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Original Article

Study of Adverse Drug Effects of Antiepileptic Drugs used in Pediatric Patients in a Tertiary care rural Hospital–a Pharmacovigilance Study

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ABSTRACT

Objective: To assess the prescription pattern & Adverse Drug Reaction (ADR)) profile of Antiepileptic drug (AEDs) therapy in children of rural population. **Materials and Methods:** This prospective open label, observational study was carried out over one and half year duration on 142 newly diagnosed epileptic children below 12 yrs age receiving AEDs in pediatric department in a tertiary care rural hospital. Follow up was done every month for 6 months duration. Prescription pattern and incidence, causality and severity of ADRs due to AEDs were assessed at each visit. **Results:** Out of 142 patients on AEDs, 97.2% patients were on mono-therapy and 2.8% patients were on poly-therapy. Valproic acid was the most commonly prescribed drug (58) and Lorazepam was the least prescribed drug (1). Central nervous system related ADRs (50%) were most common followed by gastrointestinal system (14.7%). Sedation and gastrointestinal distress were among the most frequently reported ADRs and29.4% of probable category while 70.5% ADR's were possible category. 72% ADRs were mild, 22% were moderate and 5.8% of ADRs were severe. **Conclusions:** Children receiving AEDs should be closely monitored for the development of any ADRs, especially related to their behavior and cognition. as it can influence their learning and memory, Active surveillance can help in knowing the exact incidence of ADRs. This study emphasizes on the role of patient / parent education and importance of health care professionals in pharmacovigilance studies.

Key words: Adverse Drug Reactions, Antiepileptic Drugs, Pharmacovigilance

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INTRODUCTION

Epilepsy is a common neurological condition affecting 0.5-1% population. Epidemiological studies of epilepsy all over the world have shown higher prevalence rate for developing countries.[1] Cumulative lifetime incidence of epilepsy in children is 3%.[2]

Most patients with epilepsy depend on medical treatment with antiepileptic drugs (AEDs) to achieve control of their seizures[3]. The overall aim in the treatment of epilepsy should be complete control of seizures and no adverse reaction due to medication with an optimal quality of life.[4]

Commonly used AEDs for epilepsy are carbamazepine (CBZ), valproate (VPA), phenytoin (PHT) and phenobarbitone (PB).[5] These drugs due to their complex pharmacological properties and narrow therapeutic index lead to various adverse drug reactions(ADRs) which often dictate the choice of AEDs and subsequent adjustment of therapy.[6]

In a meta-analysis by fatal ADRs were ranked as fourth to sixth leading cause of death among both adults and children in United States.[7] Meta-analysis of 17 prospective studies conducted in the US and Europe showed incidence of ADRs among hospitalized children to be 9.5% with severe reactions accounting for 12% of the total.[8] One study reported that AEDs were responsible for 11% of overall ADRs. Specific drugs lorazepam (3%) and VPA (3%) were associated most commonly with ADRs.[9] In another study on assessment, monitoring and reporting of ADRs in an Indian hospital, AEDs were responsible for 5% of ADRs among all of the prescribed drugs. In this study CBZ and PHT were attributed to ADRs in anticonvulsant group.[10]

There are limited studies in India to report ADRs in children.[11] Though pharmacovigilance(PV) programme was started in India in 1982, awareness about it is very low.[12] Underreporting of ADRs is a major problem affecting PV programme in India. So the drug regulators in India are dependent on other countries for data regarding drug safety especially in children. Also Due to differences in social and ethnic factors from other countries, scenario of ADRs in country like India may be different from other countries.

Clinical trials involving neonates, infants, children and adolescents are limited therefore safety and tolerability of many drugs used in this group is not well established.[9] Paucity of data regarding efficacy, potency, safety and tolerability of drugs in children leads to medical errors like overdosing and accidental exposure. Also there is difficulty in extrapolating ADR pattern of adults to children. Therefore it is important for health care professionals to monitor routinely for ADRs and report all ADRs.

Hence current study was done to analyze profile of ADRs due to AED therapy in children of rural area in developing country like India.

MATERIAL AND METHODS

The study protocol was approved by the Institutional Ethics Committee and the study was conducted in accordance with the Declaration of Helsinki.

Study Design

This was a prospective observational study and was conducted over one and half year duration (December 2010 to May 2013) in a rural tertiary care hospital.

