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A STUDY ON THE IMPACT OF P-GLYCOPROTEIN TRANSPORT SYSTEM ON HIGH ALERT MEDICATIONS- ASSESSMENT, EVALUATION AND MANAGEMENT IN TERTIARY CARE HOSPITAL

NAME	DESIGNATION
Posani Bhavani	Pharm D Avanthi institute of pharmaceutical sciences, India
Sambu Ravi teja	Pharm D Avanthi institute of pharmaceutical sciences, India
Dr.Sai khesava reddy	Pharm D, Assistant professor Avanthi institute of pharmaceutical sciences, India
N. Revathi	Pharm D Avanthi institute of pharmaceutical sciences, India
K. Sai sriram	Pharm D Avanthi institute of pharmaceutical sciences, India

ABSTRACT:

BACKGROUND AND OBJECTIVES:

High alert medications are Narrow therapeutic index drugs where a minute change in dose or blood concentration results in sub therapeutic, toxic effects or therapeutic failure. Thus, a strict monitoring is needed. Our study focused on the influence of P-glycoprotein transport system on high alert medications and its associated risks on subjects, preventing and managing of adverse drug events and its resulting morbidity rate.

METHODS:

After granting the protocol by the ethical committee, data was collected from the patient's case sheet, drug-drug interactions and its adverse events in patients were observed, finally the documentation and its reporting were done.

RESULTS:

Based on the results of the study, it was found that each subject's prescription is subjected to a minimum of 30% and maximum of 80% of drug interactions resulting in therapeutic inefficacy /toxicities of high alert medications under the influence of P- glycoprotein transport system (inhibitors/ inducers). Thus, to prevent drug adverse events and for effective management, 47% of DI needs monitoring, 12% of DI needs dose adjustment, 11% of DI needs drug replacement and for 8% of DI management involves avoiding of concomitant administration. The observed morbidity rate was found to be 91.6 per 1000 and possible morbidity rate was found to be 833.3 per 1000. The incidence rate of adverse effects due to drug interaction was found to be 22.9 per 100. Prevalence rate of adverse effects due to drug interaction was found to be 49.16 per 100.

The order of high alert medications being altered (high to low) are

ANTIARRYTHMICS >ADRENERGIC ANTAGONIST > INOTROPIC AGENTS > ANTIPLATELETS > ANTIBIOTICS AND ANTI FUNGALS > IMMUNOSUPPRESANTS > NEUROMUSCULAR BLOCKING AGENTS

INTERPRETATION AND CONCLUSION:

About 83% of the subject's prescription needs modification. To improve the quality of life and to decrease morbidity rate, prescription auditing and also monitoring of drugs that alters the metabolism, distribution (Vd), Cmax, elimination and drug activation of high alert medications is required.

Key words: Antihypertensive agents, Drug interactions, High alert medications, Management, narrow therapeutic drugs, P-glycoprotein transport system

INTRODUCTION

HIGH ALERT MEDICATIONS:

High alert medications are Narrow therapeutic index drugs where a minute change in dose or blood concentration results in sub therapeutic, toxic effects or therapeutic failure[2]. Thus, a strict monitoring is needed. Our study focused on the influence of P-glycoprotein transport system on high alert medications and its associated risks on subjects, preventing and managing of adverse drug events and calculating its resulting morbidity rate.

P-GLYCOPROTEIN:

P-glycoprotein (P-gp, Pgp or multidrug resistance protein 1 (MDR1) is an essential protein of the cell membrane that removes toxins[endotoxin or exotoxins] from the cell.

HIGH ALERT MEDICATION LIST:

The Institute for Safe Medication Practices (ISMP) has 19 categories and 14 specific medications in its list of High Alert Medications

1. Adrenergic agonists, IV (e.g. adrenaline, noradrenaline)
2. Adrenergic antagonists, IV (e.g. propranolol, labetalol)
3. Anaesthetic agents, general, inhaled and IV (e.g. propofol, ketamine, dexmedetomidine)
4. Antiarrythmics IV (e.g. lignocaine (lidocaine), amiodarone,)
5. Antifibrinolytics, hemostatic
6. Antithrombotic agents (e.g. warfarin, heparin, tenecteplase, streptokinase)
7. Antivenom (eg. Sea snake, cobra, pit viper antivenom)
8. Chemotherapeutic agents, parenteral and oral
9. Dextrose, Hypertonic, 20% or greater
10. Epidural and intrathecal medications
11. Glyceryl Trinitrate injection
12. Inotropic medications, IV (e.g. digoxin, dobutamine, dopamine)
13. Insulin, subcutaneous and IV
14. Magnesium Sulphate Injections
15. Moderate sedation agents, IV
16. Neuromuscular blocking agents (eg.pancuronium, atracurium, rocuronium, vecuronium)
17. Opiates and Narcotics
18. Parenteral Nutrition preparations
19. Potassium salt injections
20. Sodium Chloride Solution (greater than 0.9%)

