Pattern of Adverse Drug Reactions to Conventional Anti-epileptic Drugs Monotherapy in Nepalese Children

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Adverse drug reactions (ADRs) are common with anti-epileptie drug (AED) therapy. Knowledge about ADRs helps the clinician in planning the treatment course and facilitates early detection of ADRs and intervention.

Present study was done to find out the pattern of ADRs to conventional AEDs monotherapy in Nepalese children. This is a prospective study done at a medical college, teaching hospital, pediatric out patient department, epilepsy clinic. New patients on monotherapy of one of the four conventional major AEDs were followed up, monitored and recorded for adverse effects.

Total number of patients were 74 of whom ADR was observed in 32 patients (43.24%). Maximum ADRs rate was seen with phenobarbitone (83.33%). CNS side effect was most commonly seen (43.75%). Most ADRs were of mild severity (60%) and recovery occurred spontaneously.

AED is one of the three commonest drug classes associated with ADRs in children. Present study is of small size but it Has increased ADRs awareness and encouraged it's early detection. Further larger studies are needed.

Key words: Adverse drug reactions, Anti-epileptic drugs, Conventional Monotherapy

Adverse drug reaction (ADR), as defined by WHO, is any response to a drug which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis, or treatment.[5] All anti-epileptic drugs (AEDs) have potentially serious adverse effects which are a major cause of poor patient compliance and treatment failure.[2,3] Knowledge about ADRs helps the clinician to form good prescribing habit and guides him in planning treatment course.[15, 17] Although even preventable ADRs may not be entirely eliminated their awareness leads to early detection and intervention to minimize patient discomfort.[16] At least

ten new AEDs have entered the worldwide market after 1993, however the conventional anti-epileptic drugs are still among the most frequently prescribed AESs.[9, 2] The present study was done to find out the pattern of adverse drug reactions to conventional antiepileptic drugs in Nepalese children.

Particulars	Control group (n=42)	ADR group (n=32)
Male		
➢ **Number**	27	15
➢ **Percentage(%)**	64.29	46.87
Female		
➢ **Number**	15	17
➢ **Percentage (%)**	35.71	53.13
M:F Ratio	1.8:1	0.88:1
Age (Years)		
➢ **Range**	1-14	4-11
➢ **Mean**	8.72	10.15

Table 1. Sex and Age profile of patients of control group and ADR group, receiving AEDs monotherapy

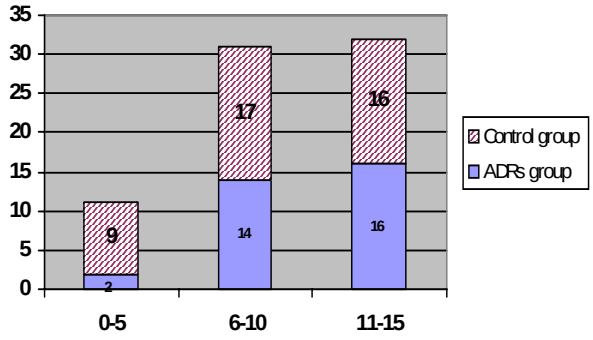

Figure 1. Age distribution in control and ADRs groups. ADRs group: < 5 years- (2/11 = 18.18%), 6-10 years- (4/31 =45.16%), 11-15 years :-(16/32 =50%).

Materials and Methods

This is a prospective pragmatic study with long term follow up to find the pattern of adverse reactions of coventional four standard antiepileptie drugs used as monotheray in children with newly diagnosed epilepsy. The study was done in the pediatric epilepsy clinic of a medical college, teaching hospital with protocol design according to standard clinical practice. Patients on monotherapy of carbamazepine (CBZ), Valproic acid (VPA), Phenytoin (PNT) and phenobarbitone (PBT) were included in the study. Those who were concomitantly on other medications likely to have interaction with the AEDS were excluded from the study. Clinical evaluation and laboratory monitoring for ADRs were done on each follow up visit and any adverse effect reported was recorded. The data was collected under two groups of patients. Control groups and ADRs group (those with adverse reactions). ADRs data was collected according to WHO guidelines. The study duration was from 1st January, 2006 to 31st December, 2007. The data was analysed to find the pattern and extent of the ADRs using appropriate statistical tools.

