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Pharmacology

Pattern of adverse drug reactions to anti –epileptic drugs in a tertiary care hospital

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ABSTRACT

Objectives: To assess the pattern of ADRs in Medicine, Psychiatry and Paediatric departments of a tertiary care hospital.

Material & Methods: A prospective, observational study was conducted for 5 months after approval from Institutional Ethics Committee. Patients' demographic details, details of AEDs received, ADR details were recorded and assessed by Excel2007.

Results: Out of 150 patients studied, 68% were males and 32% were females. Majority of patients were affected by GTCS(50%) and CPS(25.3%). 70.67% and 29.33% patients received monotherapy and combination therapy respectively. Sodium valproate(27.33%) and carbamazepine(18.67%) were most commonly prescribed drugs. Out of 150 patients, 47 patients developed ADRs. A total 97 different ADRs were observed. Majority of ADRs were belong to CNS(56.7%) and GIT(17.52%). Phenytoin followed by phenobarbitone and carbamazepine were involved in causing majority of ADRs.

Conclusion: Early detection of ADRs and ADR reporting is necessary to improve patients' compliance, cost of therapy, and clinical outcome.

KEYWORDS : Adverse drug reactions, Antiepileptic drugs, Causality assessment, Pharmacovigilance.

INTRODUCTION:

An Adverse drug reaction (ADR) is defined as "a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.[1]" ADRs due to drug are very common but most often preventable cause of morbidity and mortality.[2] Therefore, comprehensive ADR surveillance program is crucial to detect, evaluate and develop strategies to prevent ADRs.[3] Worldwide about 65 million people have epilepsy,[4] making it the most common neurological disorder after stroke and a major burden for public health systems.[5,6] While effective pharmacological treatment of epilepsy is vital, likewise it is equally important to consider possible adverse events due to anti-epileptic medications.[7]

Prior to 1993, there were only six major drugs available; subsequently, new drugs have entered the worldwide market. These include—felbamate(FBM), gabapentin(GBP), lamotrigine (LTG), topiramate(TMT), tiagabine(TGB), oxcarbazepine(OXC), levetiracetam (LTC), zonisamide(ZNS), clobazam(CLZ) and vigabatrin (VGB).[8] The conventional anti –epileptic drugs(AEDs) are often associated with ADRs and treatment failure, which explains the need for treatment of some patients with new AEDs.[9] There are few systematic pharmaco-epidemiological studies investigating ADRs related to AEDs available, making it difficult to assess accurately the incidence of AED-related ADRs.[10]

Although it is claimed that new AEDs offer improved safety and similar efficacy to that of conventional AEDs,[11] the data regarding safety profile of newer AEDs is not clear.

With this state of affairs, present study is designed to evaluate the pattern and extent of ADRs with AEDs at medicine, psychiatry and paediatric departments of a tertiary care hospital.

MATERIALS & METHODS:

This was a prospective observational study conducted in department of medicine, psychiatry and paediatrics over period of 5 month duration (October 2016 to February 2017), where the epileptic patients were referred and treated in a tertiary care hospital. Patients with seizures and diagnosed to have epilepsy by a clinician, of both sex and all age groups, who are prescribed an AED, were included in the study. Patients with status epilepticus and seizures associated with acute conditions like stroke, head injury, metabolic disorders, trauma, malignancy and patients/ guardians of the patient not willing to give informed consent were excluded from the study. The study was approved by the Institutional Ethics Committee.

Detailed data of the patients visited to out-patient department (OPD) and admitted to in-patient department(IPD) of Medicine, Psychiatry, Paediatrics during the study period and received AEDs as treatment was recorded after taking written informed consent from patient/ guardian of the patient. All the patients were asked about ADRs. All adverse events reported spontaneously as well as founded by researcher during every interview were recorded in case record form and ADR reporting form available on the website of CDSCO (Central Drugs Standard Control Organisation) [12]. Reported ADRs were analyzed for causality by the World Health Organization – Uppsala Monitoring Centre (WHO – UMC) Scale[13] and for severity by modified Hartwig and Siegel Scale[14]. Data were analyzed according to the age and sex distribution, system-wise, drug-wise and type of epilepsy for which drug is prescribed.