OBJECTIVES:

- To know the influence of P-glycoprotein transport system on high alert medications.
- To prevent and manage adverse drug events due to P- glycoprotein transport system on high alert medications
- To assess the risks of drug interactions on human body
- To estimate the morbidity rate resulted from drug interactions.

RESEARCH METHODOLOGY

STUDY DESIGN : Prospective observational Study

STUDY SITE : Gleneagles Global hospital, Lal bahadur nagar, Hyderabad

STUDY DURATION : 6-months (August 2018 - February 2019)

STUDY POPULATION : Patients who are receiving high alert Medications along with other drugs acting on P-glycoprotein transport system

SAMPLE SIZE : 120

INCLUSION CRITERIA: Subjects who were on receiving high alert Medications and another drugs acting on P-Glycoprotein transport system.

EXCLUSION CRITERIA: Pediatrics, geriatrics, subjects with liver Failure.

STUDY MATERIAL :

- Informed consent form.
- Patient standard data collection form,
- Drug interaction checker database online- drugs.com

METHODOLOGY:

- Literature survey was done.
- Protocol was prepared and submitted to the institutional review board or ethical committee for approval.
- Patients were recruited based on eligibility criteria.
- Patient related data was collected.
- Data processing and analysis were done.
- Result was documented and submitted.

RESULTS AND DISCUSSION:

A sample size of 120 patients was eligible for the study based on inclusion and exclusion criteria with a mean age of 58.5years. Among 120 subjects 69% were males and 31 % were females with a simple sex ratio of 2:2. About 38 subjects's prescriptions involved high alert medications interacting with p-glycoprotein transport system (38%) with a total of 78 interactions. Among 78 drug interactions, 77 drug interactions (98%) were due to inhibition and 1drug interaction (2%) was due to induction of P-glycoprotein transport system.

Among the inhibitory drug interactions, 2% (DI) were due to induction between antihypertensive agents (alpha beta blocker-carvedilol) and calcium channel blocker (diltiazem) leading to decreased therapeutic activity of carvedilol(moderate), hence it is managed by avoiding diltiazem.

Table no- I Drug interactions with examples

Drug Interactions Between Different Classes Of Drugs	Examples	Number of drug interactions(%)
Antiarrythmic + antiplatelet	Amiodarone + dabigatron	1(1.2%)
Antiarrythmic + antihypertension	Amiodarone + diltiazem	2(2.6%)
	Diltiazem + tolvaptan	2(2.6%)
Antiarrythmic + cardiac glycoside	Amiodarone + digoxin	20(25.7%)
Antibiotic + cardiac glycoside	Clarithromycin + digoxin	2(2.6%)
Antibiotic + antihistamine	Clarithromycin + fexofenadine	4(5.1%)
Antibiotic + antihypertension	Azithromycin + tolvaptan	1(1.2%)
Antibiotic + antihyperlipidemic	Azithromycin + atorvastatin	4(5.1%)
Antihypertension + antihyperlipidemic	Atorvastatin + tolvaptan	1(1.2%)
	Losartan + atorvastatin	1(1.2%)
	Prazosin + atorvastatin	1(1.2%)
Antihypertension + antiplatelet	Carvedilol + dabigatron	1(1.2%)
	Carvedilol + rivaroxaban	2(2.6%)
	Carvedilol + ticagrelor	2(2.6%)
	Spirinolactone + ticagrelor	2(2.6%)
Antihypertension + cardiac glycoside	Metoprolol + digoxin	3(3.8%)
	Carvedilol + digoxin	2(2.6%)
	Labetalol + digoxin	3(3.8%)
	Bisoprolol + digoxin	1(1.2%)
	Tolvaptan + digoxin	1(1.2%)