Patient Population

Children aged 0-12yrs of age of either gender and newly diagnosed as having seizure disorder and of those parents willing to give consent were included in this study. Parents not willing to give written consent and those patients with status epilepticus & with seizures associated with paralytic stroke, trauma, malignancy and patients with co medications were excluded from the study.

Study procedure

Children visiting pediatric OPD at tertiary care teaching hospital with complaints of convulsions for the first time were assessed and examined by the treating physician for the presenting complaint.

To confirm the diagnosis of convulsion EEG (Electric Encephalography) was done. Radiological investigations like CT scan and MRI were done to rule out organic cause for convulsions. Based on the history and finding of EEG and radiological examination, appropriate AED was prescribed to children by the pediatrician.

Detailed personal, demographic and history about onset, duration and frequency of convulsions was also taken. Parents of each child were individually counseled regarding benefits and dosing schedule of AEDs therapy. They were also informed to observe and report any change in sleeping pattern, change in dietary habits, bladder and bowel habits, skin reactions or any other symptom in their child after taking AEDs therapy. Information about AEDs prescribed was recorded which included- pharmaceutical company, batch no., manufacturing date, expiry date and dose prescribed.

Patients receiving AEDs were evaluated for ADR, every 4 weeks (1 month) through detailed interview of parents on the basis of preformed questionnaire. Significant ADRs were also brought to the notice of treating pediatrician. Final decision regarding continuation of the drug, decreasing the dose of drug, withholding the drug or whether to change the drug was left to the treating pediatrician. Causality assessment of ADRs was done according to Naranjo Algorithm.[13] Severity assessment of ADRs was done according to modified Hartwig's and Siegel Scale.[14] Serum level of AED was done in patient complaining of ADR, in case of non respondent and to check compliance in patient. The estimation of AED concentration was done for PTH and VPA but the monitoring for CBZ was not done due to nonavailability of tests in our Institution.

Statistical analysis

Statistical analysis was done by using EPI INFO software. Descriptive analysis of demographic data was expressed as Mean± SDM. Statistical analysis was done in percentages for the patients on different AED therapy and for the system and drug-wise distribution of ADR's. Incidences of ADR's were also calculated in percentages accordingly.

RESULTS

Total 142 patients below 12 years of age (mean ± SD 5.36 ± 4.06 yrs) were evaluated, out of which 86(60.5%) were males and 56(39.4%) were females.

Out of 142 patients on AED therapy, 138 (97.2%) patients were on montherapy and 4 (2.8%) patients were on polytherapy.

VPA was the most commonly prescribed drug (58), followed by PHT (24), PB (21) and CBZ(16). Lorazepam was the least prescribed drug with one patient.(Figure 1)

A total of 43 patients reported 68 different ADRs involving different systems. (Figure 1)

Study reveals that CNS was the commonest affected system majority with PHT, followed by VPA. (Figure 2). CNS ADRs reported were sedation, ataxia, giddiness, convulsions and tremors. (Figure 3)

Second most common ADR was associated with gastrointestinal system. (Figure 2) GIT ADR reported were nausea, vomiting, heartburn, pain in abdomen, increased appetite, constipation etc.(Figure 4) GIT ADRs were mostly caused by VPA followed by PHT. The other systems involved were skin, metabolic, dental, hematological, eye, hepato-biliary systems and miscellaneous.(Figure 2)

Less reported ADRs like nocturnal enuresis and increased frequency of micturition were also observed in patients receiving VPA. Newer ADRs like swelling all over the body due to PHT and neutrophilic leukocytosis due to VPA were also observed.

Causality analysis showed out of total 68 ADRs, 20 were probable while 48 were possible. No ADR can be attributed to certain category and hence no dechallenge was done in our study.(Figure 5)

Out of these 68 ADRs, severity assessment showed 49 ADRs were mild, 15 ADRs were moderate and 4 ADRs were severe.(Figure 6)

