Precipitates                   | Contraindicated                                    | 01                                              | 05                         |
| 41     | Ceftriaxone + Warfarin      | Rheumatic Heart Disease                                | Increased risk of bleeding                          | Avoid or Use Alternate drug                         | 03                                              | 05                         |
| 42     | Ciprofloxacin + Ondansetron | Rabies, Dysphagia                                      | Increased risk of QT interval prolongation, Bradyarrhythmia’s | Avoid or Use Alternate drug                         | 01                                              | 05                         |
| 43     | Clarithromycin + Clopidogrel | Lower Respiratory tract Infection                      | Decrease activity of Clopidogrel, Increase risk of thrombotic event | Avoid or Use Alternate drug                         | 01                                              | 05                         |
| 44     | Clarithromycin + Heparin     | Lower respiratory tract infection, Heart Failure        | Increased risk of bleeding                          | Avoid or Use Alternate drug                         | 02                                              | 05                         |
| 45     | Clarithromycin + Ondansetron | Lower respiratory tract infection, Heart Failure        | Increased risk of QT interval prolongation, Bradyarrhythmia’s | Avoid or Use Alternate drug                         | 02                                              | 05                         |
| 46     | Clarithromycin + Rosuvastatin | Lower respiratory tract infection, Heart Failure       | Increased risk of Myopathy or Rhabdomyolysis        | Avoid or Use Alternate drug                         | 01                                              | 05                         |
| 47     | Clonazepam + Midazolam      | OP Poisoning                                            | Increased risk of hypoventilation                   | Use Caution/Monitor                                 | 01                                              | 3b                         |
| Sr. No. | Drug Interaction | Disease Condition | Effect of Drug interaction | Management as per Drug Interaction Database | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|---------|------------------|--------------------|----------------------------|---------------------------------------------|-----------------------------------------------|--------------------------|
| 48.     | Clonidine + Metoprolol | Ischemic Heart Disease, Left Ventricular SYSTOLIC Dysfunction | Increase risk of Bradycardia | Avoid or use Alternate Drug | 01 | 05 |
| 49.     | Clopidogrel + Diltiazem | Heart Failure, Diabetes Mellites | Increased risk of thrombotic events | Use Caution | 02 | 2b |
| 50.     | Clopidogrel + Duloxetine | Cerebrovascular Accident, Hemiparesis, | Increased Risk of Bleeding | Monitor patient for any signs of bleeding | 01 | 05 |
| 51.     | Clopidogrel + Fluconazole | Neuropathy with Cerebrovascular Accident | Increased risk of thrombotic events | Consider avoiding concomitant use. | 01 | 05 |
| 52.     | Clopidogrel + Heparin | Small Vessel Disease, Congestive Cardiac Failure | Increased Risk of Bleeding | Monitor patients closely for signs or symptoms of blood loss | 15 | 05 |
| 53.     | Clopidogrel + Nicardipine | Small Vessel Disease, Cerebrovascular accident | Increase the risk of atherothrombotic events | Use caution if clopidogrel and nicardipine are used concurrently and monitor patients for loss of clopidogrel efficacy. | 01 | 2b |
| 54.     | Clopidogrel + Warfarin | Left Side Deep Vein Thrombosis | Increased Risk of Bleeding | Monitor patients closely for signs or symptoms of blood loss | 01 | 05 |
| 55.     | Dexamethasone + Tramadol | Vasculitis with Polyarteritis Nodosa, Guillen Barre Syndrome, Hypertension | Decreased effectiveness of tramadol | Use Caution and Monitor | 02 | 05 |
| 56.     | Dextromethorphan + Haloperidol | Schizophrenia, Left Side Hemiparesis | Exacerbation of dextromethorphan adverse effects (CNS excitement, mental confusion, respiratory) | Monitor patient for signs and symptoms of dextromethorphan toxicity | 02 | 3a |
| Sr. No. | Drug Interaction          | Disease Condition                                | Effect of Drug interaction                                                                 | Management as per Drug Interaction Database                        | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|---------|--------------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------|------------------------------------------------|----------------------------------|