Antihypertension + corticosteroid	Dexamethasone + diltiazem	1(1.2%)
	Prazosin + methylprednisolone	1(1.2%)
Cardiac glycoside + antiulcer	Digoxin + pantoprazole	9(11.5%)
Cardiac glycoside + antihyperlipidemic	Digoxin + atorvastatin	1(1.2%)
Cardiac glycoside + antiplatelet	Digoxin + ticagrelor	2(2.6%)
Antifungal + antihistamine	Fluconazole + fexofenadine	1(1.2%)
Antihyperlipidemic + anticoagulant	Atorvastain + dabigatron	2(2.6%)
Antiplatelet + muscle relaxant	Ticagrelor + vecuronium	1(1.2%)
Steroid + antihyperlipidemic	Methylprednisolone + atorvastatin	2(2.6%)
Steroid + immunosuppressant	Methylprednisolone + tacrolimus	2(2.6%)

Table No- II Severity Of Drug Interactions:

Severity	**Number of interactions (%)**
Major	11(15.4%)
Moderate	66(84.6%)
Minor	0

Figure- 1 Risks associated with drug interactions are:

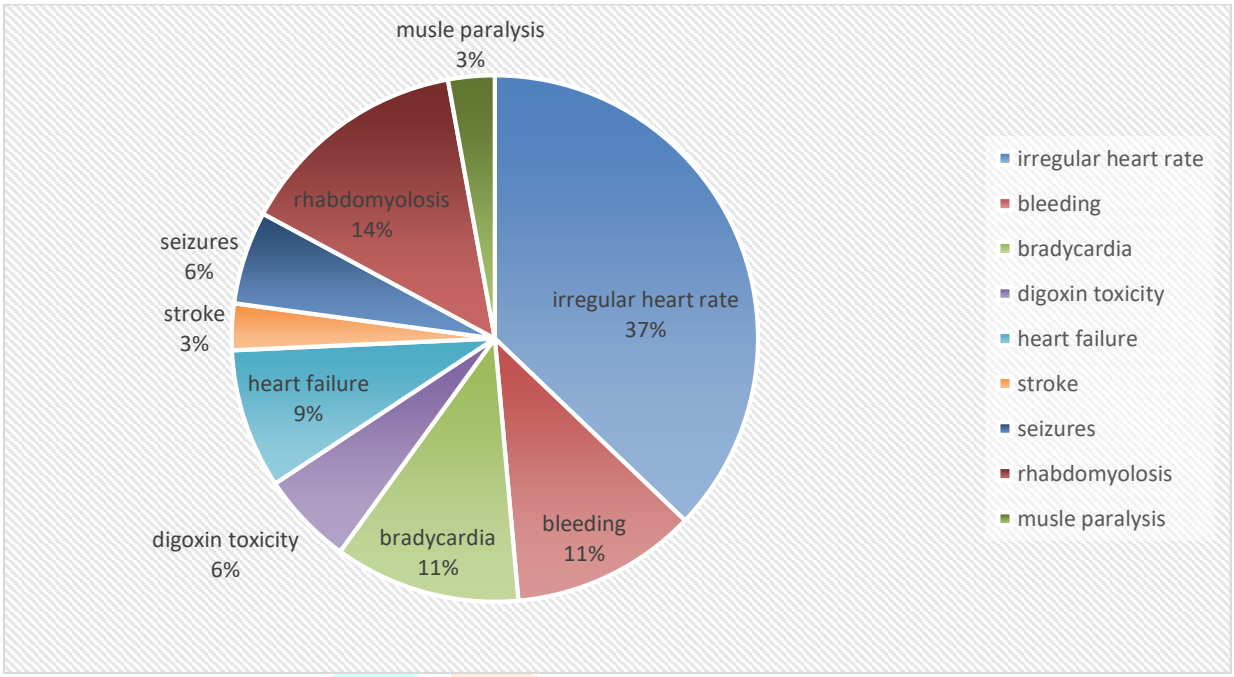

Table no- III Adverse events

Adverse effects	Number of drug interactions (%)
Irregular blood pressure	4(3.3%)
Irregular heart rate	2(1.6%)
Hemiplegia	3(2.5%)
Indigestion	2(1.6%)

