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Full Length Research Paper

Drug-drug interaction occurring during hospital stay among stroke patients

Subash Vijayakumar*, Ravi kanth S, Ayesha Siddiqua and Dheeraj Kumar G

Department of Pharmacy Practice, Vaagdevi College of Pharmacy, MGM Hospital, Warangal, Andhra Pradesh, India.

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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. DDI in patients receiving multiple drug therapy is a major concern. Such interactions may lead to an increased risk of hospitalization and higher health care costs. The present study was designed to assess the incidence and pattern of DDIs in hospitalized stroke patients in a tertiary care hospital. A prospective observational study was carried out for a period of 11 months (October 2010 to August 2011) in a tertiary care teaching hospital. A total of 290 prescriptions were analyzed during the study period and it was found that 115(53.4%) patients were confirmed with minimum of one DDI. A significant proportion of patients with DDIs were males 81 (70.4%). Patients with age group of >51 years had 37(32%) DDIs, and was followed by other age groups. Moreover, 62(54%) patients prescribed with more than 5 drugs developed higher number of DDIs. Some of the most common drug classes involved in DDIs in our study were anti-platelets, antihypertensive and antihyperlipidemic drugs. Among these drugs, clopidogrel and amlodipine, and clopidogrel and phenytoin were common. Our study highlights the drug-drug interactions, which is high among stroke patients prescribed with antihypertensive drug with clopidogrel in a tertiary care teaching hospital. Hence physicians should be aware of interactions among those drugs while prescribing and careful monitoring is required. However, further studies are needed to investigate the effect of individual antihypertensive drug interacting with clopidogrel.

Key words: Stroke, drug-drug interactions (ddis), gender, prescriptions, hospital, drugs.

INTRODUCTION

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 (Peterson and Bates, 2001). DDI in patients receiving multiple drug therapy is a major concern as such interactions may lead to an increased risk of hospitalization and higher health care costs (Hamilton et al., 1998). The incidence of actual occurrence of drug interactions have been disability and has enormous socio-economic impact on patients, their family and health service. Well established studies have reported cases ranging from 0 to 1.3% (Kurfees et al., 1987; Ho et al., 2002). Some studies have found that up to 11% of the patients experiencing symptoms associated with DDIs are responsible for up to 2.8% of hospital admissions (Grymonpre et al., 1988; Jankel et al., 1990). Research has also shown that DDIs are associated with increased health care use (Jankel et al., 1994).

According to recently published study, aspirin has been prescribed for the primary prevention of cardiovascular events in low risk patients because of a small risk for gastrointestinal bleeding and hemorrhagic stroke. Additionally, specific cyclooxygenase (COX)-2 inhibitors (coxibs) have become attractive anti-inflammatory drug alternatives to aspirin, a COX-1 inhibitor because they cause less gastrointestinal bleeding, although they may not be as effective in preventing thrombotic events. Now, aspirin resistance has been described and has been defined either as the failure of aspirin to prevent individuals from clinical thrombotic complications or as the failure to produce an expected response on a laboratory measurement of platelet activation or aggregation. Potential drug–drug interactions have also

*Corresponding author. E-mail: vijayvijay66@yahoo.co.in.

Table 1. Patient Characteristics of drug interaction of stroke prescriptions.

Patient Characteristics	Number (%) of ADRs	Standard deviation	Confidence interval
Gender group			
Male	81 (70.4%)	13.0	2.8
Female	34 (29.5%)	13.7	4.6
Age (years)			
18-30	5 (4.3%)	2.7	2.3
31-40	14 (12.7%)	3.10	1.6
41-50	29 (25.2%)	2.4	0.8
51-60	37 (32.1%)	2.4	0.7
61-70	26 (22.6%)	2.5	0.9
71-80	4 (3.4%)	2.8	3.2
No. of drugs taken with interactions			
<5 (less than 5)	53	0.7	0.1
>5 (more than 5)	62	1.0	0.2

been described with aspirin. Aspirin inhibits the synthesis of vasodilating prostaglandins. Whereas angiotensin converting enzyme inhibitors (ACEI) increase prostaglandin production by inhibiting the breakdown of bradykinin. Co-administration could reduce the prostaglandin mediated decrease in arterial pressure associated with ACEI and potentiate depression of renal function by decreasing synthesis of renal vasodilatory prostaglandins, resulting in increased sodium and water retention (Eric and Bates, 2003).

