

ASSESSMENT OF POTENTIAL DRUG-DRUG INTERACTION IN STROKE PATIENTS

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Received: 04 Jul 2016 Revised and Accepted: 05 Oct 2016

ABSTRACT

Objective: To assess the incidence and pattern of potential drug-drug interaction (pDDI) in hospitalized stroke patients.

Methods: A retrospective study was carried out in a medical record from a tertiary care teaching hospital for a 4 mo period from November 2015-February 2016. The total of 200 prescriptions was analyzed during the study period.

Results: A significant proportion of patients with pDDIs were males (61.5%) followed by females (38.5%). Among the 200 prescriptions, 179(89.5%) were confirmed with minimum one potential drug-drug interaction. Moreover, patients prescribed with more than 5 drugs developed a higher number of interactions. Based on severity scale, there were 125 major, 375 moderate and 128 minor interactions were observed. The pharmacodynamic interactions were 286 while the pharmacokinetic were 342.

Conclusion: The study highlighted the pDDIs which were high in stroke patients greater than 40 y. pDDIs in prescriptions contained multi-drug therapy is a major concern as such interaction may lead to increased risk of hospitalization and higher health care cost. The majority of interactions were pharmacokinetic in nature, having moderate severity. In this study pDDIs mainly occurred between antihypertensive, anticoagulants and antiplatelet.

Keywords: Stroke, Potential drug-drug interactions, Prescriptions, Pharmacokinetic and pharmacodynamic

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DOI: <http://dx.doi.org/10.22159/ijpps.2016v8i12.13878>

INTRODUCTION

Presently, drug therapy is growing more complex; as a result, making an appropriate decision on drug therapy is increasingly challenging. Drug-drug interactions (DDIs) are defined as two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered on the administration of the other. A drug interaction is the quantitative or qualitative modification of the effect of a drug by the simultaneous or successive administration of a different one [1]. Cardiovascular diseases account major part of all morbidities and mortalities worldwide. It has been predicted that by the year 2020, the worldwide cardiovascular diseases burden will be amplified by almost 75% [2]. Hypertension is directly accountable for 57% of all stroke and 24% of all coronary heart disease mortalities in India [3]. The WHO clinically defines a stroke as the rapid development of clinical signs and symptoms of a focal neurological disturbance lasting more than 24 h or leading to death with no apparent cause other than vascular origin [4]. Stroke may cause serious disabilities, where stroke mortality rates are declining or stabilizing in developed countries, experts are concerned of the emerging stroke epidemic in India [5].

Whenever 2 or more drugs are taken concurrently, there is a chance that there will be an interaction between the drugs. The likelihood of the drug interactions increases as the number of drugs which are taken by patient increases. The factors which are significantly associated with having 1 or more potential interactions include: taking 5 or more medicines, patient age of 60 y or older and those suffering from cardiovascular diseases [6].

The mechanism of interaction can be important in predicting the time course of interaction, and provides a way to minimize the risk of an adverse outcome [7]. Even though DDIs are considered as preventable medication-related problems, studies found that up to 11% of patients experience symptoms associated with DDI and these are responsible for nearly 2.8% of hospital admissions [8]. Monitoring of DDIs may improve the quality of prescribing and dispensing, and it might form a basis for education focused on appropriate prescribing [9].

Drug-Drug Interactions (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 [8]. Hence, as they are an important hazard to the health of millions of patients, drug-drug interactions have to be tackled and it is the need of the hour.

Micromedex Drug Reax[®] is an interactive drug interactions program that allows clinicians to check for interacting drug ingredients, their effects, and clinical significance. It classifies interactions as minor, moderate and major. It provides drug-drug (including additive adverse effects), drug-food, drug-disease, drug-ethanol, drug-tobacco, drug-alternative medicine, and drug-laboratory interactions, 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 [10].

This retrospective drug-drug interaction analysis study will be helpful to improve current prescription pattern, minimize drug-drug interaction and improve pharmaceutical care practices. The present study was designed to assess the incidence and pattern of pDDIs in hospitalized stroke patients in a tertiary care hospital, which is high among stroke patients prescribed with antihypertensive, antiplatelets, and anticoagulants.

MATERIALS AND METHODS

A retrospective study was carried out for a period of 4 mo (November 2015-February 2016) in a tertiary care teaching hospital. Approval from the Institutional Ethical Committee and hospital authority was obtained prior to the study. Prescriptions of 200 stroke patients admitted consecutively to inpatient wards of a tertiary care hospital were analyzed during this study.

Prescriptions with two or more drugs prescribed during the hospitalization were only selected for the study. The study population comprised all patients aged 30 y or older admitted to the hospital and had a length of stay greater than 24 h. Stroke patients with other comorbidities were included and patients with psychiatric conditions and pregnant women were excluded from the study.