Results

Total number of patients included in the study was 74, who were on monotherapy with one of the four conventional, major AEDs. There were 32 on carbamazepine, 27 on valproic acid, 9 on phenytoin and 6 on phenobarbitone. Of those, ADRs were observed in 32 patients (43.24%). The sex and age profile of all patients (both, control and ADRs groups) is given in Table 1. M:F ratio was slightly higher in the control group (1.8:1) than in the ADRs group (0.88:1). But the mean age was higher in the ADRs group (10.15 years) as compared to the control group (8.72 years). Age distribution of patients is shown in Figure 1. Equal number of patients (16,16) were present in both the groups in age group 11-15 years, where, comparatively more numbers of patients were present in the control group (9,17) than in the ADRs group (2,14), in the corresponding age ranges. The number of each class AEDs prescribed along with the observed number of ADRs is illustrated in Figure 2. Maximum ADRs was observed with phenobarbitone (83.33%) although minimum number of patients (6/74=8.1%) belonged to this group. It was followed by phenytoin (66.66%), valproic acid (40.75%) and carbamazepine (31.25%).

Figure 3 shows the pattern of system affected which may be arranged in a decreasing order as CNS (43.75%), GIT (21.87%), skin (12.5%), liver (12.5%), mouth (6.25%) and blood (3.12%), The common ADRs observed with each class of AEDs were given in Table 2.

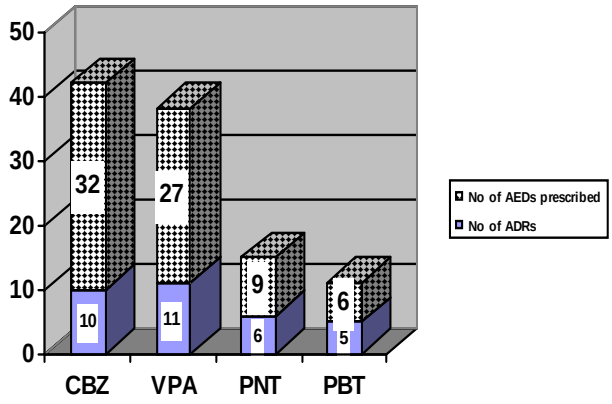

Figure 2. Relationship between drugclass and ADRs in patients receiving AEDs monotherapy. CBZ (Carbamazepine): (10/32 = 31.25%), VPA (Valproic acid): (11/27 = 40.74%), PNT (Phenytoin): (6/9 = 66.66%), PBT (Phenobarbitone): (5/6 = 83.33%)

AED monotherapy	ADRs	No.	%
Carbamazepine (CBZ) (n=32)	▪ Drowsiness	3	9.37
	▪ Rashes	2	6.25
	▪ Vertigo	1	3.12
	▪ Diplopia	1	3.12
	▪ SGPT Elevation	2	6.25
	▪ Leucopenia (count less than 4000/cumm)	1	3.12
	▪ Total	10	31.25
Valproic Acid (VPA) (n=27)	▪ Weight gain	2	7.40
	▪ Vomiting	3	11.11
	▪ Thinning of hair	1	3.70
	▪ SGPT Elevation	1	3.70
	▪ Drowsiness	2	7.40
	▪ Headache	2	7.40
	Total	11	40.74
Phenytoin (PNT) (n=9)	▪ Gingival hypertrophy	2	22.22
	▪ Hirsutism	1	11.11
	▪ Vomiting	2	22.22
	▪ SGPT Elevation	1	11.11
	▪ Total	6	66.66
Phenobarbitone (PBT) (n=6)	▪ Irritability	1	16.66
	▪ Hyperactivity	2	33.33
	▪ Drowsiness	2	33.33
	Total	5	83.33

Table 2. Pattern of ADRs most commonly recorded in patients receiving AEDs monotherapyPercentage of ADR (Organ / system affected)CNS:(14/32=43.75%), GIT: (7/32=21.87%), Skin: (4/32=12.5%), Liver: (4/32 = 12.5%), Mouth: (2/32=6.25%), Blood: (1/32=3.12%)