| 57.     | Diclofenac + Prednisolone| Systematic Lupus Erythematosus                   | Increased risk of gastrointestinal ulcer or bleeding                                         | Use Caution and Monitor                                           | 02                                             | 05                              |
| 58.     | Digoxin + Bisoprolol     | Rheumatic Heart Disease, Decompensated Cardiac Myopathy | Increase risk of bradycardia                                                               | Avoid or use Alternative drug                                     | 01                                             | 05                              |
| 59.     | Digoxin + Diltiazem      | Alcoholic Cardiomyopathy, Heart Failure           | Increased risk of complete heart block                                                     | Reduce the oral digoxin dose by approximately 15% to 30% or modify the dosing frequency. | 01                                             | 3b                              |
| 60.     | Digoxin + Metoprolol     | Rheumatic Heart Disease, Decompensated Cardiac Myopathy | Increased risk of bradycardia and possible digitalis glycoside toxicity                      | Avoid or use Alternative drug                                      | 03                                             | 3b                              |
| 61.     | Digoxin + Norepinephrine | Rheumatic Heart Disease, Decompensated Cardiac Myopathy | Increased risk of cardiac arrhythmias                                                      | Individualize the dosage of digoxin                               | 01                                             | 5                               |
| 62.     | Digoxin + Spironolactone | Alcoholic cardiomyopathy                          | Increased risk of cardiac arrhythmias                                                      | Reduce the digoxin dose by approximately 15% to 30%, or modify the dosing frequency and continue monitoring | 04                                             | 3b                              |
| 63.     | Diltiazem + Budesonide   | Ischemic Heart Disease, Lower Respiratory Infection | Closely monitor for signs and symptoms of corticosteroid excess                            | Use Alternative                                                   | 02                                             | 5                               |
| 64.     | Diltiazem + Nebivolol    | Lower respiratory tract infection, Rheumatic      | Increase risk of Bradycardia                                                               | Avoid or use Alternative drug                                      | 01                                             | 1b                              |
| Sr. No. | Drug Interaction | Disease Condition | Effect of Drug Interaction | Management as per Drug Interaction Database | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|---------|------------------|-------------------|-----------------------------|---------------------------------------------|-----------------------------------------------|-------------------------|
| 65.     | Diltiazem + Metoprolol | Hypertension, Left side Hemiparesis | Increase risk of Bradycardia | Avoid or use Alternative drug | 02 | 1b |
| 66.     | Domperidone + Hydroxychloroquine | Systemic Lupus Erythematosus | Increased risk of QT – Interval prolongation | If concomitant use is required, consider close ECG monitoring at baseline and during therapy | 02 | 04 |
| 67.     | Domperidone + Ondansetron | Dengue, Menorrhagia | Increased risk of QT – Interval prolongation | initiated at the lowest possible dose and titrated with caution. If coadministration cannot be avoided, monitor ECG for signs of QT interval prolongation | 03 | 05 |
| 68.     | Enalapril + Telmisartan | Hypertension | Hypotension, Syncope, Hyperkalemia, acute renal failure | Avoid or use Alternative drug | 01 | 1a |
| 69.     | Enoxaparin + Warfarin | Rheumatic Heart Disease | Increased risk of bleeding | Avoid or use Alternative drug | 02 | 05 |
| 70.     | Escitalopram + Ondansetron | OP Poisoning | Increased risk of QT – Interval prolongation | Avoid or Use Alternate Drug. | 02 | 05 |
| 71.     | Fluconazole + Ondansetron | Paraoquat Dichloride Poisoning | Increased risk of QT – Interval prolongation | Avoid or use alternative, ECG Monitoring | 01 | 05 |
| 72.     | Fluconazole + Tramadol | Vasculitis with Polyarteritis nodosa | Increased risk of respiratory depression. | Consider reducing the dose of tramadol and closely monitor for seizures, serotonin syndrome, or respiratory depression | 01 | 05 |