The prescriptions of stroke patients were screened for pDDI using computerized database system Micromedex. This computer program describes all potential interactions and states whether the information is available on specific drugs within a class of drugs. It also briefly indicates the clinical relevance of the interaction, whether the interaction has been well established in the literature and gives literature citations [11]. Certain demographic characteristics, such as gender, age, social habits, prescription pattern and type of stroke were studied based on inclusion and exclusion criteria. The interactions observed were classified into mild, moderate and severe according to severity scale which was obtained from the DDI database system. Frequencies with percentage were used to summarize sex, a number of drugs dispensed, the frequency of pDDIs and severity of pDDIs.

RESULTS

The total of 200 prescriptions for stroke patients was included in the study. A significant proportion of prescription with pDDI was occupied by males (61.5%) followed by females (38.5%) in table 1. Most of the stroke patients were in between the age ranges 41-70 y (77.5%). About 90% of the patients were a smoker, 77.5% were alcoholic, and 21.5% were betel nut chewed. Prescription with more than 5 drugs (87.5%) developed a higher number of pDDI. Among them, Ischemic stroke was 190(95%), followed by hemorrhagic stroke 10(4%). All the prescriptions were analyzed during the study period, and it was found that 179 (89.5%) prescriptions were confirmed with least of one pDDI. The most common drug classes (fig. 1) involved in pDDI were the aspirin-94(47%), clopidogrel-

124(62%), anti-hypertensive drugs 143(72%) and statins 117(59%). Based on severity scale there was 125(20%) major, 375(60%) moderate and 128(20%) minor interactions (fig. 2). Among these, pharmacodynamics interactions were 286(46%) and the pharmacokinetic were 342(54%) in fig. 3. In table 2, clopidogrel was most interacting drug with objective drugs which may produce serious consequences.

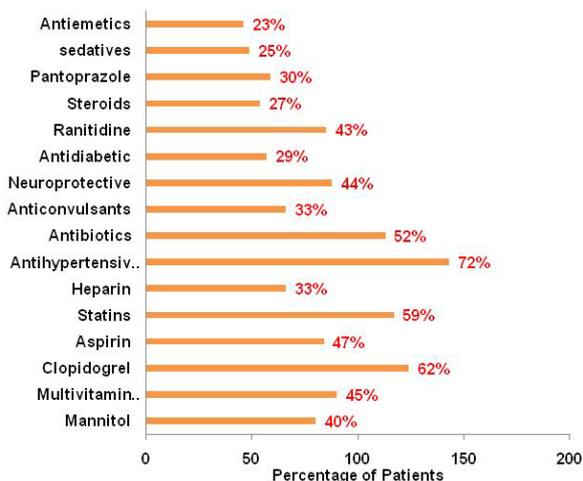


Fig. 1: Drug utilization pattern

Table 1: Demographic profile of stroke patients

Parameter	Total no of patients (n= 200)	Percentage of patients
Gender wise distribution		
Male	123	61.5%
Female	77	38.5%
Age Wise Distribution		
30-40 y	2	1%
41-70 y	155	77.5%
71-90 y	43	21.5%
Social habits		
Smoker	180	90%
Alcoholic	155	77.5%
Betel nut	43	21.5%
No. of drugs in Prescription		
>5 drugs	175	87.5%
<5 drugs	25	12.5%
Type of Stroke		
Haemorrhagic stroke	8	4%
Ischemic stroke	190	95%
Transient Ischemic Attack (TIA)	2	1%