Statistical analysis: All data obtained from 150 patients was entered in Microsoft 2007 excel sheet. The categorical variables were reported in percentage. Statistical analysis was done in percentages for the patient on different AEDs.

Results: This study was conducted in 150 epileptic patients. Out of 150 patients studied 102 (68%) were males and 48 (32%) were females. Patients between age group 0-14 years were dominant with 55 (36.67%) participants followed by patients from the age group 15-29 years (27.33%). Majority of the patients in the study were affected with generalized seizures with 75 (50%) participants having generalized tonic-clonic seizure followed by 38 (25.33%) cases of complex partial seizure. 82.67% study participants were out-patient and 17.33% were in-patients (Table 1).

Table 1: demographic and clinical profile of study participants.

Sr No	Parameter	No. of patients
1	**Gender**	
	Male	102 (68%)
	Female	48(32%)
2	**Age (years)**	
	0-14	55 (36.67%)
	15-29	41 (27.33%)

	30-44	23 (15.33%)
	45-59	18 (12%)
	60 & above	11 (7.33%)
3	**Type of seizure**	
	GTCS*	75 (50%)
	CPS#	38 (25.33%)
	Atonic	5 (3.33%)
	Myoclonic	15 (10%)
	Unclassified seizure	17 (11.33%)
4	**Type of patient**	
	Out-patient department	124 (82.67%)
	In-patient department	26 (17.33%)

*GTCS- Generalized tonic clonic seizures; #CPS- Complex partial seizures

Out of 150 study participants, 106 (70.67%) patients were under monotherapy and 44 (29.33%) patients were under combination therapy. Sodium valproate was the most commonly prescribed drug in monotherapy (27.33%) followed by carbamazepine (18.67%). Most commonly prescribed two drug combination was carbamazepine and sodium valproate (6.67%), followed by phenytoin and phenobarbitone combination (4.67%). Six patients were on three drug combination therapy, among which sodium valproate, carbamazepine and clobazam combination was commonly prescribed (1.33%) (Table 2).

Table 2: AED regimen used in the study participants

AED regimen	Number of patients	AED regimen	Number of patients
Monotherapy	**106 (70.67%)**	**Combination therapy**	**44(29.33%)**
Phenytoin (PHT)	7(4.67%)	**Dual therapy**	
Phenobarbitone (PBT)	17(11.33%)	CBZ + SV	10 (6.67%)
Carbamazepine (CBZ)	28(18.67%)	PHT+ PBT	7 (4.67%)
Sodium valproate (SV)	41(27.33%)	CBZ + LTC	4(2.67%)
Clobazam (CLZ)	6(4%)	SV + LTC	4(2.67%)
Topiramate (TMT)	2(1.33%)	SV + CLZ	3(2%)
Levetiracetam (LTC)	5 (3.33%)	CBZ + CLZ	5(3.33%)
		TMT + LTC	5(3.33%)
		Three drug therapy	
		SV + CBZ + CLZ	2(1.33%)
		SV + CBZ + PBT	3(2%)
		SV + CBZ + LTC	1(0.6%)

Out of total 150 patients, 47 (31.33%) patients developed ADRs. A total 97 different ADRs were observed in 47 patients. Out of 106 patients who received monotherapy, 22 (20.75%) patients experienced ADRs and Out of 44 patients who received polytherapy, 25 (56.8%) patients experienced ADRs. Majority of ADRs were belong to central nervous system (CNS) (56.7%), followed by gastrointestinal system (17.52%), skin (12.38%) (Table 3). The most commonly suspected AED for development of ADR was phenytoin followed by phenobarbitone and carbamazepine. (Table 4.)