DISCUSSION

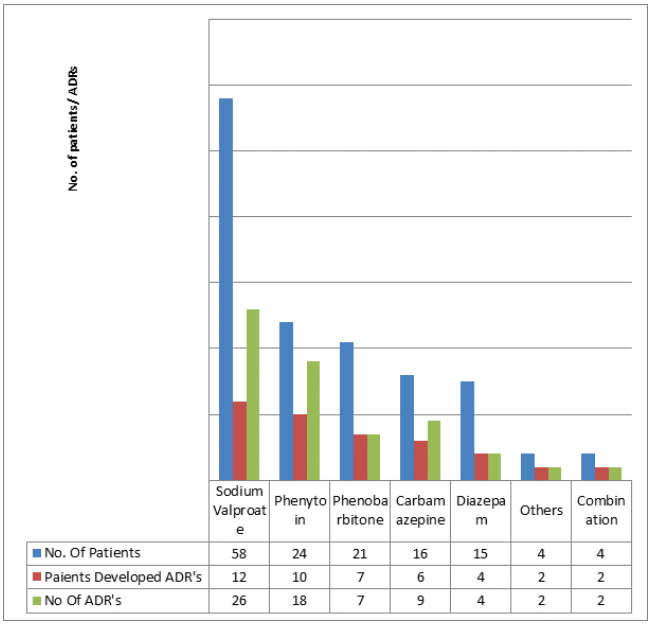
Salient features of our study are as follows: In our study, monotherapy was the main modality of treatment i.e. in 97% of the patients possibly in view of less ADRs, cost, convenience, better compliance and adherence to standard treatment guidelines.

In our study, VPA was the most commonly prescribed drug (40.8%) which is similar to the practice followed in France.[15] Review of current literature[16-18] indicates growing concern about impairment of cognitive functions due to AED therapy which was relatively less common with the use of VPA. Hence VPA is gradually becoming a mainstay of therapy for pediatric epilepsy[19] the finding consistent with our study.

PHT is the drug causing maximum number of ADRs amongst the prescribed AEDs.

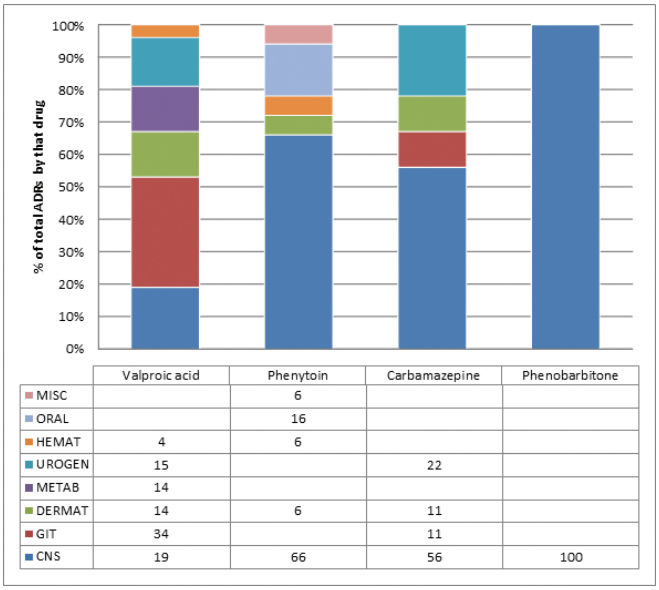
Our study showed that out of all ADRs due to AED, CNS related ADRs(50%) are the most frequently reported ADRs followed by gastrointestinal (14.7%) and Dermatology (13. 2%). Results of our study are in concordance with the other study.[20] Sedation is the most common ADR i.e. 11.2% of total ADRs and 47% of CNS ADRs which is slightly higher than the other studies [21] and this may be due to active method of surveillance for ADR in our case. Of all the AEDs, sedation is associated with PHT in majority of cases. Peculiarity of sedation as ADR was that after 4-6 weeks of initiation of therapy it disappeared. This might be due to development of tolerance by the patient. This tolerance can be pharmacokinetic as it can be with many drugs which stimulate hepatic microsomal enzyme induction. It can also be due to pharmacodynamic alteration in the functioning of receptors[22]

Other common ADR in CNS was ataxia seen in 4 patients (2.8%) which was seen commonly with PHT. Of all the ADR caused by PHT, ataxia accounted for 16.6% after sedation. In 4 patients, who developed ataxia, serum levels were evaluated in 2 patients. Drug concentrations were found to be 29 µgm/dl, and 33 µgm/dl respectively which were significantly high (10-20 µgm/dl). The doses were decreased and the patients were relieved of symptoms. One patient, who was otherwise well controlled of his symptoms with PHT therapy, presented with history of convulsions. Drug serum concentration was done and expected to be below the therapeutic range, but to our surprise the drug serum concentration was on toxic side. As the symptom disappeared on decreasing the dose, a convulsion as an ADR of PHT was thus confirmed.