A potential drug–drug interaction between aspirin and ibuprofen has also been noted and associated with increased mortality risk in one retrospective study. Ibuprofen seems to inhibit the access of aspirin to the acetylation site in platelet COX-1, antagonizing irreversible platelet inhibition. Clopidogrel, a thienopyridine, is a platelet ADP receptor inhibitor. Like aspirin, it reduces cardiovascular events and appears to have added benefit, when given with aspirin as dual anti-platelet therapy in patients with acute coronary syndromes or undergoing percutaneous coronary intervention (PCI). Hence, the present study was designed to assess the incidence and pattern of DDIs in hospitalized stroke patients in a tertiary care hospital.

MATERIALS AND METHODS

Study design, population and data collection

A prospective observational study was carried out for a period of 11 months (October 2010 - August 2011) in a tertiary care teaching hospital with prior approval from the Human Ethics Committee (HEC/19/2010). Patients admitted consecutively to inpatient wards of a tertiary care hospital, aged 18 years or older, and who had a length of hospital stay >24 hours were included in the study. Demographic information (age and gender), number of drugs prescribed, length of hospital stay, main diagnosis (ICD-10) and the number of additional diagnoses and laboratory investigations made were obtained from the clinical records. Patients with prescriptions of two or more prescribed drugs during the hospitalization were only selected and were screened for DDIs using computerized DDI database system (Micromedex 2011). For determining the adverse drug reactions (ADRs), both the medications added and as well as discontinued were considered. All drugs were classified as per Anatomical Therapeutic Chemical Classification (ATC code, level one) (Micromedex 2011). Certain demographic characteristics, such as patient characteristics (gender, age (more than 18 years old), concurrent morbidities and length of stay), drug characteristic (number of drugs) and laboratory investigations [International Normalized Ratio (INR), bleeding time, serum creatinine and serum potassium level] were studied to find out the predictors of DDIs.

To classify the causality of the hospital admission to the drug, the Naranjo algorithm was used. Values obtained from this algorithm are sometimes used in peer reviews to verify the validity of author's conclusions regarding ADRs (Naranjo et al., 1991). The interactions observed were classified into mild, moderate and severe according to severity and undesirable effects. The data on severity was obtained from the DDI data of the drug database. A statistical analysis was performed using Graph pad prism version. 5.0.

RESULTS

Patients, drug characteristics and DDIs

A total of 290 stroke patients were included in the study, and among them Ischemic stroke were 198 (68.2%), followed by hemorrhagic stroke 92 (31.8%). All the patient prescriptions were analyzed during the study period and it was found that 115 (39.6) patients were confirmed with minimum of one DDI. A significant proportion of patients with DDIs are occupied by males 81 (70.4%). Patients with age group of >51 years had 37(32%) DDIs, and was followed by other age groups. 62(54%) Patients prescribed with more than 5 drugs developed higher number of DDIs. The patient characteristics and statistical significance of the results are summarized in Table 1. In total, 67 (58.26%) patients

Table 2. Clinically important DDIs among the prescribed drugs.

Objective drug	Precipitant drug (n, %)	Clinical consequences
Amlodipine	Clopidogrel (5, 3.4%)	Decreased response of clopidogrel
	Clopidogrel (4, 2.7%)	Decreased response of clopidogrel
Nimodipine	Aspirin (5, 3.4%)	Gastro intestinal hemorrhage and /or antagonism of hypotensive effect
Propranolol	Diclofenac (3, 2.0%)	Blunting of the diuretic and antihypertensive efficacy
Enalapril	Furosemide (6, 4.1%)	Postural hypertension (first dose)
	Aspirin (7, 4.8%)	Decreased effect of enalapril
Atorvastatin	Phenytoin (9, 6.2%)	Decreased atorvastatin plasma concentration and efficacy
Aspirin	Furosemide (2, 1.3%)	Blunting of the diuretic and antihypertensive efficacy
	Ranitidine (17, 11.7%)	Reduced salicylate plasma levels; decreased anti-platelet effect of aspirin
	Insulin (3, 2.0%)	Hypoglycemia (CNS depressant, seizures)
Clopidogrel	Phenytoin (5, 3.4%)	Ataxia, hyperreflexia, nystagmus, tremor
	Omeprazole (4, 2.7%)	Reduction in clinical efficacy, thrombosis
	Aspirin (2, 1.3%)	Bleeding
Spironolactone	Aspirin (2, 1.3%)	Decreased spironolactone effectiveness
Insulin	Alcohol (3, 2.0%)	Hypoglycemia
Metformin	Ranitidine (5, 3.4%)	Increase in metformin plasma concentrations
	Enalapril (3, 2.0%)	Hyperkalemic lactic acidosis
Phenytoin	Ranitidine (22, 15.1%)	Increased phenytoin concentrations
	Paracetamol (3, 2.0%)	Hepatotoxicity
Diazepam	Ranitidine (12, 8.2%)	Sedation
	Phenytoin (14, 9.6%)	Increase in serum phenytoin concentrations
	Alcohol (2, 1.3%)	Aggression, anxiety or amnesia
Omeprazole	Cyanocobalamin (1, 0.6%)	Decreased cyanocobalamin absorption
Ampicillin	Pantoprazole (5, 3.4%)	Loss of ampicillin efficacy
Ranitidine	Diclofenac (2, 1.3%)	
Ciprofloxacin	Ondasetron (1, 0.6%)	Increased risk of QT interval prolongation