Table no- IV Drug interactions involved in adverse events

Adverse events	Drug interactions
Irregular bp	Digoxin+bisoprolol
	Diltiazem+tolvaptan
Irregular heart rate	Labetalol + digoxin
	Amiodarone+digoxin
	Diltiazem+tolvaptan
Hypotension	Amiodarone+diltiazem
Indigestion	Atorvastatin+dabigatron

Table no- V Factors Intensifying Drug Interaction Effect (%):

This drug interactions causes the progression of patient's medical condition

Comorbidities	Number of drug interactions(%)
Myocardial infarction	8(14%)
Left ventricular failure	5(8%)
Decompensate cardiomyopathy	5(8%)
Stroke	7(12%)
Heart failure	3(5%)
Hypertension	20(34%)

Table no- VI Management of drug interactions:

Management methods	Number of interactions(%)
Monitor	47(60.2%)
Dose adjustment	12(15.3%)
Drug replacement	11(14.1%)
Avoid	8(10%)

Table No- VII Management of Drug Interactions with Examples:

Drug interaction	Number of drug interactions(%)	Management
Amiodarone + dabigatron	1(1.2%)	Avoid
Amiodarone + diltiazem	2(2.6%)	Monitoring
Diltiazem + tolvaptan	2(2.6%)	Monitoring
Amiodarone + digoxin	20(25.7%)	Monitoring
Clarithromycin + digoxin	2(2.6%)	Avoid
Clarithromycin + fexofenadine	4(5.1%)	Dose adjustment
Azithromycin + tolvaptan	1(1.2%)	Monitoring
Azithromycin + atorvastatin	4(5.1%)	Monitoring

Atorvastatin + tolvaptan	1(1.2%)	Drug replacement
Losartan + atorvastatin	1(1.2%)	Monitoring
Prazosin + atorvastatin	1(1.2%)	Monitoring
Carvedilol + dabigatron	1(1.2%)	Avoid
Carvedilol + rivaroxaban	2(2.6%)	Drug replacement
Carvedilol + ticagrelor	2(2.6%)	Monitoring
Spirinolactone + ticagrelor	2(2.6%)	Avoid
Metoprolol + digoxin	3(3.8%)	Dose adjustment
Carvedilol + digoxin	2(2.6%)	Dose adjustment
Labetalol + digoxin	3(3.8%)	Avoid
Bisoprolol + digoxin	1(1.2%)	Monitoring
Tolvaptan + digoxin	1(1.2%)	Monitoring
Dexamethasone + diltiazem	1(1.2%)	Monitoring
Prazosin + methylprednisolone	1(1.2%)	Monitoring
Digoxin + pantoprazole	9(11.5%)	Dose adjustment
Digoxin + atorvastatin	1(1.2%)	Monitoring
Digoxin + ticagrelor	2(2.6%)	Monitoring
Fluconazole + fexofenadine	1(1.2%)	Monitoring
Atorvastain + dabigatron	2(2.6%)	Monitoring
Ticagrelor + vecuronium	1(1.2%)	Monitoring
Methylprednisolone + atorvastatin	2(2.6%)	Monitoring
Methylprednisolone + tacrolimus	2(2.6%)	Monitoring

Limitations of the study:

Study was done for a limited period (6 month) with a limited sample size.

Discussion and Conclusion:

Based on the results of the study "the impact of P-glycoprotein transport system on high alert medications- assessment, evaluation and management, in 38 prescriptions it was found that each subject's prescription is subjected to a minimum of 30% and maximum of 80% of drug interactions resulting in therapeutic inefficacy /toxicities of high alert medications under the influence of P- glycoprotein transport system (inhibitors/ inducers). Thus, to prevent adverse events and for effective management, 47% of DI needs monitoring, 12% of DI needs dose adjustment, 11% of DI needs drug replacement, 8% of DI needs avoiding of concomitant administration is needed.

Morbidity rate: The observed morbidity rate was found to be 91.6 per 1000 and possible morbidity rate was found to be 833.3 per 1000.

The incidence rate of adverse effects due to drug interaction was found to be 22.9 per 100.

Prevalence rate of adverse effects due to drug interaction was found to be 49.16 per 100.

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About 83% of the subject's prescription need modifications. To improve the quality of life and to decrease morbidity, prescription auditing is required and also monitoring of drugs that alters the metabolism, distribution (Vd), Cmax, elimination and drug activation of high alert medications is required.

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Conflicts of interest:

No conflicts of interest are present

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