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Original Article

Others Section

Assessment of Potential Drug-drug Interactions among Ischaemic Stroke Patients in a Charitable Hospital

AMALA JOHNSON[1], AKSHAY ABRAHAM THOMAS[2], SHANTY MARY JOSE[3], UDAY VENKAT MATETI[4], ADITHI KELLARAI[5], SHRADDHA SHETTY[6], RAUSHAN KUMAR CHAUDHARY[7], KALA BAHADUR RAWAL[8]

ABSTRACT

Introduction: Incidence of stroke is more frequently found among the elderly who are mostly dealing with co-morbidities and polypharmacy, were found to be significant in high risk of potential Drug-drug Interactions (pDDIs).

Aim: To identify potential drug-drug interactions in ischaemic stroke patients.

Materials and Methods: This retrospective study was conducted in the General Medicine Department at Justice KS Hegde Charitable Hospital, Mangaluru, Karnataka, India, from January 2018 to August 2020. All the stroke patient's data were collected based on the inclusion criterion. Prescriptions were obtained from the case sheets and the pDDIs were identified using UpToDate software.

Results: The mean age of the study population (N=350) was found to be 61.07±11.460 years, The incidence of stroke was high in males (66%) than in females (34%) from the total of 350 patients. The prescribing patterns were antiplatelet single (69.4%) and fixed-dose combination (1.42%), anticoagulants (11.14%), antihypertensive agents (63.42%), followed by lipid-lowering agents (65.14%) as single and fixed dose combinations (0.85%), gastrointestinal agents (70.57%). The class prescribed the most was antiplatelet agents (aspirin 61.4%). The total number of 402 pDDIs were found among 350 patients. Based on the Lexi-Interact® severity scale moderate interactions were the most commonly found then followed by the major and minor with 301 (74.87%), 66 (16.41%) and 35 (8.70%), respectively. The most frequent interaction found were clopidogrel with pantoprazole, and atorvastatin with clopidogrel with same incidence of in 44 (12.57%) patients.

Conclusion: The majority of the interaction was found to be moderate interactions which were followed by major and minor interactions. The pDDIs mostly occurred among the antiplatelet agents, gastro-intestinal agents and antihypertensives.

Keywords: Drug interactions, Pharmacodynamic, Polypharmacy, Prescriptions

INTRODUCTION

Potential Drug-Drug Interaction (pDDI) is defined as the probability of occurrence of pharmacological or clinical response to the administration of a drug combination which is different from that expected from the known effects of the two agents when given alone [1]. Patient's age more than 60 years and those with co-morbidities are the other common causes for the occurrence of Drug-drug interactions (DDIs) [2]. Drug-drug interaction is considered a major risk to public health. Drug-drug interactions even though being preventable medication related problem, whereas the prevalence of pDDIs was found in 61-81% of stroke patients [3]. Overall, 11% of patients experience symptoms associated with pDDIs, responsible for nearly 2.8% of hospital admissions [4].

Based on the severity and mechanisms by which drugs interact with each other the DDI can be categorised. On the basis of severity, DDIs can be mild, moderate, or severe. Life-threatening or interactions which can cause prolonged or permanent damage to patients falls under major DDI. Moderate DDIs may require medical intervention or change in therapy and whereas, minor DDIs do not usually require a change in therapy [5]. The significant risk factors for DDI are the patient's age, pharmacokinetic and pharmacodynamic nature of drugs, common disease state and polypharmacy, the influence of disease on drug metabolism and inadequate knowledge of prescribers [2]. Ischaemic stroke is an episode of neurological dysfunction caused by a focal cerebral, spinal, or retinal infarction [6]. Thrombotic stroke appears when there is a blood clot (or thrombus) in any part of the brain which leads to destruction or improper functioning of brain cells due to reduced oxygen supply or lack of blood flow to an artery in the brain which is clinically referred to as cerebral thrombosis or cerebral infarction [7].

