Original Article

TO ESTIMATE THE INCIDENCE OF POTENTIAL DRUG-DRUG INTERACTION IN STROKE PATIENTS ADMITTED IN A TERTIARY CARE HOSPITAL, TELANGANA

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ABSTRACT

Objective: To determine the frequency and pattern of potential drug-drug interactions in hospitalized stroke patients.

Methods: A retrospective study was carried out among patients treated for ischemic and haemorrhagic stroke at a tertiary care hospital, Hyderabad for a period of 1 y. A total of 177 prescriptions were analyzed during the study period. The potential drug-drug interactions were identified using Clinirex software.

Results: Among the 177 prescriptions, 63.8% were male and 36.2% were female. Out of 177, 79 % of prescriptions had shown potential drug-drug interactions. The patients prescribed with more than 5 drugs developed higher incidence of drug-drug interactions. Based on severity scale we observed 12% major, 71% moderate and 17% minor drug-drug interactions. The incidence of pharmacodynamic interactions was 68% and the pharmacokinetic interactions were 32%.

Conclusion: This study suggests that patients with stroke are frequently exposed to potential drug-drug interactions. The incidence of potential drug-drug interactions was higher in patients above 40 y. Most of the prescriptions contained polypharmacy which may lead to increased risk of hospitalization and higher health care cost. It is essential to identify potential drug-drug interactions especially in elderly patients as early as possible in order to prevent adverse drug reactions and ensure patient's safety.

Keywords: Stroke, Drug-drug interactions, Pharmacodynamic interactions, Pharmacokinetic Interaction, Clinirex software

INTRODUCTION

Drug therapy is an essential part of disease management. The use of multiple drugs which are required either to manage a single disease or co-morbidities can cause harmful interactions between them. A drug-drug interaction (DDI) occurs when the effect of one drug is altered by another drug [1]. Adverse drug reactions may occur as a result of DDIs and clinicians may be unaware of the clinical risks of some drug combinations.

Multiple drug therapy including prescription and over the counter medication leads to drug-drug interactions. Sometime patients are seen by multiple prescribers who prescribe interacting medications which causes drug-drug interactions. Elderly patients are especially at a greater risk because of co-morbid conditions for which many drugs are prescribed which may result in the increase in frequency of potential drug-drug interactions [2].

Drug interactions are classified as pharmacokinetic, pharmacodynamics and pharmaceutical interactions. Pharmacokinetic interaction occurs when the drug affects the absorption, distribution, metabolism and elimination of another drug. Pharmacodynamics interaction occurs when a drug alters the effect of another drug by antagonistic, synergistic, or additive effect. Pharmaceutical interactions occur due to physical or chemical incompatibility, when two or more drugs are mixed.

Based on severity, DDIs are classified into contraindicated, major, moderate, and minor. Major drug interactions are life threatening and need medical intervention to prevent adverse effect. Moderate drug interactions results in increase in the severity of patient's condition and require adjustment or alteration in therapy. Minor drug interactions have limited effects [3].

Polypharmacy is an important factor for the DDIs. It occurs when two or more drugs are administered simultaneously. When one drug interacts with another drug leads to unpredictable adverse effect. Cardiovascular disease is the leading cause of death, more than 17.3 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030. It represented 31% of deaths worldwide, with 80% of those deaths taking place in low-and middle-income countries [4]. According to the study of Global Burden of Diseases (GBD) conducted in 1990, stroke was the second leading cause of death in the world [5]. The following updated GBD study reported nearly 5.87 million stroke deaths globally in 2010, as compared to 4.66 million in 1990. This indicated a 26 per cent increase in global stroke deaths during the past two decades. With the rising proportion of mortality, stroke still remains the second leading cause of death worldwide [6]. DDIs are estimated to account for 6%-30% of all the adverse drug events, and they continue to pose a significant risk to the patient's health outcomes and a considerable economic burden on the healthcare system [7]. Therefore, as the DDIs pose a major risk to the health of many patients, it has to be tackled and, it is the need of the hour.

