Prospective Monitoring and Reporting of Adverse Drug Reactions associated with Antiplatelet and Antiepileptic Drugs in a South Indian Tertiary Care Teaching Hospital

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A prospective monitoring of adverse drug reactions associated with antiplatelet and antiepileptic drugs was carried out in a tertiary care teaching hospital. Patients diagnosed with Acute Coronary Syndrome (ACS) or ischemic stroke receiving antiplatelet drugs (Aspirin and Clopidogrel) and epileptic patients receiving antiepileptic drugs were followed for a period of six months prospectively at a tertiary care teaching hospital. WHO probability scale and Naranjo's algorithm, Modified Hartwig and Seigel scale, and Modified Shumock and Thornton scales were applied to assess the causality, severity and preventability of the reported ADRs. At the end of the study period, 15 ADRs were observed with Aspirin and 14 ADRs were observed with Clopidogrel in antiplatelet agents' class and 24 ADRs with Phenytoin and 12 ADRs with Valproic acid in antiepileptic agents' class. Among the antiplatelet agents, 82.75% of ADR's were found probable and 37.93% ADRs were possible. In antiepileptic drug class, 73.33% ADRs were found probable. In assessment of severity level, 6 ADRs were found in severity level 1 and 20 ADRs were in level 3 in severity in antiplatelet agents class and in antiepileptic drugs class 9 ADRs were found in level 1 and 23 ADRs were found level 2 severity, and 15 ADRs were found preventable in anti epileptic agents. Medications were discontinued in 14 cases and the dose was adjusted in 10 cases. Phenytoin and Sodium Valproate were found responsible for majority ADRs in Anti epileptic drugs class and Aspirin accounted for more number of ADRs in antiplatelet agents' class.

Keywords: Adverse Drug Reactions, Antiplatelets, Antiepileptic drugs.

INTRODUCTION

World Health Organization defines ADR as a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, and therapy of disease, or for modification of physiological function.[1] Adverse drug reactions (ADRs) occur frequently in modern medical practice due to various pre disposing factors, resulting in increasing the morbidity, mortality and cost of care. Worldwide clinically significant ADRs occur approximately in 20% of hospitalized patients and found to be the fourth leading cause of mortality.[2]

Patients with cardiovascular diseases and epilepsy are particularly vulnerable to ADRs due to their advanced age, polypharmacy, pathophysiology of the disease, age related changes in liver and kidney function and the influence of heart disease on drug metabolism. The ADR potential for a particular drug varies with the individual, the disease being treated, and the extent of exposure to other drugs. Majority of significant ADRs involving cardiovascular drugs are predictable and therefore preventable.[2,3]

Across the world, after the stroke and the dementia, epilepsy constitutes the common neurological condition seen by neurologists in elderly.[4] In India approximately 5.5 million people are suffering from Epilepsy, among them 4.1 million patients resides in rural area and every year half million new patients are added to the existing list.[5] The ultimate goal of the epilepsy treatment is to make the patient free from seizures without adverse effects of medication and improved quality of life. Over 80% of patients may achieve seizurefree state with one suitable antiepileptic medication. But the remaining 20% of patients may require poly therapy for seizure control. Majority antiepileptic agents suppress the pathological neuronal hyper excitability that constitutes the final substrates in many seizure disorders was considered to be responsible for adverse drug reactions. The other drug related problems such as drug interactions also contribute to Adverse Drug Reactions that may add to the economic burden.[6] Assessing and resolving the potential drug related problems such as ADRs will improve the therapeutic outcomes and also helps in improving patients' quality of life.

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METHODS

A prospective observational study was carried out over a period of 6 months from June to December 2009 in a tertiary care teaching hospital in Mysore. All patients who visited as the out-patients and admitted as in-patients in the departments of Neurology and Medicine of JSS Hospital, Mysore with a clinical diagnosis of epilepsy, Acute Coronary Syndrome and Ischemic stroke were enrolled in to the study. The Institutional Ethical Committee of JSS College of Pharmacy, Mysore has approved the study and strict confidentiality was assured for all the collected data.