The anticoagulant medications such as warfarin, heparin are the drugs have a narrow therapeutic index, which makes them more susceptible to cause DDIs. The DDI can alter the therapeutic significance in a few cases and can cause significant harm; if recognised in time, they can be prevented either by changing the treatment regimen or by monitoring the therapy, i.e., why they are considered preventable Adverse Drug Reactions (ADRs), as a result, it is critical to consider the significance of pDDIs, even though, in most situations, no intervention is required other than increased surveillance. To detect pDDIs in routine practice, many online checkers (Lexi-Interact Micromedex, EpocratesRx, Drug Interaction Facts, Pharmavista®) with varying sensitivity and specificity are available; and as for this study, UpToDate was considerably used. Various DDI checking performance assessments revealed that the Lexi-Interact has high sensitivity (87-100%) and specificity (80-90%). It is obvious that identifying potentially Contraindicated Drug-drug Interactions (pCDDI) needs careful consideration when administering drug combinations [3,4].

The current study seeks to include a detailed understanding of DDIs, to develop practical decisions thereby increase the clinician's knowledge on DDI and support tools for encounters in their daily practice for stroke patients.

MATERIALS AND METHODS

This retrospective study was conducted in the General Medicine Department at Justice KS Hegde Charitable Hospital, Mangaluru, Karnataka, India, from January 2018 to August 2020. All the stroke patient's data were collected based on the inclusion criterion in the study period. Analysis of data was done between December 2020 and May 2021. The study was carried out after the approval

of Institutional Ethics Committee (Ref. No: NGSMIPS/IEC/14/2020) and was also registered in clinical trial registry of India (Ref. No: CTRI/2020/12/029886).

Sample size calculation: The sample size calculated for this study using master software of version 2 based on the expected proportion of antihypertensive is 35%, Precisionis 5% at a 95% confidence level. The minimum required sample size for this study was 350 patients.

Inclusion criteria: The Ischaemic stroke patients diagnosed on the basis of clinical presentations, Computed Tomography (CT), Magnetic Resonance Imaging (MRI) between the age group 18-80 years were the included in the study.

Exclusion criteria: Patients diagnosed with haemorrhagic stroke, old cerebrovascular accidents, and incomplete case sheets were excluded from the study.

Data Collection

The patient data collection form was prepared and all the relevant details, including patient socio-demographic parameters such as age, gender, co-morbidities and the drugs prescribed were recorded. The drugs prescribed were checked for the pDDI using the UpToDate software system [8].

Potential drug-drug interactions (pDDIs)

The pDDIs were classified according to the level of severity:

- Mild DDIs are clinically significant interactions where specified agents interact with each other. If benefits overcome the risk, they can be used concomitantly with monitoring or adjusting the dose of one or both agents, but the therapy will not be changed.
- Moderate DDIs are clinically significant interactions where two agents interact with each other. These may be used concomitantly if the benefit is realised over the risk. A specific action is necessary to minimise the risk, such as close monitoring, empiric dosage changes and or change in the therapy.
- The major DDIs are clinically significant life-threatening interactions that require medical intervention to prevent or mitigate the risk. Usually, concomitant use of these agents is avoided.

Based on risk rating, pDDIs are classified as

- X: Avoid combination,
- D: Consider therapy modification,
- C: Monitor therapy,
- B: No action needed,
- A: No known interactions.

Based on the severity, pDDIs are classified as major, moderate, and minor [9].

STATISTICAL ANALYSIS

The data was analysed using Statistical Package for Social Sciences (SPSS) version 20.0.

RESULTS

Out of the 1081 data of stroke patients admitted in past two years and eight months, data of 350 patients,who met the inclusion criteria, were selected for the study. Single-agent therapy was prescribed in all 350 (100%) patients and combination therapy to 247 (70.5%) patients. The most commonly prescribed single agent was gastrointestinal agents 247 (70.57%) followed by antiplatelet agents 243 (69.42%).

The male (66%) population dominated the female (34%). The incidence of stroke was maximum between the age group 51-65 (47.71%) years, followed by 66 and above (34%). The median length of stay was found to be 6 days. Also, the common co-morbidities found among stroke patients were diabetes mellitus (38%), hypertension (69.71%), transient ischaemic attack (1.71%), cardiovascular diseases and others [Table/Fig-1].