The mechanism of interaction is important in predicting the time course of interaction, and provides a way to minimize the risk of an adverse outcome [8]. Even though drug-drug interactions are considered as preventable, studies found that up to 11% of patients experience symptoms associated with DDIs and nearly 2.8% of patients needed hospital admissions. Monitoring of drug-drug interactions may improve the prescribing and dispensing quality. It might form a basis for education focused on appropriate prescribing of drugs [9]. Gathering more information on drug-drug interactions could help to decrease adverse effects [10].

Clinirex is software that allows clinicians to check for interacting drug ingredients, their effects and their clinical significance. It classifies interactions as minor, moderate and major. It provides information on drug-drug interaction, drug-food interaction and

drug-disease interaction, along with previous allergic reactions. More than 8,000 medications may be tested as to possible drug interaction with any number of drugs may be entered [11].

MATERIALS AND METHODS

Study design

A retrospective study was carried out for a period of 1 y in a tertiary care hospital, Hyderabad.

Sampling method

Prescriptions of 177 patients admitted for ischemic and haemorrhagic stroke to inpatient wards of the hospital were collected and analyzed during this study.

Data collection procedure

All the study specific data were collected and documented in the designed data collection form. It included the patient demographic details, IP number, admission and discharge date, current diagnosis, past medical history, co-morbidities, current medications with their dose, frequency and duration of the treatment. The data was collected from patient files and treatment charts.

Inclusion criteria

- Patients aged 20 y or older and of any gender.
- Patients with stroke and other co-morbidities.
- Patients who were admitted to the hospital and had a length of stay greater than 24 h.
- Patients taking more than two medications.

Exclusion criteria

- Patients whose stay was less than 24 h.
- Patients on other system of medications like Ayurveda, Sidha, Unani.

- Patients with psychiatric conditions and pregnant women.

The potential drug-drug interactions were identified by using Clinirex software. This software briefly indicates the clinical relevance of the interaction, whether the interaction has been well established in the literature if so gives the literature citations. The interactions observed were classified into minor, moderate and major according to severity scale which was obtained from the drug-drug interactions database system. Frequencies with percentage were used to summarize gender, age group, type of stroke, number of drugs prescribed, number of prescriptions with and without drug-drug interactions, type of drug-drug interactions based on severity and mechanism, co-morbidities associated with stroke patients, drug classes and potential drug-drug interactions.

RESULTS

A total of 177 prescriptions were analyzed, out of which 63.8% were male patients and 36.2% were female patients. Most of patients with stroke were seen in the age group of 41-70 (67.7%) years old. 94.9% of prescription had more than 5 drugs, which mainly developed a higher number of drug-drug interactions. Incidence of Ischemic Stroke (83.7%) was greater when compared to the hemorrhagic stroke (16.3%) as given in table 1. All the prescriptions were analysed; it was found that 79% prescriptions were confirmed with least of one drug-drug interaction as shown in fig. 1. Based on severity scale of DDIs, there were 12% major, 71% moderate and 17% minor interactions as shown in fig. 2. Among these, pharmacodynamics interactions were 68% and the pharmacokinetic were 32% as shown in fig. 3. The most common co-morbidity associated with stroke was hypertension (65%), followed by diabetes mellitus (44%), and coronary artery disease (10%). The least were asthma (2%) and Parkinson's disease (2%), thyroid disorders (5%), seizure disorders (3%) etc. which is shown in fig. 4. The most common drug classes prescribed were the cerebral activators (11.72%), antacids (9.25%), anti-platelet drugs (8.84%), lipid lowering agents (8.63%) and multivitamins (8.22%) as shown in fig. 5. On the basis of severity, some of the major drug-drug interactions which were seen in the prescriptions are mentioned in table 2.

