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Surveillance Report on Drug-Drug Interactions in a Tertiary Care Hospital

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Srihitha Pendota*[1], S. Sre Akshaya Kalyani[2], A. Prathyusha[3]

[1]*Department of Clinical Pharmacy, Vaageswari College of Pharmacy, Karimnagar, Telangana, INDIA.*

[2]*Department of Clinical Pharmacy, Vaageswari College of Pharmacy, Karimnagar, Telangana, INDIA.*

[3]*Department of Clinical Pharmacy, Talla padmavathi College of Pharmacy, Warangal, Telangana, INDIA.*

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ABSTRACT

Drug interactions resulting in adverse events represent a major health problem and contribute to significant risk to the patient health outcomes. Patients with two or more diseases and patients prescribed with more number of drugs are more likely to prone for these interactions resulting in the increased burden on patient. A Drug may interact with another drug or food or substance etc. The interaction with one drug may increase or decrease the effect of other drug. The main objective of the study is to identify and assess Drug-Drug Interactions (DDIs) in the hospitalized patient's case records. The study was performed by analyzing the patient demography, severity and onset of interaction by using Micromedex drug interactions software. Total of 180 case records are taken of which 221 DDIs are seen in 100(55.55%) case records. Among 221 DDIs major were found to be highly seen followed by moderate and minor in severity. 50 case records i.e. 27.77% are having more than one DDI. Among all the interacting drugs Ondansetron, Metronidazole and Aspirin were found to have more number of interactions.

INTRODUCTION

Drug interaction refers to the modification of response of one drug by another when they are administered simultaneously or in quick succession. The modification is mostly quantitative, i.e. the response is either increased or decreased in intensity, but sometimes it qualitative, i.e. an abnormal response is produced[1].

Based on the mechanism of interaction DDIs can be classified into two main groups:

- Pharmacokinetic - involves absorption, distribution, metabolism and excretion, all of them being associated with both treatment failure or toxicity;

- Pharmacodynamic - divided into three subgroups:

(1) direct effect at receptor function,

(2) interference with a biological or physiological control process and

(3) additive/opposed pharmacological effect[2].

Based on the severity of interaction DDIs can be classified in to three categories:

- Major drug interaction - The interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects.

- Moderate drug interaction - The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy.

- Minor drug interaction - The interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of the side effects but generally would not require a Major alteration in therapy[3].

Drug interactions can be:

- Beneficial or intentional DDIs – interactions may be beneficial and intended

Example - levodopa is given in combination with carbidopa to decrease the adverse effects of levodopa.

- Adverse DDIs – these interactions alter the therapeutic effects of prescribed medications.

Example - warfarin in combination with phenylbutazone.

Risk factors for DDIs:

- Narrow therapeutic index drugs - The toxic dose may be slightly more than the therapeutic dose and may result in an interaction.

Example - Phenytoin, Digoxin, Warfarin.

- Drugs with potent pharmacological effects - A small change in the dosage of these drugs may result in a large increase in the clinical effect.

Example - Carbamazepine, Corticosteroids, Oral contraceptives.

- High risk patients - patients with co morbid condition or patients who take multiple drugs, in patients with severe form of disease.

Example – During treatment of diabetes, drug interaction may lead to metabolic disorders[4].

- Patient-specific issues such as decreased kidney or liver function, which may reduce the ability of the body to eliminate the drugs. Concomitant diseases or conditions such as malnutrition, severe heart failure, and dehydration could also increase DDI risk[5].

MATERIALS AND METHODS

It is a retrospective study done for two years, i.e. 2015 –2017 on 180 case records. The main objective of the study is to identify and analyze DDIs according to the patient demography, severity and onset of interaction.

Inclusion criteria:

Patients who were admitted in hospital.

Patients who were prescribed with more than four drugs.

Patients of all age groups

Patients of both the genders

Exclusion criteria:

Patients who were admitted in oncology department.

Patients who were admitted in gynecology department.

Statistical analysis:

Statistical analysis was performed by using the SPSS, version 14.0.

A p-value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Table 1: frequency and severity of the interactions which are seen more than 3 times:

S. no	Interacting drugs	Frequency	Severity
1	Metronidazole + Ondansetron	24	Major
2	Tramadol + Ondansetron	23	Major
3	Iron + Pantoprazole	08	Moderate
4	Aspirin + Clopidogrel	07	Major
5	Metronidazole + Diclofenac	06	Moderate
6	Aspirin + Ranitidine	05	Minor
7	Aspirin + Furosemide	05	Major
8	Ofloxacin + Ondansetron	05	Major
9	Acetaminophen + Phenytoin	03	Moderate
11	Aspirin + Hydrochlorothiazide	03	Major
12	Aspirin + Metformin	03	Major
13	Atorvastatin + Clopidogrel	03	Moderate
14	Furosemide + Metalazone	03	Major

1. Metronidazole + Ondansetron

Interaction Effect:

Concurrent use of Metronidazole and Ondansetron (QT interval prolonging drug) may result in increased risk of QT-interval prolongation and arrhythmias.