Variables	n, %
Gender	
Males	231 (66%)
Females	119 (34%)
Age groups	
18-35	9 (2.57%)
36-50	55 (15.71%)
51-65	167 (47.71%)
66 and above	119 (34%)
Co-morbidities	
Diabetes mellitus	133 (38%)
Hypertension	244 (69.71%)
Cardiac disease	70 (20%)
Transient ischaemic attack	6 (1.71%)

[Table/Fig-1]: Gender, age and co-morbid distribution among patients.

[Table/Fig-2] presents the various categories of single agents and fixed dose combinations prescribed in ischaemic stroke patients. The most commonly prescribed class of drugs were antiplatelet agents, anticoagulants, lipid-lowering agents, antihypertensive, cardiovascular agents, nootropics and gastrointestinal agents.

Drug class	n, %
Single agents	
Antiplatelet agents	243 (69.42%)
Anticoagulants	39 (11.14%)
Anticonvulsants	37 (10.57%)
Lipid-lowering agents	228 (65.14%)
Antihypertensive agents	197 (56.28%)
Hypoglycaemic agents	112 (32%)
Antipsychotics	17 (4.85%)
Antidepressants	43 (12.28%)
Cardiovascular agents	21 (6%)
Thyroid hormones	10 (2.85%)
Nootropics	28 (8%)
Antimuscarinics	2 (0.57%)
Gastrointestinal agents	247 (70.57%)
Non Steroidal Anti-Inflammatory Drugs (NSAIDs)	23 (6.57%)
Antibiotics	84 (24%)
Bronchodilators	15 (4.28%)
Antiemetic agents	48 (13.71%)
Vitamin supplements	71 (20.28%)
Fixed dose combination	
Antiplatelet+Cholesterol lowering agents	119 (34%)
Antiplatelet agents	5 (1.42%)
Cholesterol lowering agents	3 (0.85%)
Antihypertensives	25 (7.14%)
Hypoglycaemic agents	40 (11.42%)
Cardiovascular agents	0
Antiparkinsonian agents	5 (1.42%)
Bronchodilators	8 (2.28%)
Thyroid hormones	2 (0.57%)
Proton pump inhibitors	3 (0.85%)
NSAIDS	24 (6.85%)
Antibiotics	39 (11.14%)
Multivitamins	112 (32%)

[Table/Fig-2]: Categories of single agents and fixed dose combinations prescribed in ischaemic stroke patients.

The potential drug-drug interactions for the prescribed drugs among stroke patients was categorised according to severity such as major (66), moderate (301) and minor (35) depicted in [Table/Fig-3-6]. Clopidogrel with pantoprazole (12.57%), Warfarin with aspirin (2%) and atorvastatin with phenytoin (1.14%) were the top three most frequently found pDDI among the drug interactions with major severity

Interacting pair of supportive care drug	Outcome	Severity	Risk rating	Number of patients n (%)
Antiplatelet agents+Gastrointestinal agents				
Clopidogrel+pantoprazole	Decrease serum concentrations of the active metabolites of clopidogrel	Major	C	44 (12.57%)
Anticoagulants+Antiplatelet agents				
Warfarin+Clopidogrel	Clopidogrel may enhance the anticoagulant effect of Warfarin	Major	C	2 (0.57%)
Anticoagulants+Antiplatelet agents				
Warfarin+Aspirin	Aspirin can escalate the warfarin effects.	Major	D	7 (2%)
Anticoagulants+Antiplatelet agents				
Acenocoumarol+Aspirin	Aspirin may enhance the anticoagulant effect of Acenocoumarol	Major	D	2 (0.57%)
Anticoagulants+Antiplatelet agents				
Dabigatran+Aspirin	Aspirin may enhance the adverse effect of dabigatran.	Major	D	2 (0.57%)
Cholesterol lowering agents+Anticonvulsants				
Atorvastatin+Phenytoin	Phenytoin may increase the metabolism of atorvastatin	Major	D	4 (1.14%)
Atorvastatin+Carbamazepine	Carbamazepine may increase the metabolism of atorvastatin	Major	D	2 (0.57%)
Antiplatelet agents+Antidepressants				
Aspirin+amitriptyline	Tricyclic Antidepressants (Tertiary Amine) may enhance the antiplatelet effect of Aspirin	Major	C	3 (0.85%)

[Table/Fig-3]: Potential drug-drug interactions: Major interactions.