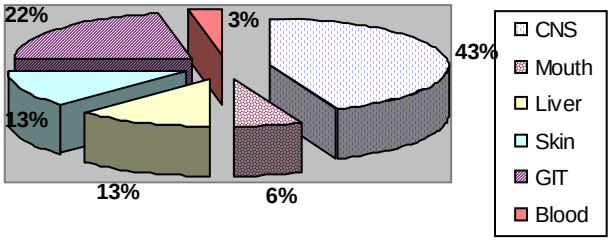

Figure 3. Pattern of organ / system most commonly affected with ADRs in patients receiving AEDs monotherapy (n32). Percentage of ADRs (Organ / system affected)CNS:(14/32=43.75%), GIT: (7/32=21.87%), Skin: (4/32=12.5%), Liver: (4/32 = 12.5%), Mouth: (2/32=6.25%), Blood: (1/32=3.12%)

Most of the adverse reactions were mild (60%) and severe reaction was not observed (as shown in Table 3). Definite causality was noted in 40% ADRs and another 40% were probable. Mild ADRs cases recovered spontaneously with observation and monitoring. However, moderate reactions were managed by therapeutic drug level monitoring, dose adjustment or discontinuation and substitution with another class AEDs. Type of most commonly recorded ADR was probable as noted in Table 4.

Level of severity	CBZ		VPA		PNT		PBT	
	No	%	No	%	No	%	No	%
Mild	6	60	8	72.72	3	50	3	60
Moderate	4	40	3	27.27	3	50	2	40
Severe	-	-	-	-	-	-	-	-
Total	10	100	11	100	6	100	5	100

Table 3. Level of severity and type of ADR (n=32) in patients receiving AEDS monotherapy

Type of ADR	CBZ		VPA		PNT		PBT	
	No	%	No	%	No	%	No	%
Probable	3	30	7	63.63	2	33.33	2	40
Possible	4	40	2	18.18	1	16.66	1	20
Unlikely	-	-	-	-	-	-	-	-
Total	10	100	11	100	6	100	5	100

Table 4. Type of ADR (n=32) in patients receiving AEDS monotherapy

Discussion

Adverse drug reaction (ADR) is well known for under diagnosis and under reporting even in developed countries with a system of pharmacovigilance.[12, 13] Of the reported ADRs, over 50% resulted in treatment intervention and or temporary patient harm.[16] Earlier studies have confirmed anticonvulsants, opoids and antibiotics as the three most commonly associated with ADRs in children.[16,7] With conventional AED monotherapy 10.24% ADRs have been reported.[13] This is lower than the rate seen in our study (43.24%), which may be due to differences in the study age range. Monotherapy is associated with fewer and easily recognizable side effects [12, 4] although highgher rates may be found in case of individual drug class.[8] In our study, carbamazepine was found to have the lowest ADR rate (31.25%) but rate up to 70% has been documented.[20] Potentially serious side effects of carbamazepine have been mentioned in the literature[11] but none were observed in our study.Common to all four AEDs investigated CNS side effects were were frequently found (43.75%). The incidence of drowsiness was highest with phenobarbitone (33.33%) whereas vomiting more frequently occurred with phenytoin (22.22%) and weight gain was seen with valproic acid (7.4%). Review of current literature [13, 7, 4,18, 1, 10] indicates growing concern on the impairment of cognitive function due to AED therapy, although, difficult to ascertain than other ADRs. Due to these and other factors valproic acid is gradually becoming a mainstay of therapy for pediatric epilepsy.[6] However, the potential for interactions and side effects due to enzyme induction or inhibition is reduced by most new generation AEDs as compared to the conventional four major AEDs.[19]

Present study is of small size, yet it points to the need for further larger studies and secks to increase ADR awareness and encourages early detection and intervention to minimize patient discomfort.

Conclusion

Knowledge about ADRs of AEDs is useful for the physician in planning treatment course. The ADR rate in monotherapy with conventional four major AEDs was found to be 43.24%. Lowest ADR rate was seen with carbamazepine (31.25%) Drowsiness was most commonly found with phenobarbitone (33.33%) and vomiting most frequently oceured with phenytoin (22.22%). Present study seeks to increase ADR awareness and encourages its early detection. Further larger studies are needed.

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