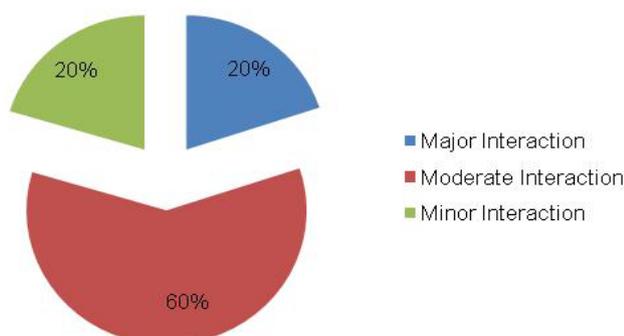


Fig. 2: Type of pDDI based on severity scale

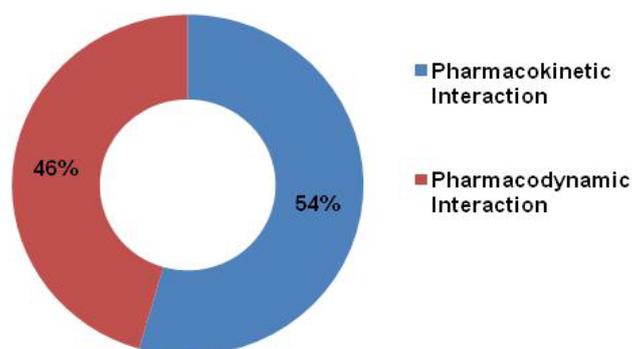


Fig. 3: Type of interactions found from database

Table 2: Clinically important pDDIs from the prescribed drugs using database

Objective drug	Precipitant drug	Clinical consequences
Amlodipine	Clopidogrel	↑ risk of thrombotic events
Aspirin	Clopidogrel	↑ risk of bleeding
Amlodipine	Aspirin	↑ risk of GIT hemorrhage
Clopidogrel	Phenytoin	Hyperreflexia, ataxia, nystagmus, tremor
Atorvastatin	Clopidogrel	High platelet reactivity
Enalapril	Furosemide	Postural hypotension
Heparin	Clopidogrel	Increased risk of bleeding
Clonidine	Bisoprolol	Sinus Bradycardia
Furosemide	Amikacin	Ototoxicity and nephrotoxicity
Amlodipine	Labetalol	Bradycardia
Amlodipine	Domperidone	↑ risk of QT prolongation
Aspirin	Insulin	↑ risk of hypoglycemia
Phenytoin	Paracetamol	Hepatotoxicity
Alteplase	Clopidogrel	↑ risk of bleeding

DISCUSSION

This study revealed the overall incidence of pDDIs among stroke patients. A total of 200 prescriptions of stroke patients were included in the study. Out of 200 stroke patients, 51.5% were male and 38.5% were female. The occurrence of stroke was more in men than women because the secondary factors like high blood pressure and vasoconstriction are more common in men, on the other hand, estrogen helps in the health of brain capillaries in women thereby lowering the risk of stroke [12]. Stroke patients with age group of 41-70 y were more common than another age group. The majority of the study population were adults since aging is a risk factor for the occurrence of stroke. It may be due to the change in the drug metabolism after the age of 45 y. This corresponds to the result of other studies reporting that DDIs are common in elderly people who are on multiple drug regimens [13, 14].

Smoking, alcoholism, and tobacco use are some root causes for the occurrence of stroke which is also proven in our study. Jeyaraj *et al.* [12] conducted a study on stroke epidemiology and stroke care services in India which coincides with the demographic data in our study. Patients prescribed with greater than 5 drugs are responsible for a higher number of pDDIs. Since polypharmacy is a major depending factor for the development of drug interactions. Our finding complies with the data of drug-drug interaction study carried out in a tertiary care hospital by another author [14]. Out of 200 patients, ischemic stroke patients were higher than hemorrhagic stroke. Sridharan *et al.* [15] also conducted a study which states almost similar finding related to the type of stroke as in our study.

It was also observed in this study that use of multiple medications was associated with significantly increased risk of being prescribed with the potentially harmful drug-drug combination. Polypharmacy had been a major factor for the development of drug-drug interactions which agreed with the study conducted by Sridharan *et al.* [15].

From this data, anticoagulants, antiplatelets, statins and anti-hypertensive were more administered in ischemic stroke for the lysis of clot that occludes the cerebral artery while in hemorrhagic stroke surgical interventions are mainly the primary step undertaken. This result complies with the assessment of drug-related problems carried out among stroke patients by Celin *et al.* [16].

On account of the severity assessment of the reactions, the majority of the reactions were categorized as moderate in nature, followed by minor and major/severity and these findings were same with a previous study [17].

In our study, most of the potential drug interactions were pharmacokinetic (54%) in nature followed by pharmacodynamic interactions (46%). These were correlated with the studies conducted by Sivva *et al.* [18].

Most of the interacting combinations in present study like aspirin/heparin, clopidogrel/heparin, clopidogrel/aspirin, alteplase/clopidogrel, and amlodipine/aspirin might increase the risk of

bleeding. This result correlates with the results of similar studies [19]. The results showed that during concomitant administration of clopidogrel and aspirin at therapeutic doses, pDDIs might occur; therefore the dosage adjustment is needed for the patient. Concurrent use of many drugs and frequent addition of new drug makes this group of patient vulnerable to pDDIs. These interactions have a different effect upon the patients it either increase the therapeutic effects which are may cause toxicity or antagonize the potentials of other drugs, which directly lead to therapeutic failure [20]. The ultimate consequences of these interactions may increase the cost and decrease patients' compliance to therapy; it may also increase the incidence of mortality and morbidity.

Limitation of this study is its short duration without any intervention component. Further prospective studies are needed for the observation, identification and management of DDIs and its adverse drug reactions among the stroke patients.

CONCLUSION

The study highlighted the pDDIs which were high in stroke patients greater than 40 y. pDDIs in prescriptions contained multi-drug therapy is a major concern as such interaction may lead to increased risk of hospitalization and higher health care cost. The majority of interactions were pharmacokinetic in nature, having moderate severity. In this study pDDIs mainly occurred between anti-hypertensives, anticoagulants and antiplatelet.

The physicians should be aware of interactions among those drugs 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 might help to prevent potentially harmful drug interactions.

ACKNOWLEDGEMENT

I wish to thank my management, head of the institution, colleagues, and coworkers in the department of pharmacy practice for their support in the execution of this project work.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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How to cite this article

- Venkateswaramurthy N, Krishnaveni K, Mercy Freeda R, Sambath Kumar R. Assessment of potential drug-drug interaction in stroke patients. *Int J Pharm Pharm Sci* 2016;8(12):221-224.