	Sodium Valproate	Phenytoin	Phenobarbitone	Carbamazepine	Diazepam	Others	Combination
No. Of Patients	58	24	21	16	15	4	4
Paients Developed ADR's	12	10	7	6	4	2	2
No Of ADR's	26	18	7	9	4	2	2

Figure 1: Column diagram showing total number of patients receiving AEDs, number of patients who developed ADRs and number of ADRs



	Valproic acid	Phenytoin	Carbamazepine	Phenobarbitone
MISC		6		
ORAL		16		
HEMAT	4	6		
UROGEN	15		22	
METAB	14			
DERMAT	14	6	11	
GIT	34		11	
CNS	19	66	56	100

Figure 2: Column diagram showing distribution of different ADRs related to different Systems

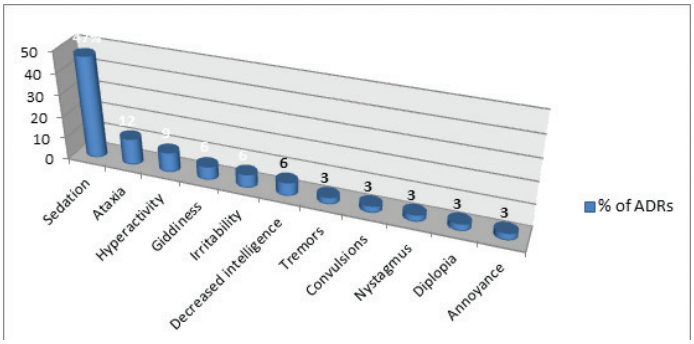


Figure 3: Percentage Distribution of Central Nervous System ADRs

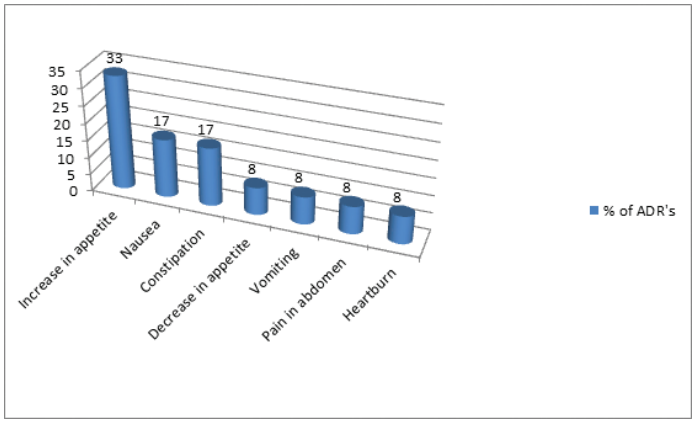
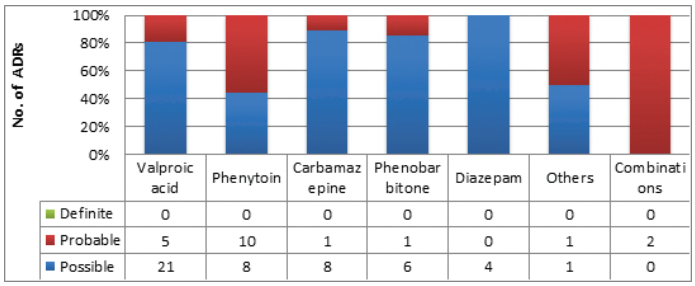
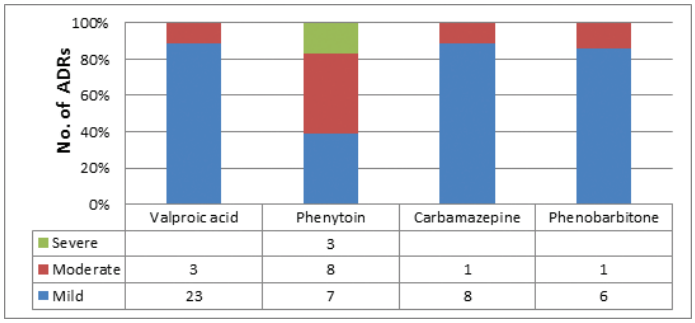


Figure 4: Percentage Distribution of Different Gastrointestinal System ADRs



	Valproic acid	Phenytoin	Carbamazepine	Phenobarbitone	Diazepam	Others	Combinations
Definite	0	0	0	0	0	0	0
Probable	5	10	1	1	0	1	2
Possible	21	8	8	6	4	1	0

Figure 5: Drug Wise Causality Assessment of ADRs



	Valproic acid	Phenytoin	Carbamazepine	Phenobarbitone
Severe		3		
Moderate	3	8	1	1
Mild	23	7	8	6

Figure 6: Severity assessment of ADRs

GIT is the second most common system affected with 14.7% of the ADRs. VPA is the most commen AED causing maximum no of ADRs related to GIT (34.6%) followed by CBZ (11%).Increase appetite (40%) may be the commonest ADR related to GIT system as parents are able to witness the change in dietary habits after starting AED treatment. Whereas other ADRs like nausea, pain in abdomen and heartburn are difficult for children to report to their parents. Hence we are expecting underreporting of these two ADRs. Gastrointestinal adverse effects are due to direct effect of the drug on GIT. This can be minimized by taking drugs with meals.