Clinical Management:

Metronidazole can cause QT-interval prolongation and has caused torsades de pointes with concomitant administration of another QT-interval prolonging drug 7. Susceptible patients may require ECG monitoring (5) and avoidance of medications known to cause QT prolongation (6)

Probable Mechanism:

Additive QT-interval prolongation[6,7].

2. Tramadol + Ondansetron

Interaction Effect:

Concurrent use of Tramadol and Ondansetron (serotonergic drug) may result in increased risk of serotonin syndrome.

Clinical Management:

Concomitant use of tramadol with serotonergic drugs has resulted in serotonin syndrome. If coadministration of tramadol and a serotonergic agent is required, carefully observe the patient, particularly during treatment initiation and dose adjustment. The onset of symptoms generally occurs within several hours to a few days of concomitant use but may occur later than that. Discontinue tramadol if serotonin syndrome is suspected.

Probable Mechanism:

Additive serotonergic effects.

3. Iron + Pantoprazole

Interaction Effect:

Concurrent use of iron and pantoprazole may result in reduced iron bioavailability.

Clinical Management:

Absorption of iron may be affected due to the profound and long lasting inhibition of gastric acid secretion by pantoprazole. Consider monitoring the patient for iron efficacy if pantoprazole is being used concurrently.

Probable Mechanism:

Reduced gastric pH, resulting in decreased absorption of iron.

4. Metronidazole + Diclofenac

Interaction Effect:

Concurrent use of Metronidazole and Diclofenac (CYP2C9 inhibitor) may result in increased exposure of Diclofenac.

Clinical Management:

Do not exceed the Diclofenac dose to more than 50mg twice daily.

Probable Mechanism:

Diclofenac will increase the level or effect of metronidazole by altering drug metabolism.

5. Aspirin + Clopidogrel

Interaction Effect:

Concurrent use of Aspirin and Clopidogrel may result in an increased risk of bleeding.

Clinical Management:

Concomitant use of aspirin with a platelet activation and aggregation inhibitor, such as clopidogrel, may increase the risk of bleeding. If co administration is required, monitoring of blood counts may be warranted.

Probable Mechanism:

Additive effects.

6. Aspirin + Ranitidine

Interaction Effect:

Concurrent use of Aspirin and Ranitidine may result in reduced salicylate plasma levels and decreased antiplatelet effect of aspirin.

Clinical Management:

The combined use of aspirin and ranitidine may cause decreased salicylate blood levels and decreased the antiplatelet effect of aspirin. Use caution with co-administration of aspirin and ranitidine.

Probable Mechanism:

Reduced absorption of aspirin[8].

7. Aspirin + Furosemide

Interaction Effect:

Concurrent use of Furosemide (loop diuretics) and NSAIDs may result in reduced diuretic effectiveness and possible nephrotoxicity.

Clinical Management:

Risk of renal toxicity is increased with combined use of NSAIDs and diuretics and use of NSAIDs with loop diuretics has reduced the natriuretic effect of the diuretic in some patients. During concomitant use of NSAIDs and diuretics, monitor for signs of worsening renal function and assure diuretic efficacy, including appropriate effects on blood pressure.

Probable Mechanism:

Decreased renal prostaglandin synthesis[9,10].

8. Ofloxacin + Ondansetron

Interaction Effect:

Concurrent use of Ofloxacin and Ondansetron may result in increased risk of QT interval prolongation.

Clinical Management:Co-administration of ofloxacin and ondansetron, both drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of serious cardiac effects. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.

Probable Mechanism:

Additive effects on QT interval prolongation.

9. Acetaminophen + Phenytoin

Interaction Effect:

Concurrent use of acetaminophen and phenytoin may result in decreased acetaminophen effectiveness and an increased risk of hepatotoxicity.

Clinical Management:

Patients receiving phenytoin therapy should avoid large and/or chronic doses of acetaminophen. Monitor the patient for evidence of hepatotoxicity.

Probable Mechanism:

Induction of CYP3A4-mediated acetaminophen hepatic metabolism[11,12].

10. Aspirin + Hydrochlorothiazide

Interaction Effect:

Concurrent use of NSAIDs and thiazide diuretics may result in reduced diuretic effectiveness and possible nephrotoxicity.

Clinical Management:

Risk of renal toxicity is increased with combined use of NSAIDs and diuretics and use of NSAIDs with thiazide diuretics has reduced the natriuretic effect of the diuretic in some

patients. During concomitant use of NSAIDs and diuretics, monitor for signs of worsening renal function and assure diuretic efficacy, including appropriate effects on blood pressure

Probable Mechanism:

Decreased renal prostaglandin production[13,14].