Table 1: Demographic data of stroke patients

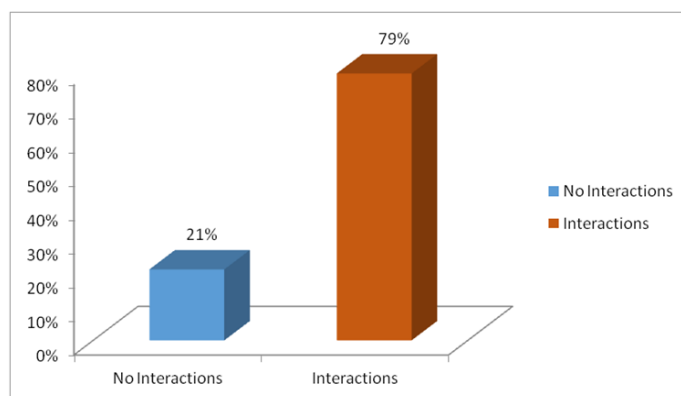| Parameter	Total number of patients (n=177)	Percentage of patients
Gender wise distribution		
Male	113	63.8%
Female	64	36.2%
Age wise distribution		
21-40 y	24	13.5%
41-70 y	120	67.7%
71-90 y	33	18.8%
Number of drugs per Prescription		
>5 drugs	9	5.1%
6-10 drugs	107	60.4%
<10 drugs	61	34.5%
Type of stroke		
Haemorrhagic stroke	29	16.3%
Ischemic stroke	148	83.7%

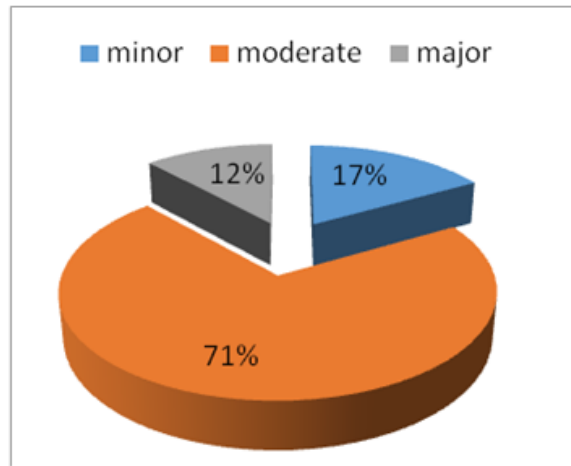**Fig. 1: Percentage of prescriptions with and without interactions**

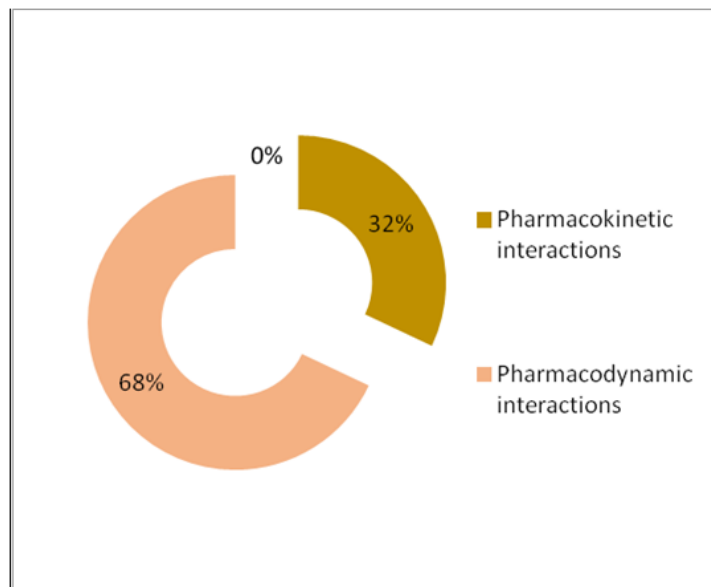**Fig. 2: Type of interactions based on severity**
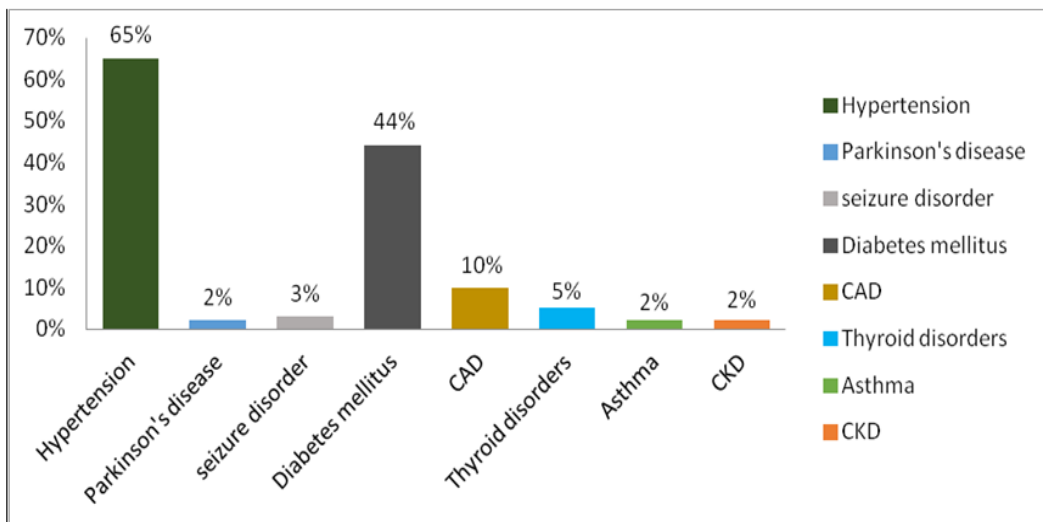