13.2% of all the ADRs due to AEDs were related to Dermatological system. Of these ADRs, 44.4% of ADRs reported were rash. Overall incidence of rash in our study was 2.8% of total ADRs. Dooley and Thoma Souza have reported overall incidence of rash due to antiepileptic 7-12% in their studies.[23,24]

Out of 4 cases which reported with rash, 2 cases were on combination of AEDs (PB + PHT and PB+ CBZ). Other 2 cases were due to PHT and CBZ monotherapy. Concerned Pediatrician was advised by dermatologist

to stop PHT and CBZ in polytherapy group. In other 2 cases PHT and CBZ were stopped. In patients on monotherapy (PHT and CBZ) was reintroduced after rash was subsided. One patient who received inj Lorazepam developed Steven Johnson's syndrome (SJS). Other dermatological system related ADRs were reversible transient hair loss and thinning of hair which constitute 1.4% of total ADRs in patients on VPA therapy, accounted for 15.3% of dermatological reactions (hair changes). Results of our study correlate with the results of other studies.[25] Possibly, the chelating properties of VPA can explain the effects on the hair structure. Several metals are essential for hair growth and keratinisation[26] Decreased copper, zinc and magnesium concentrations were found in subjects treated with VPA.[27]

Of all the ADRs in our study 4.4% of the ADRs were related to urogenital system, which included nocturia and increased frequency of micturition were observed in patients on VPA therapy. Overall incidence of nocturia (enuresis) was 1.4% and increased frequency of micturition was 0.07%. Results of our study are in accordance with other studies on use of VPA in children.[28] Two most likely explanations for VPA induced enuresis are that it could be secondary to a central effect on the thirst center, resulting in polydipsia, or secondly is a consequence of the increased depth of sleep commonly associated with VPA.[29] Increased thirst has been demonstrated in several other studies with VPA.[30] As it can be a manifestation of seizure itself and hence change of therapy or further investigations may be required.

Of all the ADRs in our study, 4.4% were oral cavity related ADRs. All of these ADRs were gingival enlargement in children who were on PHT therapy i.e. 16.6% of PHT induced ADRs. Incidence of gingival enlargement due to PHT in our study was 12.5% which correlates with results of previous studies, which reported incidence of gingival enlargement ranging from 3% to 93%.[31] The condition appears to be a result of interaction of susceptible subpopulation of fibroblasts, keratinocytes and collagen with PHT & its metabolite,[31] which can be prevented by maintaining good oral hygiene.

Other ADRs were weight gain (2% incidence) and increase in transaminase levels in patients on VPA therapy which is much lesser as compared to Egger Jetal study (40%).[28] The possible reasons for the low incidence of weight gain in our study could be due to difference in the nutritional status and other socio-economical factors.

In our study one patient who was on PH, suffered from microcytic anemia. Similarly leucocytosis was observed in another patient on VPA therapy.

There were different responses to the ADRs by the physician like stopping the drug in (8 ADRs), withholding the drug (6 ADRs), decreasing the dose of drug (4 ADRs) and continuing the same dose of drug (50 ADRs)

No ADR was "definite" on causality assessment, as rechallenge in strict sense was not done. Using different scales can change the outcome as different causality assessment scales give different results.[32]

Impact of the study

This was evident in our study that parents coming for subsequent follow up were more vigilant regarding noticing and reporting ADRs.

The physicians of our study, started noticing and reporting even the milder ADRs which were initially thought to be non significant and this continued even after the completion of our study.

Our study on PV will definitely contribute in generating the hospital ADR database and also can further help in curbing cost of treatment, better clinical outcome and compliance of the patients.

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CONFLICT OF INTEREST

No conflict of interest are declared.

ABBREVIATION USED

AEDs: Antiepileptic drug; **CBZ:** swingscabamazepine; **VPA:** Valproate; **PHT:** Phenytoin; **PB:** Phenobarbitone; **ADRs:** Adverse drug reactions.

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