Interacting pair of supportive care drug	Outcome	Severity	Risk rating	Number of patients
Hypoglycaemic agents+Antihypertensive agents				
Insulin+nebivolol	Nebivolol may enhance the hypoglycaemic effect of insulin	Moderate	C	1 (0.28%)
Antidepressants+Anticonvulsants				
Amitriptyline+Levetiracetam	CNS depressants may enhance the adverse/toxic effect of other CNS Depressants	Moderate	C	2 (0.57%)
Antiplatelet agents				
Aspirin+clopidogrel	Enhances the antiplatelet properties	Moderate	C	41 (11.71%)
Antiplatelet agents+Nootropics				
Aspirin+Piracetam	Enhance the toxic effect of Aspirin	Moderate	C	12 (3.42%)
Antiplatelet agents+Antihypertensive agents				
Clopidogrel+Amlodipine	CCB may diminish the effect of clopidogrel	Moderate	C	34 (9.71%)
Antiplatelet agents+Hypoglycaemic agents				
Aspirin+Insulin	Aspirin may enhance the hypoglycaemic effect of agents with blood glucose lowering effects	Moderate	C	37 (10.57%)
Antiplatelet agents+Antihypertensive agents				
Clopidogrel+Cilnidipine	Calcium Channel Blockers may reduce the therapeutic effect of Clopidogrel	Moderate	C	14 (4%)
Antiplatelet agents+Hypoglycaemic agents				
Aspirin+Metformin	AP agents may enhance the hypoglycaemic effect of Metformin	Moderate	C	22 (6.28%)
Antiplatelet agents+Hypoglycaemic agents				
Aspirin+Voglibose	Aspirin can escalate the effect of Voglibose	Moderate	C	8 (2.28%)
Antiplatelet agents+Antihypertensive agents				
Aspirin+Diltiazem	CCB's (nondihydropyridine) may elevate levels of aspirin	Moderate	C	4 (1.14%)
Antiplatelet agents+Hypoglycaemic agents				
Aspirin+Glimepiride	Aspirin may enhance the hypoglycaemic effect of Glimepiride	Moderate	C	5 (1.42%)
Antiplatelet agents+Antihypertensive agents				
Clopidogrel+Diltiazem	Diltiazem may diminish the therapeutic effect of Clopidogrel	Moderate	C	2 (0.57%)
Antiplatelet agents+Hypoglycaemic agent				
Aspirin+Teneligliptin	Aspirin may increase the hypoglycaemic effect of Teneligliptin	Moderate	C	6 (1.71%)
Antiplatelet agents+Hypoglycaemic agents				
Aspirin+Sitagliptin	Aspirin might surge the effect of agents with blood glucose lowering effects	Moderate	C	1 (0.28%)
Antiplatelet agents+Hypoglycaemic agents				
Aspirin+Pioglitazone	Antiplatelet agents may shoot up the effect of Pioglitazone	Moderate	C	2 (0.57%)
Antiplatelet agents+Hypoglycaemic agents				
Clopidogrel+Pioglitazone	Clopidogrel may increase the serum concentration of Pioglitazone	Moderate	C	2 (0.57%)