| 73.     | Fluconazole + Clopidogrel | Neuropathy, uremia, electrolyte imbalance, | Increased risk of thrombotic event | Avoid or use alternative, ECG Monitoring | 01 | 05 |
| Sr. No. | Drug Interaction                  | Disease Condition                        | Effect of Drug Interaction                                                                 | Management as per Drug Interaction Database                  | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|--------|----------------------------------|------------------------------------------|------------------------------------------------------------------------------------------------|-------------------------------------------------------------|------------------------------------------------|------------------------------------------|
| 74.    | Fluoxetine + Lithium             | Paraquat Dichloride Poisoning            | Risk of neurotoxicity                                                                        | Modify Therapy/Monitor Closely.                              | 02                                             | 3b                                       |
| 75.    | Fluoxetine + Ondansetron         | Paraquat Dichloride Poisoning            | Increased risk of QT – Interval prolongation                                                 | Avoid or Use Alternate Drug                                  | 02                                             | 05                                       |
| 76.    | Fosphenytoin + Oxcarbazepine     | Seizure                                  | Increase risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)               | Use Caution/Monitor                                          | 01                                             | 2a                                       |
| 77.    | Gabapentin + Tramadol            | Guillen Barre Syndrome with Hypertension | Coadministration of CNS depressants can result in serious, life-threatening, and fatal respiratory depression | Use Caution/Monitor                                          | 01                                             | 05                                       |
| 78.    | Glycopyrrolate + Potassium Chloride | OP Poisoning                             | Retention of Potassium Chloride tablet in GI can cause lesions in GI tract.                | Contraindicated                                              | 01                                             | 05                                       |
| 79.    | Haloperidol + Ondansetron        | Left Sided Hemiparesis, Viral Encephalitis, Cerebral Malaria | QT interval prolongation and an increased risk of serious ventricular arrhythmias       | If concurrent therapy is required, ECG monitoring is recommended | 03                                             | 05                                       |
| 80.    | Haloperidol + Tramadol           | Left Sided Hemiparesis                   | Increased risk of respiratory and CNS depression.                                           | Use the lowest dose and shortest duration necessary to achieve treatment goals | 02                                             | 05                                       |
| 81.    | Heparin + Cilostazol             | Diabetic Foot                            | Enhanced risk of hemorrhage.                                                                | Contraindicated                                              | 01                                             | 05                                       |
| 82.    | Heparin + Nitroglycerine         | Anterior wall myocardial infarction, Heart Failure | May result in a decrease in partial thromboplastin time.                                    | Careful monitoring of PTT and heparin dose adjustment are recommended when heparin and nitroglycerin | 03                                             | 05                                       |
| Sr. No. | Drug Interaction                  | Disease Condition                                      | Effect of Drug interaction | Management as per Drug Interaction Database | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|---------|----------------------------------|--------------------------------------------------------|----------------------------|---------------------------------------------|------------------------------------------------|--------------------------|
| 83.     | Heparin + Prasugrel              | Anterior wall myocardial infarction, Diabetes          | Increased risk of bleeding | Contraindicated                             | 01                                             | 3b                       |