Fig. 3 Type of interactions based on mechanism

Fig. 4: Co-morbidities associated with stroke patients (n=177)

Table 2 Major drug-drug interactions

Objective drug	Precipitant drug	Clinical consequences
Ondansetron	Nortriptyline	Serotonin syndrome
Aspirin	Enoxaparin	↑ risk of bleeding
Clopidogrel	Pioglitazone	↑ risk of hypoglycemia
Linezolid	Tramadol	Serotonin syndrome
Ondansetron	Ivabradine	↑ risk of arrhythmias
Ondansetron	Tramadol	Serotonin syndrome
Atorvastatin	Clarithromycin	↑ risk of liver damage
Enoxaparin	Clopidogrel	↑ risk of bleeding
Clonidine	Metoprolol	Lowers the blood pressure and slows the heart rate
Ondansetron	Fentanyl	Serotonin syndrome
Amiodarone	Torsemide	↑ risk of irregular heart rhythm
Naproxen	Enoxaparin	↑ risk of bleeding
Potassium Chloride	Meclizine	Ulcers, bleeding, and other gastrointestinal injury
Diclofenac	Enoxaparin	↑ risk of bleeding
Clarithromycin	Ivabradine	Slowing of heart rate
Spironolactone	Perindopril	Hyperkalemia
Ondansetron	Amiodarone	↑ risk of irregular heart rhythm
Amiodarone	Fentanyl	Slows heart rate
Nortriptyline	Potassium Chloride	Ulcers, bleeding, and other gastrointestinal injury
Nortriptyline	Tramadol	Cause seizures

DISCUSSION

In this study 177 prescriptions of stroke patients were included. Out of 177 prescriptions, 63.8% were male and 36.2% were female. The occurrence of stroke was more in men than women. This was similar to the study conducted by Jeyaraj DP in which the incidence rate of stroke was higher in male than female [12].

Stroke patients belonged to the age group of 41-70 y were more common than other age groups. The majority of the patients were adults since aging is an important risk factor for the occurrence of many diseases. The results of this study correspond to the result of the study conducted by Eric R *et al.* Reports are there which says that drug-drug interactions are common in elderly people who are on multiple drug regimens [13].