A suitably designed documentation form was used to collect the demographic details, clinical diagnosis, dose, frequency and dosage form of Anti Epileptic Drug (AED) and antiplatelet agents, tests performed etc. During the study period, the patients were followed up regularly to monitor and report suspected adverse drug reactions (ADRs) using CDSCO ADR notification form. The causality association between the drugs and the reactions were assessed using Naranjo's Algorithm [7] and WHO probability scale [8]. Severity of the ADRs was assessed with the help of Modified Hartwig and Siegel scale [9]. Preventability of the ADRs was assessed by the modified Shumock and Thornton scale [10].

RESULTS

A total of 439 patients with a clinical diagnosis of epileptic seizures and 170 patients with a diagnosis of Acute Coronary Syndrome (ACS) and Ischemic stroke were followed over a period of six months. During the study period, 45 ADRs were detected from 45 epileptic patients with an incidence rate of 10%. Patients with ACS and Ischemic Stroke experienced 29 ADRs with an incidence rate of 17%. Out of 45 patients in the antiepileptic group, 23 patients were male in the age group of 8 years to 60 years and 22 patients were female patients in the age group of 11 years to 40 years. In the antiplatelet agents group 17 patients were male patients, and 12 female patients in the age group of 41 to 70 years.

Phenytoin (23 ADRs) and Valproic acid (13 ADRs) were the drugs responsible for more ADRs in anti epileptic drugs class and Aspirin (15 ADRs) and Clopidogrel (14 ADRs) have contributed for ADRs in antiplatelet agents' class. Details of antiepileptic medications and antiplatelet agents implicated in ADRs are presented in Table. 1.

The organ systems affected predominantly by the ADRs are central nervous system (21) Gastrointestinal (15) and Skin (14). Majority of the reported ADRs belong to level 2 of mild severity in antiepileptic class of drugs and antiplatelet agents caused ADRs belonging to level 3 of moderate severity. Majority ADRs of the study medications were found not preventable. Details of Severity and Preventability are presented in Table.2.

Table :1 Antiplatelet and antiepileptic Medications implicated in ADR

Anti epileptic Medications implicated in ADR	Number of ADRs (n=45)	Percentage (%)
Phenytoin	24	53.33
Valproic acid	12	26.66
Carbamazepine	4	8.88
Phenobarbitone	3	6.66
Divalproex sodium	1	2.22
Levetiracetam	1	2.22
Anti platelet agents implicated in ADR	**Number of ADRs (n=29)**	**Percentage (%)**
Aspirin	15	51.72
Clopidogrel	14	48.27

ADR: Adverse Drug Reaction.

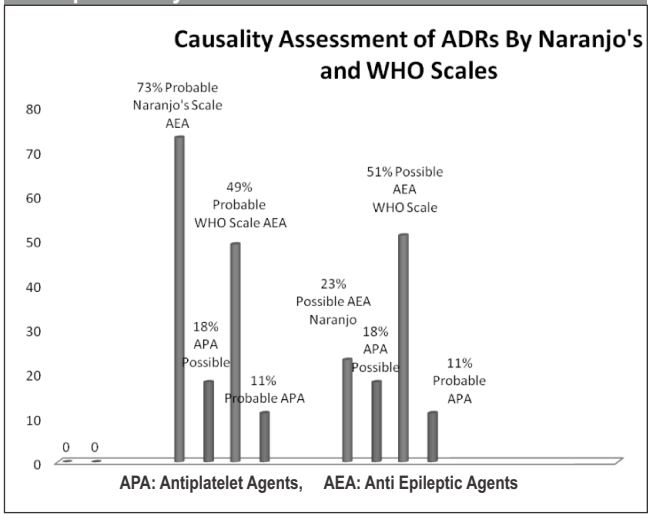
Table 2: Preventability and severity of ADRs