| 84.     | Heparin + Tirofiban              | Anterior wall myocardial infarction, Diabetes          | Increased risk of bleeding | Contraindicated                             | 01                                             | 3b                       |
| 85.     | Heparin + Warfarin               | Left Side Deep vein thrombosis, Rheumatic Heart Disease | Increased risk of bleeding | Avoid or Use Alternate Drug                 | 04                                             | 3b                       |
| 86.     | Isoniazid + Rifampin             | Tuberculosis, Diabetes Mellitus                        | Risk of hepatotoxicity     | Use Caution/Monitor                         | 02                                             | 3b                       |
| 87.     | Ivabradine + Ondansetron         | Sepsis, Acute Myocardial Infarction, Cardiogenic Shock, | Increased risk of QT – Interval prolongation | Use caution                                 | 01                                             | 5                        |
| 88.     | Labetalol + Metoprolol           | Acute kidney injury, Chronic Kidney disease, Hypertension | Increase risk of hypotension | Avoid or Use Alternate Drug                 | 02                                             | 5                        |
| 89.     | Lactated Ringer Solution + Ceftriaxone | Meningitis                                             | Ceftriaxone – Calcium Precipitates | Contraindicated                             | 01                                             | 4                        |
| 90.     | Levofoxacin + Norfloxacin        | Community Acquired Anemia with Iron Deficiency Anemia   | Increased risk of QT – Interval prolongation | Avoid or Use Alternate Drug                 | 01                                             | 5                        |
| 91.     | Levofoxacin + Ondansetron        | Community Acquired Anemia with Iron Deficiency Anemia   | Increased risk of QT – Interval prolongation | Avoid or Use Alternate Drug, ECG monitoring recommended with concomitant medications that prolong QT interval, electrolyte abnormalities, CHF, or bradyarrhythmia’s. | 02                                             | 5                        |
| 92.     | Lithium + Ondansetron            | Paraquat Dichloride                                    | Increase risk of serotonin  | Use Caution/Monitor                         | 02                                             | 5                        |
| Sr. No. | Drug Interaction | Disease Condition | Effect of Drug interaction | Management as per Drug Interaction Database | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|---------|------------------|-------------------|-----------------------------|---------------------------------------------|-----------------------------------------------|--------------------------|
| 93.     | Metronidazole + Ondansetron | Poisoning syndrome Ischemic Stroke, Acute kidney injury, Chronic Kidney disease, Hypertension | Increased risk of QT – Interval prolongation | Susceptible patients may require ECG monitoring | 06 | 4 |
| 94.     | Metronidazole + Phenytoin | Intracranial Hemorrhage, Hypertension, Acute respiratory failure | Increased risk of Phenytoin toxicity, Arrhythmias | Use Caution/Monitor | 06 | 3b |
| 95.     | Moxifloxacin + Ondansetron | Community Acquired Anemia with Iron Deficiency Anemia | QTc Interval Prolongation, can worsen the existing cardiac condition. | Avoid or Use Alternative | 01 | 5 |
| 96.     | Nifedipine + Phenytoin | Seizure Disorder, Cerebrovascular accident | Decreased Nifedipine Efficacy | Avoid or Use Alternative | 03 | 3b |
| 97.     | Norfloxacin + Ondansetron | Community Acquired Anemia with Iron Deficiency Anemia | QTc Interval Prolongation | Avoid, If concomitant therapy is required, monitor ECG for QT interval prolongation | 01 | 5 |
| 98.     | Octreotide + Ondansetron | Hematemesis, Liver disease | Increased risk of QT – Interval prolongation, electrolyte abnormalities, CHF, or bradyarrhythmia’s | Avoid or Use Alternative | 01 | 3b |
| 99.     | Ondansetron + Risperidone | Tuberous Sclerosis | Increased risk of QT – Interval prolongation, electrolyte abnormalities, CHF, or bradyarrhythmia’s | Avoid or Use Alternative | 02 | 5 |
| 100.    | Ofloxacin + Ondansetron | Alcoholic Liver Disease, Pancytopenia | Increased risk of QT – Interval prolongation, | Avoid or Use Alternative | 05 | 5 |