11. Aspirin + Metformin

Interaction Effect:

Concurrent use of aspirin and oral hypoglycemics may result in increased risk of hypoglycemia.

Clinical Management:

The effectiveness of oral hypoglycemic drugs may be increased with concomitant use of moderate doses of aspirin. This may lead to hypoglycemia. Monitor blood sugar carefully if concomitant use is required.

Probable Mechanism:

Increased effectiveness of oral hypoglycemic agent.

12. Atorvastatin + Clopidogrel

Interaction Effect:

Concurrent use of clopidogrel and cyp3a4 metabolized statins may result in decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity.

Clinical Management:

If a patient develops high on-treatment platelet reactivity during treatment with clopidogrel and a statin metabolized by CYP3A4 (ie, atorvastatin, lovastatin, or simvastatin), discontinue the statin and substitute a statin that is not metabolized by CYP3A4 (ie, pravastatin or rosuvastatin)

Probable Mechanism:

Competition with CYP3A4-mediated metabolism and inhibition of P-glycoprotein efflux transport of clopidogrel by CYP3A4-metabolized statins[15].

13. Furosemide + Metolazone

Interaction Effect:

Concurrent use of metolazone and loop diuretics may result in increased risk of electrolyte and fluid imbalance.

Clinical Management:

Use caution if metolazone and a loop diuretic are used concomitantly, as unusually large and prolonged loss of fluid and electrolytes may occur. Closely monitor fluids and electrolytes status.

Probable Mechanism:

Unknown.

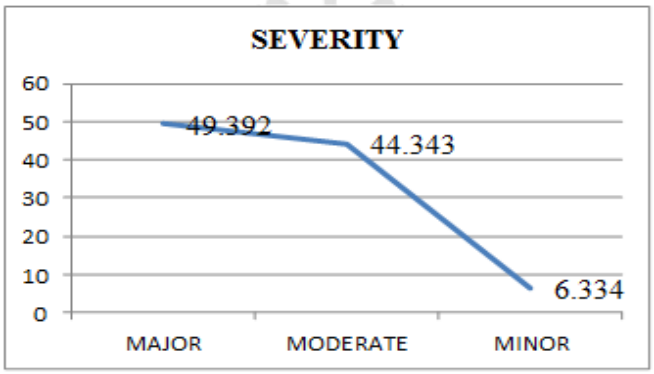

Figure A: severity of DDIs

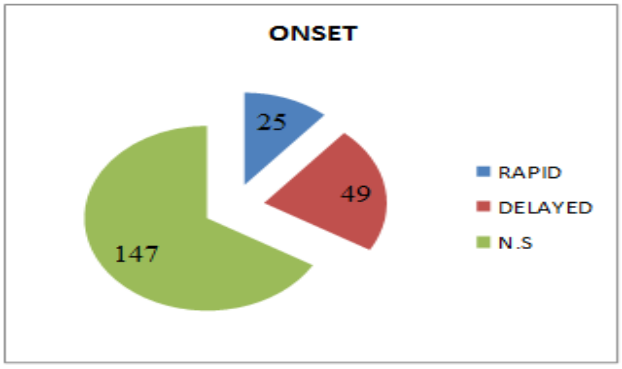

Figure B: onset of DDIs

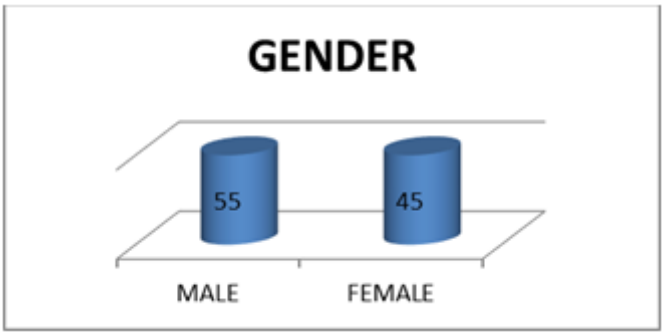

Figure C: gender wise distribution of DDI

CONCLUSION

Major DDIs were 109 (49.392%), moderate were 98 (44.343%) and minor were 14 (6.334%) in severity as mentioned in fig A. Rapid were 25, delayed were 49, not specified were 147 in onset of interaction as mentioned in fig B. Gender wise distribution of DDIs stated there is no significant difference as mentioned in fig C. Among all the interacting drugs ondansetron and aspirin was found to have more number of interactions with other drugs i.e., 20.814% and 15.384% respectively**.** The most commonly seen DDIs which were reported in this study may help to bring awareness among healthcare professionals and thereby decreases the risk of such interactions. This study has detailed the common interactions and thorough knowledge of these can decrease the incidence of DDIs.

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