	Antiplatelets	Antiepileptics
PREVENTABILITY		
Probably preventable	14	1
Not preventable	15	44
Definitely preventable	-	-
SEVERITYMILD		
Level 1	6	9
Level 2	-	23
MODERATE	-	-
Level 3	20	10
Level 4(a)	2	3
Level 4(b)	1	-
SEVERE	-	-
Level 5	-	-
Level 6	-	-
Level 7	-	-

The suspected ADRs were also classified using W.H.O preferred terms. Ataxia (Carbamazapine and Phenytoin), somnolence (Divalproate Sodium, Carbamazapine, Phenytoin) dizziness (Carbamazapine, Phenytoin, Divalproate Sodium), tremors (Levitaracetam), euphoria (Phenobarbitone, Divalproate Sodium) rashes (Phenytoin, Clopidogrel), allergic reactions (Phenobarbitone, Phenytoin), gum hyperplasia (Phenytoin), urticaria (Phenytoin and Aspirin), weight increase (Sodium Valproate), gastric ulcer (Gastric Ulcer), rash (Phenytoin, and Clopidogrel), angioedema (Clopidogrel), head ache (clopidogrel), and constipation (Clopidogrel) were the adverse drug reactions reported during the study with the antiepileptic and anti platelet agents.

A patient presented with anticonvulsant hypersensitivity syndrome with the combined use of phenytoin and phenobarbitone. Causality association between drug and reaction was found probable in 73.33% (n=33) on WHO ADR probability scale and 48.88% (n=22) on Naranjo's scale respectively. Among antiplatelet agents, Aspirin was found responsible for 51.72% (n=15) and Clopidogrel was found responsible for 48.27% (n=14) of ADRs. Causality association between drug and reaction was probable in 62.06% (n=18) and 37.93% (n=11) as assessed by using WHO probability scale and Naranjo's algorithm respectively. Causality association of adverse drug reaction with the antiepiletic medications and antiplatelet agents using causlity assesment algorithms is presented in Figure.1.

Fig.1: Causality assessment of ADRs of anti epileptic agents (AEA) and Anti Platelet Agents (APA) using Naranjo's and WHO probability scales



After development of an adverse drug reaction, antiepileptic medications were discontinued in 13 cases and dose was altered in 5 cases. In antiplatelet group, medications were discontinued in one case and dose was altered in 5 cases. Symptomatic treatment was given in 33 cases for ADRs such as rash, urticaria, GI ulcer, and abnormal behaviour and specific treatment such as use of tranexemic acid was given in 11 cases for GI bleed due to aspirin. The ADRs were continued in 38 cases (51.31%) and 26 patients (35.13%) were recovered from ADRs. The details regarding the discontinuation of the medication, symptomatic treatment and outcomes of ADRs are presented in Table.3.

DISCUSSION

Antiplatelet agents have demonstrated effective clinical outcomes in the management of post-acute myocardial infarction (AMI), ischaemic stroke or transient ischaemic attack, and in patients with stable or unstable angina, peripheral arterial occlusive disease or atrial fibrillation and reduce the risk by 25%.[11] The pooled incidence rate of aspirin induced gastro intestinal hemorrage in meta analysis of 14 studies was found as 0.12%[11]. In the present study, the incidence rate was found to be 0.9% which is close to the findings of the meta analysis. Studies have also shown that incidence rate will increase in elderly patients, people with previous history of peptic ulcer disease, and use of coricosteroids and NSAIDs. In a study conducted by Shehab N et al mentioned that the risk of GI bleeding is very high when antiplatelet agents are given in combination as aspirin with clopidogrel.[12] The risk was estimated as 1.2:1000 in individuals receiving dual antiplatelet therapy cautioning the prescribers to be more vigilant.[13] However antiplatelet agents are known to pose risk to the patients by causing gastro intestinal hemorrhage, skin rashes, neutropenia and cholestatic jaundice. [14]