| Sr. No. | Drug Interaction | Disease Condition | Effect of Drug Interaction | Management as per Drug Interaction Database | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|---------|------------------|-------------------|---------------------------|---------------------------------------------|-----------------------------------------------|--------------------------|
| 101.    | Olanzapine + Ondansetron | Alcoholic liver Cirrhosis, | Increased risk of QT – Interval prolongation, electrolyte abnormalities, CHF, or bradyarrhythmia’s | Avoid or Use Alternative                        | 01                                           | 5                       |
| 102.    | Ondansetron + Escitalopram | Hepatic Encephalopathy, Decreased Intelligence | Increased risk of serotonin syndrome and QT interval prolongation. | Monitoring ECG and for the emergence of serotonin syndrome. Discontinue treatment with ondansetron and institute supportive therapy if symptoms of serotonin syndrome occur | 01                                           | 5                       |
| 103.    | Ondansetron + Tramadol | Left side Hemiparesis, Acute Pancreatitis, with chronic alcoholic. | Increased risk of serotonin syndrome. | Discontinue tramadol if serotonin syndrome is suspected | 06                                           | 5                       |
| 104.    | Oxcarbazepine + Phenytoin | Seizure | Increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor) and decreased effectiveness of oxcarbazepine | Use Caution/Monitor.                             | 01                                           | 2a                      |
| 105.    | Pantoprazole + Diclofenac | Decompensated Cardiomyopathy | Increased risk of bleeding | Avoid or Use Alternative                        | 02                                           | 5                       |
| 106.    | Penicillin G + Warfarin | Rheumatic Heart Disease | Increased risk of bleeding | More frequent monitoring of the patient's INR is | 01                                           | 1a                      |
| Sr. No. | Drug Interaction      | Disease Condition                                      | Effect of Drug interaction                                                | Management as per Drug Interaction Database                              | Frequency of Interactions (In 250 Prescriptions) | Highest level of Evidence |
|--------|-----------------------|--------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------|--------------------------|
| 107.   | Phenytoin + Nifedipine| Hepatic Encephalopathy, Decreased Intelligence         | Phenytoin decreases systemic exposure of nifedipine by about 70%          | Avoid or Use Alternative                                                 | 02                                            | 3b                       |
| 108.   | Piperacillin + Heparin | Sepsis, Acute MI, Cardiogenic Shock, Cardio Embolic Stroke | Increased risk of bleeding                                               | Avoid or Use Alternative                                                 | 04                                            | 5                        |
| 109.   | Pyrazinamide + Rifampin| Tubercular Pleural Effusion                            | may result in severe hepatic injury.                                      | Monitor serum potassium levels for persistent elevations in patients on this combination, | 10                                            | 2b                       |
| 110.   | Ramipril + Spironolactone | Tubercular Pleural Effusion                            | may result in severe hepatic injury.                                      | Avoid or Use Alternative                                                 | 03                                            | 4                        |
| 111.   | Spironolactone + Potassium Chloride | Alcoholic Cardiomyopathy, Heart Failure                | Increased risk of Hyperkalemia                                            | Avoid or Use Alternative                                                 | 01                                            | 5                        |
| 112.   | Torsemide + Spironolactone | Alcoholic Cardiomyopathy, Heart Failure                | Increased risk of Hyperkalemia                                            | Avoid or Use Alternative                                                 | 01                                            | 5                        |
| 113.   | Venlafaxine + Dosulepin | Anxiety, Neurosis, Breathlessness, Decreased Intelligence | Increased risk of serotonin syndrome                                      | Use Alternative                                                          | 01                                            | 5                        |
Table 3. Level of evidence for the identified drug interaction