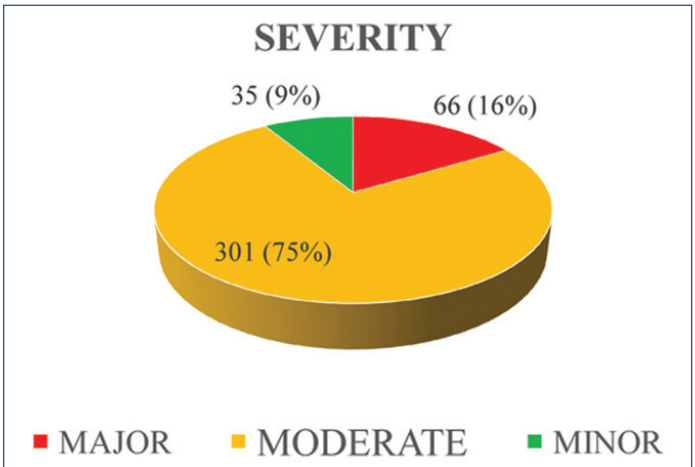
Antiplatelet agents+Antihypertensive agents				
Clopidogrel+Nifedipine	Nifedipine may diminish the therapeutic outcome of Clopidogrel	Moderate	C	1 (0.28%)
Anticoagulants+Antiplatelet agents				
Heparin+Aspirin	Agents with antiplatelet properties may enhance the anticoagulant effect of heparin	Moderate	D	10 (2.85%)
Anticoagulants+Anticoagulants				
Warfarin+Heparin	Anticoagulantsmay enhance the anticoagulant effects	Moderate	C	4 (1.14%)
Anticoagulants+Anticoagulants				
Acenocoumarol+Heparin	Anticoagulants may enhance the anticoagulant effects	Moderate	C	2 (0.57%)
Anticoagulants+Penicillin				
Warfarin+Amoxicillin Clavulanate	The effect of warfarin may be enhanced by penicillin's	Moderate	C	3 (0.85%)
Anticoagulants+Antiplatelet agents				
Enoxaparin+Clopidogrel	The anticoagulant effect of enoxaparin may be elevated by agents with antiplatelet properties	Moderate	D	2 (0.57%)
Anticoagulants+Antiplatelet agents				
Enoxaparin+Aspirin	Agents with antiplatelet properties may enhance the anticoagulant effect of enoxaparin	Moderate	D	2 (0.57%)
Anticoagulants+Antiplatelet agents				
Heparin+Clopidogrel	Agents with antiplatelet properties may enhance the heparin effect	Moderate	D	2 (0.57%)
Anticoagulants+Gastrointestinal agents				
Warfarin+Pantoprazole	Pantoprasole may enhance the anticoagulant effect of warfarin	Moderate	B	2 (0.57%)
Cholesterol lowering agents+Antihypertensive agents				
Atorvastatin+Diltiazem	Diltiazem may increase the serum concentration of Atorvastatin	Moderate	C	5 (1.42%)
Antiplatelet agents+NSAIDS				
Aspirin+Indomethacin	NSAIDS may enhance the adverse/toxic effect of aspirin and can also cause increased risk of bleeding	Moderate	D	1 (0.28%)
Antiplatelet agents+Antihypertensive agents				
Aspirin+Ramipril	Aspirin may diminish the therapeutic effect of ramipril	Moderate	C	1 (0.28%)
Antiplatelet agents+Nootropics				
Clopidogrel+Piracetam	Agents with Antiplatelet properties may enhance the antiplatelet effect of other agents with antiplatelet properties	Moderate	C	10 (2.85%)
Antiplatelet agents+cholesterol lowering agents				
Atorvastatin+Clopidogrel	Atorvastatin may diminish the antiplatelet effect of Clopidogrel	Moderate	B	44 (12.75%)
Hypoglycemic agents+Antihypertensive agents				
Insulin+Metoprolol	Metoprolol may enhance the hypoglycaemic effect of insulin	Moderate	C	1 (0.28%)
Antihypertensive Agents+Anticonvulsants				
Amlodipine+Phenytoin	Phenytoin may decrease the serum concentration of amlodipine	Moderate	C	2 (0.57%)
Hypoglycemic agents+Hypoglycaemic agents				
Insulin+Glimepiride	Hypoglycaemia associated Agents may enhance the hypoglycaemic effect of other hypoglycaemia associated Agents	Moderate	C	3 (0.85%)
Hypoglycaemic agents+Antihypertensive agents				
Insulin+Atenolol	Atenolol may enhance the hypoglycaemic effect of insulin	Moderate	C	2 (0.57%)
Hypoglycaemic agents+Hypoglycaemic Agents				
Insulin+Metformin	Antidiabetic agents may enhance the hypoglycaemic effect of hypoglycaemia associated Agents	Moderate	C	11 (3.14%)

[Table/Fig-4]: Potential drug-drug interactions: Moderate interactions.