who stayed for 4 days developed DDIs more frequently than other groups. The most common drug classes involved in DDIs were the anti-platelets 33 (22.75%) and anti-hypertensive drugs 28 (19.3%) and statins 9 (6.20%). Among these, clopidogrel and amlodipine, clopidogrel and phenytoin were common clinically important DDIs among the prescribed drugs as summarized in Table 2. The data evaluated for the specific systems affected by DDIs are summarized in Table 3.

Causality and severity of DDIs

All the DDIs were assessed to have the "probable" causality using the Naranjo algorithm. The interacting drugs were withdrawn in 102 cases (88.69%) and dose was altered in 13 cases (11.38%). Meanwhile, 94 (81.73%) patients improved after withdrawal of interacting drugs. Upon causality assessment, majority of the DDI reports were rated as probable 64 (55.67%), followed by possible rating for 38 (33.04%) reports. These DDIs were assessed for severity in which 63 cases (54.78%) were classified as moderate, followed by 28 severe cases (24.34%) and 24 mild cases (20.86%).

DISCUSSION

This study revealed that the overall incidence rate of

Table 3. Effect of organ affected by the DDIs.

Organ	Complication of DDIs	Number (%)
Central Nervous System Disorder	Sedation, Aggression, Anxiety or Amnesia, Nystagmus	75 (51.6%)
Heart	Hyperkalemia, QT interval Prolongation	17 (11.6%)
Whole body general disorders	Hyperreflexia, decreased absorption, efficacy, weakness	34 (23.3%)
Bleeding and clotting disorders	Bleeding	2 (1.3%)
Liver	Hepatoxicity	3 (2.0%)
GI	GI hemorrhage, antagonism of hypotensive effect	5 (3.4%)
Kidney	Nephrotoxic	9 (6.2%)

clinically important DDIs is different from the incidence rate compared with another study published from the setting on potential DDIs in cardiology department (Mateti et al., 2010). This study focused on the incidence of actual DDIs compared to the reported study on potential DDIs, which was about the possible DDIs that may arise out of the given combination (Patel et al., 2011). Findings of the present study showed that the patterns of incidence of DDIs are positively associated with patient's age, gender, number of drugs prescribed and length of hospital stay. A higher rate of DDIs was present in elderly patients. This corresponds to result of other studies reporting that DDIs are common in elderly people who are on multiple drug regimens (Bjorkman et al., 2002; Kohler et al., 2000). Concurrent use of many drugs and frequent addition of new drug makes this group of patient vulnerable to DDIs. The results showed that during concomitant administration of clopidogrel and aspirin at therapeutic doses, DDIs occur; therefore the dosage adjustment is needed for the patient. These results were in accordance with the observation of reported studies (Mateti et al., 2011).

Meanwhile, some of these drug combinations are used for therapeutic benefit in clinical practice and other are introduced internationally despite the increased risk of DDIs. The patient characteristics were identified as the risk factors for developing DDIs, consistent with previous research. It was also observed in this study that use of multiple medications was associated with significantly increased risk of being prescribed with potentially harmful drug-drug combination. In fact the odds of prescribing potentially interacting drug more than doubled for each additional medication prescribed, after controlling as reported in previous studies (Nightingale et al., 2000) with regards to management approach for DDIs. Drug withdrawal or dose reduction is usually the first step to be employed for the management of DDIs.

On causality assessment of DDIS using the Naranjo algorithm, DDIs were confirmed to have the probable causality. Considering the severity assessment of the reactions, majority of the reactions were categorized as moderate in nature, followed by severe and mild severity and these finding are same/different when compared with the reports of spontaneous studies (Nightingale et al., 2000). The usefulness of computerized screening depends on the quality, including proper validation of a data held in the software; furthermore, updating such systems requires knowledge, judgments and continuous effort by specialist maintaining the DI database.

Conclusion

From a pharmacologic perspective, drug-drug interactions are real with uncertain clinical implications. Therefore, our study highlights the drug-drug interactions, which is high among stroke patients prescribed with antihypertensive drug with clopidogrel in a tertiary care teaching hospital. It is recommended that physicians should be aware of interactions among those drugs while prescribing, and careful monitoring is also required. However, further studies are needed to investigate the effect of individual antihypertensive drug interacting with clopidogrel.

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