Table 3: Action taken, treatment initiated and outcomes of the reported ADRs

	Anti Epileptic agents		Anti Platelet agents	
	Number (n=45)	Percentage (%)	Number (n=29)	Percentage (%)
Action Taken				
No Change	27	60	23	79.3
Dose Altered	05	11.11	05	17.2
Discontinued	13	28.88	01	3.4
Treatment Initiated				
Specific	10	22.22	01	03.44
Symptomatic	15	33.33	18	62.06
No Treatment	20	44.44	10	34.48
Outcome of ADR				
Continued	21	46.66	17	58.60
Recovered	20	44.44	06	20.70
Unknown	04	08.88	06	20.70

Independent of the Anti Epileptic Drug use profile (either monotherapy or combination therapy) phenytoin (42.14%) was the most frequently prescribed AED followed by valproic acid (39.40%), carbamazepine (25.05%), phenobarbitone (16.62%), clobazam (14.12%) and miscellaneous AEDs include clonazepam, levetiracetam, oxcarbazepine etc (9.69%). In antiplatelet agents group, 83.53% patients received dual antiplatelet therapy that is both Aspirin and Clopidogrel and 16.47% patients received monotherapy.

Number of ADRs involved with Phenytoin was 23 [Gum hyperplasia(9), somnolence(2), asthenia(1), ataxia(2),

rash(3), fixed drug eruptions(1), dizziness(2), insomnia(1), somnolence(2)]. Valproic acid had caused 13 ADRs [weight increase (5), abnormal behavior (2), fatigue (1), menstrual disorder (1), dizziness (1), liver function test abnormality (1), somnolence (2)]. Carbamazepine had caused 4 ADRs [ataxia (2), dizziness (1), lethargy (1)]. Phenobarbitone had caused 2 ADRs [abnormal behavior (1), gum hyperplasia (1)]. Tremor was developed in one patient while increasing the dose of Levetiracetam.

Many research studies have corroborated the phenytoin may cause the gingival hyperplasia.[15,16] Despite having high incidence of gingival hyperplasia with phenytoin, patients are still recommended with phenytoin because of economic considerations. Valproic acid is reported to cause weight gain[17] hepatic and renal damage, syndrome of inappropriate anti diuretic hormone hypersecretion (SIADH) in patients. In our study, weight gain was observed in 5 patients. In such cases, the strategy adopted to decrease the weight was diet counseling and life style modifications to the patients.

The ADRs involved with Aspirin use were Urticaria (6) Gastric ulcer (8) and gastrointestinal bleeding (1) and with Clopidogrel use were Rash (4), Angioedema (2), Headache (3), and constipation (5).

Among the ADRs developed by antiepileptic agents the highly affected organ system class is Gastro intestinal disorders followed by Central peripheral nervous system disorders. Among ADRs developed by antiplatelet agents the highly affected organ system class is Gastro Intestinal Disorders followed by skin and appendages disorder.

No change in the treatment was observed in 50 cases as those ADRs were mild and self limiting in nature. Even though there was no overdose situation among the study population, 10 patients improved when dose was altered. Medications were discontinued in 14 patients as the ADRs were so severe like gastrointestinal bleeding, liver damage, anticonvulsant hypersensitivity syndrome etc.

Majority of patients did not receive any treatment for the ADRs because either these reaction were mild and self limiting in nature or there is no specific or symptomatic treatment for some reactions. Also among few cases, patients were not ready to withdraw the drug as the benefit from the drug (phenytoin) was outweighing the risk and the alternative drug was more costly than the existing one. As the study duration was only for nine months we could able to report only few reactions. Long duration study will help us in finding the incidence, prevalence, and predisposing factors influencing the occurrence of ADRs.

CONCLUSION

In the present study, Phenytoin and Valproic acid attributed to majority of adverse drug reactions in antiepileptic class. Aspirin attributed for majority of ADRs in antiplatelet class of medications. The organ system classes affected was central nervous system (antiepileptic agents) Gastrointestinal system (Antiplatelet agents) and Skin (antiepileptic agents and Antiplatelet agents).

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