| Sr. No. | Level of evidence | No. of Interactions |
|---------|-------------------|---------------------|
| 1       | 1a                | 02                  |
| 2       | 1b                | 10                  |
| 3       | 1c                | 00                  |
| 4       | 2a                | 03                  |
| 5       | 2b                | 05                  |
| 6       | 2c                | 00                  |
| 7       | 3a                | 01                  |
| 8       | 3b                | 15                  |
| 9       | 4                 | 06                  |
| 10      | 5                 | 71                  |

5. CONCLUSION

From this study it was concluded that 1/3rd of the total drug interaction was major drug interaction in critically ill patient. The most common drug interaction found were between anticoagulants, antiplatelet and antihypertensive drugs. The level of evidence provided for majority of drug interaction were of level 5, 3b, 1b and 2b. The evidence provided for majority of drug interaction in various database were poor and least reliable.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

Prior to initiation of the study ethical approval was obtained from Sumandeep Vidyapeeth Institution Ethics Committee (SVIEC). Ref. No. SVIEC/IN/PHAR/PHD/19052. The Ethical issue raised by the Ethical committee were, Permission letter from Medical Superintendent for accessing medical records of ICU patients, removal of Informed consent and Patient information sheet from study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Himanshu B, Shyam M, Yatin M. Drug-drug interactions in medical ICU. Indian Journal of Pharmacy and Pharmacology. 2015;2(1):62-9.
2. Gupta M, Chincholkar AS, Wagh RJ, Maheshwari N, Siddiqui W. A study of potential drug-drug interactions among critically ill patients at a tertiary care hospital. Int J Basic Clin Pharmacol. 2016;5(4):1281-5.
3. Reis AM, Cassiani SH. Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil. Clinics. 2011;66(1):9-15.
4. M Pereira J, A Paiva J. Antimicrobial drug interactions in the critically ill patients. Current Clinical Pharmacology. 2013;8(1):25-38.
5. Janković SM, Pejić AV, Milosavljević MN, Opančina VD, Pešić NV, Nedeljković TT, Babić GM. Risk factors for potential drug-drug interactions in intensive care unit patients. Journal of Critical Care. 2018;43:1-6.
6. Baniasadi S, Farzanegan B, Alehashem M. Important drug classes associated with potential drug–drug interactions in critically ill patients: highlights for cardiothoracic intensivists. Annals of Intensive Care. 2015;5(1):1-8.
7. Hammes JA, Pfuetzenreiter F, Silveira FD, Koenig Á, Westphal GA. Potential drug interactions prevalence in intensive care units. Revista Brasileira de Terapia Intensiva. 2008;20(4):349-54.
8. Uijtendaal EV, van Hassel LL, Hugenholtz GW, Kuck EM, Zwart- van Rijkom JE, Cremer OL, Egberts TC. Analysis of potential drug-drug interactions in medical intensive care unit patients. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2014;34(3):213-9.
9. Smithburger PL, Kane-Gill SL, Seybert AL. Drug–drug interactions in the medical intensive care unit: an assessment of frequency, severity and the medications involved. International Journal of Pharmacy Practice. 2012;20(6):402-8.
10. Payne DA, Hayes PD, Jones CI, Belham P, Naylor AR, Goodall AH. Combined therapy with clopidogrel and aspirin significantly increases the bleeding
time through a synergistic antiplatelet action. Journal of Vascular Surgery. 2002;35(6): 1204-9.

11. Tweeddale MG, Ogilvie RI. Antagonism of spironolactone-induced natriuresis by aspirin in man. New England Journal of Medicine. 1973;289(4):198-200.

12. Kumar S, Thakur PK, Shah SK. A prospective assessment of polypharmacy induced drug interactions with corticosteroids. Journal of Chitwan Medical College. 2016;6(1):24-9.

13. Favre L, Glasson PH, Riondel A, Vallotton MB. Interaction of diuretics and non-steroidal anti-inflammatory drugs in man. Clinical Science. 1983;64(4):407-15.

14. Epstein MM, Nelson SD, Slattery JT, Kalhorn TF, Wall RA, Wright JM. Inhibition of the metabolism of paracetamol by isoniazid. British Journal of Clinical Pharmacology. 1991;31(2):139-42.

15. Ding D, Liu H, Qi W, Jiang H, Li Y, Wu X, Sun H, Gross K, Salvi R. Ototoxic effects and mechanisms of loop diuretics. Journal of Otology. 2016;11(4):145-56.

16. Bodhankar SL, Thakurdesai PA, Maurya OP. Effects of (RS)-Ondansetron and its enantiomers on QTc interval in Rats. Pharmacologyonline. 2006;3:153-58.

17. Holm J, Lindh JD, Andersson ML, Mannheimer B. The effect of amiodarone on warfarin anticoagulation: A register-based nationwide cohort study involving the Swedish population. Journal of Thrombosis and Haemostasis. 2017;15(3):446-53.

18. Gandhi S, Fleet JL, Bailey DG, McArthur E, Wald R, Rehman F, Garg AX. Calcium-channel blocker–clarithromycin drug interactions and acute kidney injury. Jama. 2013;310(23):2544-53.

19. Kirigaya Y, Shiramoto M, Ishizuka T, Uchimaru H, Irie S, Kato M, Shimizu T, Nakatsu T, Nishikawa Y, Ishizuka H. Pharmacokinetic interactions of esaxerenone with amlodipine and digoxin in healthy Japanese subjects. BMC Pharmacology and Toxicology. 2020;21(1):1-0.