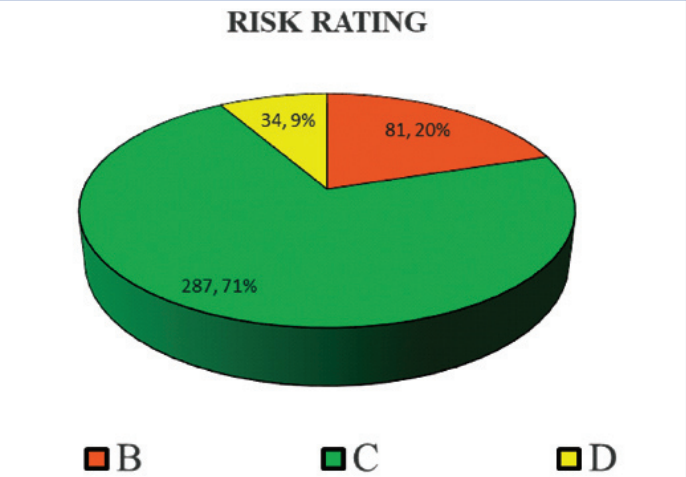
Interacting pair of supportive care drug	Outcome	Severity	Risk rating	Number of patients
Anticoagulants+Gastrointestinal agents				
Atorvastatin+Dabigatran	Atorvastatin may decrease the serum concentration of Dabigatran	Minor	B	2 (0.57%)
Anticoagulants+Gastrointestinal agents				
Dabigatran+Pantoprazole	Proton Pump Inhibitors may decrease serum concentrations of the active metabolite(s) of Dabigatran	Minor	B	2 (0.57%)
Cholesterol lowering agents+Antihypertensive agents				
Atorvastatin+Amlodipine	Amlodipine may increase the serum concentration of atorvastatin	Minor	B	26 (7.42%)
Antihypertensive Agents+Hypoglycemic Agents				
Telmisartan+Metformin	Telmisartan may decrease the serum concentration of metformin	Minor	B	5 (1.42%)

[Table/Fig-5]: Potential drug-drug interactions: Minor interactions.

[Table/Fig-3]. Further, atorvastatin with clopidogrel (12.57%), aspirin with clopidogrel (11.71%), and aspirin with insulin (10.57%) were the most frequently found moderate pDDI [Table/Fig-4]. Similarly, atorvastatin with amlodipine (7.42%), telmisartan with metformin (1.42%) and atorvastatin with dabigatran (0.57%) or dabigatran with pantoprazole (0.57%) were the most frequently observed minor pDDI among the prescribed therapy [Table/Fig-5]. However, the risk of the pDDI was assessed for the potential action to be taken if required as per the risk rate. The majority of drug interactions were of C category followed by B and D based on the distribution of risk rating as represented in [Table/Fig-7].



[Table/Fig-6]: Distribution of the pattern of severity.



[Table/Fig-7]: Distribution of risk-rating among the patients.

DISCUSSION

Out of a total of 350 case files of ischaemic stroke patients, 231 (66%) were males and 119 (34%) were females. Incidence of stroke is more common among men due to the higher prevalence of high blood pressure and vasoconstriction in men whereas, in the female estrogen helps in the health of brain capillaries thereby decreasing the risk of stroke [10]. Hence, it can be assumed that the incidence of DDIs will also be higher in males.

The mean age of the study population was 61.07±11.460 years, which shows that stroke is more prevalent among the elderly. This is in harmony with with finding in research conducted by Reganon E et al., (mean age was 65.3±8.2 years) [11]. Since the incidence of stroke was found to be more among the elderly who frequently practice polypharmacy due to the existence of co-morbid conditions they are more vulnerable to DDIs. This correlates with an Indian study by Mateti UV et al., where, they found that there was a higher rate of DDI in patients who were more than 60 years of age and prescribed with polypharmacy [12].

Polypharmacy is a major threat that leads to increased DDIs and also leads to prescription of potentially harmful drug combinations. The present study showed that single agents was given to all 350 patients (100%) and fixed dose combination to 70% of the patients. The antiplatelet agents, anticoagulants, gastrointestinal agents, lipid-lowering agents and antihypertensive agents were the most commonly prescribed classes of drugs. This was in concordance with the study carried out by Celin AT et al., [13] for the assessment of drug related problems in stroke patients. Furthermore, poststroke disorders like after stroke depression, nerve injury, and infection prevention was all reduced using antidepressants, multivitamins, and antibiotics. It was observed in the study that multiple medications were one of the main reasons for occurrence of DDI. This was supported by a research work conducted by Sridharan SE et al., [14].