Table 3: System-wise distribution of ADRs

Central nervous system	No. of patients
Headache	12
Sedation	20
Ataxia	2
Giddiness	7
Weakness	4
Memory impairment	3
Blurred vision	3
Paraesthesia	4
Total	55
Skin	
Rash	7
Hair loss	3
Itching	2
Total	12

Table 4: Suspected causal AEDs for adverse drug events

Suspected AED for AEDs	Number of ADRs in which it involved
Phenytoin	27
Phenobarbitone	22
Carbamazepine	20
Sodium valproate	14
Clobazam	4
Topiramate	5
Levetiracetam	3

The analysis using WHO-UMC causality scale showed that, causality assessment was possible (59.8%) in majority of cases, probable in 20.6% cases, whereas it was conditional/ unclassified in 19.6% cases. According to modified Hartwig and Siegel severity assessment Scale, out of 97 ADEs, 68 (70.10%) were mild, 24 (24.74%) were moderate and 5 (5.15%) were severe adverse events.

Discussion: AEDs are commonly associated with different adverse effects and most of ADRs of AEDs are dose dependent and reversible[15].

In present study out of 150 patients, 68% were male and 32% were female. Patients from all age groups were included in the study. Majority of the patients were from age group 0-14 years (36.67%) followed by patients from age group 15-29 years (27.33%). Overall, adult patients were dominant in the study which is similar to other studies.[16]

In present study, 50% of patients were affected by GTCS, 25.33% patients were affected by CPS, and 10% patients were affected by myoclonic seizures. Other studies also described GTCS to be most common type of seizure among epileptic patients.[17, 18, 19] In present study, majority of the patients were under monotherapy (70.67%) than polytherapy (29.33%). In patients receiving monotherapy, sodium valproate was most commonly prescribed drug (27.33%) followed by carbamazepine (18.67%). Study conducted by Soha et al[20] also showed preference of monotherapy over polytherapy in epileptic patients.

In present study, CNS adverse effects were common (56.7%) followed by gastrointestinal system 17.52%. Neurotoxic adverse effects of antiepileptic drugs are commonly encountered and may include sedation, dizziness, blurred vision, difficulty in concentration, and ataxia.[21] Sedation (20.61%), headache (12,38%) were common CNS adverse effects in present study. Similar findings were detected in the study conducted by Soha et al[20] in which sedation was most common central nervous system ADR. Higher incidence of sedation in present study may be due to different geographical population, different AEDs utilization pattern, higher concurrent medication prescribed to study participants.

In present study, phenytoin (27) was most commonly associated with occurrence of ADRs followed by phenobarbitone (22). Newer AEDs like Topiramate, clobazam, levetiracetam were less associated with ADRs. This lesser association of ADRs with newer AEDs may be due to less drug-drug interaction with newer AEDs and may be because of less prescription of newer AEDs. Study conducted by Gajjar et al[22], Roopa et al[23], Arul Kumaran et al[24] showed similar results.

In present study, causality assessment was done using WHO- UMC causality assessment which showed that most of the ADRs fell in the category of possible (59.8%). Similar findings were reported by study conducted by Gajjar et al[22].

In present study, out of 97 reported ADRs 68 (70.1%) were mild, 27.74% were moderate, and 5.15% were severe adverse effects. Similar results were reported by study conducted by Gajjar et al[22].

In present study, incidence of ADRs was more in patients receiving polytherapy (56.8%) than patients receiving monotherapy (20.75%). Similar findings were reported by the study conducted by Soha et al[20],

Roopa et al[23]. Higher incidence of ADRs with polytherapy may be due to enhancement/ inhibition of hepatic microsomal enzyme system caused by AEDs, narrow therapeutic index leading to increased chances of drug-drug interaction and hence, increased chances of ADRs.

Conclusion:

Present study demonstrated that conventional AEDs like phenytoin, sodium valproate, and carbamazepine still remain as most commonly prescribed drugs in the management of epilepsy. ADRs were common with polytherapy than monotherapy. CNS related ADRs were detected in most of the cases followed by gastrointestinal system adverse effects. Phenytoin was found to be associated with more number of ADRs followed by phenobarbitone. Early detection of ADRs and ADR reporting is necessary to improve patients' compliance, cost of therapy, and clinical outcome.