20. Ghenge G, Pande SD, Ahmad A, Jejurkar L, Birari T. Development and characterisation of fast disintegrating tablet of amlodipine besylate using mucilage of plantago ovata as a natural superdisintegrant. International Journal of Pharm Tech Research. 2011;3(2):938-45.

21. Cattaneo M. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. Arteriosclerosis, Thrombosis, and Vascular Biology. 2004;24(11): 1980-7.

22. Wiviott SD, Antman EM. Clopidogrel resistance: a new chapter in a fast-moving story. Circulation. 2004;109(25):3064-7.

23. Jones CK, Peters SC, Shannon HE. Synergistic interactions between the dual serotonergic, noradrenergic reuptake inhibitor duloxetine and the non-steroidal anti-inflammatory drug ibuprofen in inflammatory pain in rodents. European Journal of Pain. 2007;11(2):208-15.

24. Barbash IM, Goldbourt U, Gottlieb S, Behar S, Leor J. Possible interaction between aspirin and ACE inhibitors: Update on unresolved controversy. Congestive Heart Failure. 2000;6(6):313-8.

25. Spaulding C, Charbonnier B, Cohen-Solal A, Juilliére Y, Kromo EP, Benhamda K, Cador R, Weber S. Acute hemodynamic interaction of aspirin and ticlopidine with enalapril: Results of a double-blind, randomized comparative trial. Circulation. 1998;98(8):757-65.

26. Park MH. Should Aspirin Be Used With Angiotensin-Converting Enzyme Inhibitors in Patients With Chronic Heart Failure?. Congestive Heart Failure. 2003;9(4):206-11.

27. Bartoli E, Arras S, Faedda R, Soggia G, Satta A, Olmeo NA. Blunting of furosemide diuresis by aspirin in man. Journal of Clinical Pharmacology. 1980;20(7):452-8.

28. Jhund PS, Davie AP, McMurray JJ. Aspirin inhibits the acute venodilator response to furosemide in patients with chronic heart failure. Journal of the American College of Cardiology. 2001;37(5):1234-8.

29. Planas R, Arroyo V, Rimola A, Perez-Ayuso RM, Rodes J. Acetylsalicylic acid suppresses the renal hemodynamic effect and reduces the diuretic action of furosemide in cirrhosis with ascites. Gastroenterology. 1983;84(2):247-52.

30. Ismail M, Iqbal Z, Khattak MB, Khan MI, Javaid A, Khan TM. Potential drug-drug interactions in cardiology ward of a teaching hospital. Health Med. 2012;6:1618-24.
31. Mountokalakis T, Rallis D, Mayopoulou-Symvoulidou D, Komninos Z. Effect of combined administration of furosemide and aspirin on urinary urate excretion in man. Klinische Wochenschrift. 1979;57(23):1299-301.

32. Wilson TW, McCauley FA, Wells HD. Effects of Low-Dose Aspirin on Responses to Furosemide. The Journal of Clinical Pharmacology. 1986;26(2):100-5.

33. Vigil-De Gracia P, Dominguez L, Solis A. Management of chronic hypertension during pregnancy with furosemide, amlodipine or aspirin: a pilot clinical trial. The Journal of Maternal-Fetal & Neonatal Medicine. 2014;27(13):1291-4.

34. Fu JF, Ren QY, Zhang NY, Gao B, Tu YY, Fu GQ, Li DH, Zhang YS. Inhibition potential of glimepiride (gli) towards important UDP-glucuronosyltransferase (UGT) isofoms in human liver. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2012;67(8):715-7.

35. Shalom A, Friedman T, Westreich M. Effect of aspirin and heparin on random skin flap survival in rats. Dermatologic Surgery. 2008;34(6):785-90.

36. Bose P, Black S, Kadyrov M, Weissborn U, Neulen J, Regan L, Huppertz B. Heparin and aspirin attenuate placental apoptosis in vitro: Implications for early pregnancy failure. American Journal of Obstetrics and Gynecology. 2005;192(1):23-30.