The pDDIs identified in the study population were based on single agents given at the same frequency. There were 402 interactions found. Based on the severity scale, there were 301 moderate interactions, 35 minor and 66 major interactions which were supported by a study conducted by Mateti UV et al., [12]. The most common interacting drugs found were clopidogrel with pantoprazole in 44 (12.57%) patients. This was in harmony with a German study which showed the impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. The study proved there was a decrease in serum concentration of the active metabolites of clopidogrel [15]. There was a diminished antiplatelet effect of clopidogrel when prescribed along with atorvastatin explained by a study conducted by Lau WC et al., [16]. There were 44 (12.57%) patients in the study showing pDDIs with clopidogrel given along with atorvastatin. The other frequently found potential drug-drug interaction was aspirin with clopidogrel in 41 (11.71%) patients. A South Korean based prospective study by Kim JT et al., had the primary outcome as increase in blood concentration of the active metabolites of clopidogrel aspirin was found to enhance the antiplatelet property of clopidogrel [17]. A randomised control trial by Parker WAE et al., shows diabetes patients have a decreased antiplatelet effect of aspirin [18]. In current study, Aspirin with insulin showed a pDDI in 37 (10.57%) patients.

The other pDDI were aspirin with piracetam 12 (3.42%) patients, piracetam acts as a cerebral activator atorvastatin with amlodipine 26 (7.42%), clopidogrel with amlodipine 44 (12.57%) patients, clopidogrel with cilnidipine 14 (4%) patients, and aspirin with metformin 22 (6.28%) patients. In the study conducted by Venkateshwaramurthi N et al., aspirin and clopidogrel were found to have a pDDI due to concomitant use at therapeutic doses. Hence dosage adjustment is needed for the patients [19].

All the interactions tend to either increase the therapeutic effect or antagonise the potential of other drugs or cause toxicity which leads to therapy failure which can increase the mortality and morbidity among patients.

Limitation(s)

If the study had been conducted prospectively, actual DDI rather than pDDIs could have been identified. There was not any direct patient benefit with this retrospective study compared to the prospective study.

CONCLUSION(S)

The most frequently prescribed drugs were the antiplatelet agents as well as the gastrointestinal agents. Besides these, anticoagulants, antihypertensive, hypoglycaemic agents, cholesterol lowering agents, cerebral activators and other vitamin supplements were some of the other classes of drugs that were prescribed often. The majority of the interaction was found to be moderate interactions which was followed by major interactions and then minor interactions. Antiplatelet agents and gastrointestinal agents being the most frequently prescribed drugs, the most frequently found interactions were between clopidogrel and pantoprazole. Clopidogrel with atorvastatin, and clopidogrel with aspirin therapy

were the other regularly found interactions. Medications prescribed depend on the hospital and the physician's choices; the findings in the present study highlight those further complications can be prevented through early management of stroke.

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PARTICULARS OF CONTRIBUTORS:

1. Pharm D Intern, Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangaluru, Karnataka, India.
2. Pharm D Intern, Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangaluru, Karnataka, India.
3. Pharm D Intern, Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangaluru, Karnataka, India.
4. Assistant Professor, Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangaluru, Karnataka, India.
5. Associate Professor, Department of General Medicine, KS Hegde Medical Academy, Justice K S Hegde Charitable Hospital, Nitte (Deemed to be University), Mangaluru, Karnataka, India.
6. Lecturer Biostatistics, Department of Biostatistics, KS Hegde Medical Academy, Nitte (Deemed to be University), Mangaluru, Karnataka, India.
7. PhD Research Scholar, Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangaluru, Karnataka, India.
8. PhD Research Scholar, Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangaluru, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Uday Venkat Mateti,
Assistant Professor, Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences (NGSMIPS), Nitte (Deemed to be University), Mangaluru, Karnataka, India.
E-mail: udayvenkatmateti@gmail.com

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