References:

1. World Health Organization. Geneva, Switzerland: World Health Organization. [cited 10 April 2017]. Available from: http://www.who.int/medicines/areas/coordination/English_Glossary.pdf?ua=1.
2. Lazarou J, Pomeranz BH, Corey PN. Incidence of Adverse Drug Reactions in Hospitalized Patients-A Meta-Analysis Of Prospective. JAMA 1998; 279:15; 1200-5.
3. VitilloJosephineA. Adverse Drug Reaction surveillance: practical methods for developing a successful monitoring program.
4. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia2010;51: 883-90.
5. Schachter SC. Seizure disorders. In: Heggenhougen K, ed. International encyclopedia of public health, first edition. Elsevier, 2008;5:674-80.
6. Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia2011;52(suppl 7):2-26.
7. Wallance SJ. Newer antiepileptic drugs: advantages and disadvantages.BrainDev 2002; 23(5): 277–283.
8. McCabe PH. New anti-epileptic drugs for 21st century.ExpOpinPharmacother 2000; 1(4): 633–674.
9. Kilpatrick Christine. Newer antiepileptic drugs there is a commentfor consumers on this article. AustPrescr 1999; 22: 61–63.
10. Serrano Cstro PJ, Sanchez Alvarez JC. Controversies about thenew anti-epileptic drugs. Rev Neurol 2001; 32(2): 165–171.
11. French JA. The role of new antiepileptic drugs. Am J ManagCare 2001; 7 (Suppl): S209–S214.
12. The use of the suspected adverse drug reaction reporting form[Internet]. Available from: http://www.cdsco.co.in. [Cited 2016 Aug 20]
13. The use of the WHO-UMC system for standardized case causality assessment [monograph on the Internet].http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf [Cited 2016 Aug 20]
14. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49:2229-32.
15. Perucca E, Meador KJ. Adverse effects of antiepileptic drugs. Acta Neurol Scand Suppl. 2005;181:30-5.
16. Keerthy Jayalekshmi et al. A Study on the Adverse Drug Reactions Induced by Anti-Epileptic Drugs in the Epileptic Patients. Journal of Applied Pharmaceutical Science.2016;6(5):119-123.
17. Juny S, Adepu R, Keshava BS, Harsha S. Assessment of antiepileptic drugs usage in a South Indian tertiary care teaching hospital. Neurol Asia. 2013; 18(2): 159-165.
18. Mansur H, Sharifuddin K, Azhahul H,et al. Antiepileptic drug utilization in Bangladesh: experience from Dhaka Medical College Hospital. BMC Res Notes.2013; 6: 473-476.
19. Swetha M, Mohammad A, Vasant. RC, Raghunandan M. Antiepileptic Drugs Utilization Pattern & Their Adverse Drug Reactions in a Teaching Hospital in South India. Asian J Biochem Pharmaceut Res.2013; 3(1): 205-214.
20. Soha N, Afshin BH, Iman K. Adverse Reactions to Antiepileptic Drugs in Epileptic Outpatients: A Cross-Sectional Study in Iran. Clin Neuropharm, 2011; 4(2): 79-83.
21. Bromfield EB, Cavazos JE, Sirven JI. An Introduction to Epilepsy. West Hartford, CT: American Epilepsy Society; 2006. Available from: http://www.ncbi.nlm.nih.gov/books/NBK2513/. [Last cited on 2017 Mar 07].
22. Bharat M Gajjar et al. The pattern of adverse drug events to antiepileptic drugs: A cross-sectional study at a tertiary care teaching hospital. National Journal of Physiology, Pharmacy and Pharmacology.2016;6(6): 616-621.
23. Roopa B.S, Narayan SS, Sharma GR, Rodrigues RJ, Kulkarni C. Pattern of adverse drug reactions to anti-epileptic drugs: a crosssectional one-year survey at a tertiary care hospital. Pharmacoepidemiol Drug Saf. 2008;17(8): 807-812.
24. Arulkumaran KS, Palanisamy S, Rajasekaran A. A study on drug use evaluation of anti-epileptics at a multispecialty tertiary care teaching hospital. Int J PharmTech Res. 2009;1(4):1541-7.