37. Jameson SS, Baker PN, Charman SC, Deehan DJ, Reed MR, Gregg PJ, Van der Meulen JH. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after knee replacement: a non-randomised comparison using National Joint Registry Data. The Journal of bone and joint surgery. British Volume. 2012;94(7):914-8.

38. Hassan KA, Mudawi MM, Sulaiman MI. Pharmacodynamics drug interactions of metformin with aspirin and nifedipine. Asian Journal of Pharmaceutical Research and Health Care. 2016;6(1).

39. Tai CH, Hsu CN, Yang SC, Wu CK, Liang CM, Tai WC, Chuah SK, Lee CH. The impact of aspirin on Klebsiella pneumoniae liver abscess in diabetic patients. Scientific Reports. 2020;10(1):1-0.

40. Zanders MM, van Herk-Sukel MP, Vissers PA, Herings RM, Haak HR, Van De Poll-Franse LV. Are metformin, statin and aspirin use still associated with overall mortality among colorectal cancer patients with diabetes if adjusted for one another?. British Journal of Cancer. 2015;113(3):403-10.

41. Kirkby NS, Leadbeater PD, Chan MV, Nylander S, Mitchell JA, Warner TD. Antiplatelet effects of aspirin vary with level of P2Y12 receptor blockade supplied by either ticagrelor or prasugrel. Journal of Thrombosis and Haemostasis. 2011;9(10):2103.

42. Gilroy DW, Perretti M. Aspirin and steroids: New mechanistic findings and avenues for drug discovery. Current Opinion in Pharmacology. 2005;5(4):405-11.

43. Koomanan N, Ko Y, Yong WP, Ng R, Wong YP, Lim SW, Salim A, Chan A. Clinical Impact of Drug–Drug Interaction Between Aspirin and Prednisolone at a Cancer Center. Clinical Therapeutics. 2012;34(12):2259-67.

44. Leor J, Reicher-Reiss H, Goldbourt U, Boyko V, Gottlieb S, Battler A, Behar S. Aspirin and mortality in patients treated with angiotensin-converting enzyme inhibitors: A cohort study of 11,575 patients with coronary artery disease. Journal of the American College of Cardiology. 1999;33(7):1920-5.

45. Bomback AS, Kshirsagar AV, Klemmer PJ. Renal aspirin: will all patients with chronic kidney disease one day take spironolactone?. Nature Clinical Practice Nephrology. 2009;5(2):74-5.

46. de Lemos JA, Blazing MA, Wiviott SD, Brady WE, White HD, Fox KA, Palmisano J, Ramsey KE, Bilheimer DW, Lewis EF, Pfeffer M. Enoxaparin versus unfractionated heparin in patients treated with tirofiban, aspirin and an early conservative initial management strategy: Results from the A phase of the A-to-Z trial. European Heart Journal. 2004;25(19):1688-94.

47. Tilgner J, von Trotha KT, Gombert A, Jacobs MJ, Drechsler M, Doering Y, Soehnlein O, Grommes J. Aspirin, but not tirofiban displays protective effects in endotoxin induced lung injury. PLoS One. 2016;11(9):e0161218.
48. Kim HO, Lee KE, Park HY, Lee NR, Oh BR, Chang BC, Gwak HS. Effects of torsemide on pharmacodynamics and pharmacokinetics of warfarin in humans and rats. Journal of Pharmacy and Pharmacology. 2013;65(8):1195-203.

49. Kothari N, Ganguly B. Potential drug-drug interactions among medications prescribed to hypertensive patients. Journal of clinical and diagnostic research: JCDR. 2014;8(11):HC01.

50. Mateti UV, Rajakannan T, Nekkanti H, Rajesh V, Mallaysamy SR, Ramachandran P. Drug-drug interactions in hospitalized cardiac patients. Journal of Young Pharmacists. 2011;3(4):329-33.

51. Eljaaly K, Alshehri S. An updated review of interactions of statins with antibacterial and antifungal agents. J Transl Sci. 2017;3:1-4.