The potential drug interaction risk increases from 39% to 100% when more than six drugs were administered to patients compared to when 2-3 drugs were administered [14]. Usually elderly patients take more than one medication that is not medically required [15]. However, multiple drugs are required for treatment, to slow down the disease progression, to prevent its complications and to reduce the symptoms of the disease, thereby improving the quality of life in elderly patients.

Polypharmacy plays a major role in the occurrence of drug-drug interaction. Polypharmacy was observed in the prescription of stroke patients, where the highest number of drugs was 6-10 which was prescribed in 60.4% of prescriptions, followed by more than 10 drugs prescribed in 34.5%. The least number of drugs were 1-5 which were prescribed in 5.1% of prescriptions. The data of this study was in accordance to a drug-drug interaction study carried out by Vijayakumar S *et al.* [16].

According to our study, out of 177 stroke patients the prevalence of ischemic stroke was higher (83.7%) than haemorrhagic stroke (16.3%). This was similar to a study conducted by Sridharan SE *et al.* [17].

Out of 177 prescriptions, the number of prescriptions without interactions was 21% and the prescriptions with interactions were 79%. Severity assessment of the types of interaction was done. The highest of the interactions observed were moderate (71%), followed by minor (17%) and the least were major interactions (12%) and the findings of this data were similar to a study conducted by Mateti UV *et al.* [18].

In our study, we found that most of the potential drug interactions were pharmacodynamic (68%) in nature followed by pharmacokinetic interactions (32%). This was in contrast to a study conducted by Venkateswaramurthy *et al.* where the pharmacokinetic interactions (54%) were higher compared to pharmacodynamic interactions (46%) [19].

The most common co morbidity associated with stroke was hypertension (65%), followed by diabetes mellitus (44%), and coronary artery disease (10%). The least were asthma (2%), Parkinson's disease (2%), thyroid disorders (5%), seizure disorders (3%) etc. This was similar to a study conducted by Kumari IN *et al.* [20]. Patient with more than 5 drug interactions had higher number of co-morbidities when compared to patients with less than 5 drug interaction.

Here most of the interaction combinations like aspirin/enoxaparin, enoxaparin/clopidogrel, naproxen/enoxaparin, diclofenac/enoxaparin might increase risk of bleeding. This is similar to a study conducted by Phillips WS *et al.* [21]. Other combination such as ondansetron/ivabradine, amiodarone/torsemide, ondansetron/amiodaronecan increases the risk of irregular heart rhythm, clarithromycin/ivabradine, amiodarone/fentanyl and metoprolol/clonidine might increase risk of decrease heart rate. Most of the minor interactions were observed as one drug diminishing the effects of the other drug and also affecting the absorption, metabolism and eventually bioavailability.

Apart from prescribed medication, patients may also consume non-prescription medications, further adding to the risk of drug interactions. These interactions can increase the therapeutic effects in patients which cause toxicity or can cause therapeutic failure by antagonizing the potentials of other drugs [22].

The ultimate outcome of these interactions may increase the cost and decrease patients' compliance to the therapy; it may also increase the incidence of mortality and morbidity. Therefore, medications should be used carefully and strict monitoring is required to avoid drug-drug interactions.

CONCLUSION

Stroke is a leading cause of morbidity and disability throughout the world. Therefore, the prevention of stroke is of great importance for improving public health. Our study focused on the potential drug-drug interactions which were high in stroke patients above 40 y. The incidence of potential drug-drug interactions was 79%. It was predominant in males (63.8%). Polypharmacy and age of the patient were the predictors of drug-drug interactions. The DDIs resulted in increase in hospital stay and higher health-care cost. The majority of interactions were pharmacodynamic in nature, having moderate severity.

Hence, the physicians should be aware of drug-drug interactions while prescribing for stroke patients and thorough monitoring

should be required for the patient safety by the implementation of admonitory guidelines and computer-based screening, which may help in preventing and decreasing the frequency of potentially harmful drug-drug interactions.

AUTHORS CONTRIBUTIONS

All the authors had contributed equally.

CONFLICT OF INTERESTS

There is no possible conflict of interest related to this article was reported.

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