Original Articles

COMPARISON OF PHENOBARBITONE, PHENYTOIN WITH SODIUM VALPROATE:

Randomized, double-blind study

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Objective: *To compare the efficacy and side effects of phenobarbitone (PB), phenytoin (PHT) and sodium valproate (SVP) in controlling generalized tonic-clonk convulsions (GTC).* ***Design:*** *Randomized, double blind clinical trial.* ***Setting:*** *Out-Patients in a tertiary care hospital.* ***Patients:*** *151 children with GTC, aged 4-12 yrs, from Madras city were enrolled. At the end of 2 yrs, 127 children remained in the study.* ***Intervention****: Each child was given one active drug and 2 placebo tablets. Clinical, hematological and biochemical evaluations were done every month. Serum drug levels were assessed periodically.* ***Main outcome measures:*** *Recurrence of convulsion and side effects.* ***Results:*** *The proportion of children with recurrence did not differ among the* 3 *groups. More than one side effect ivas observed in 16* (32%) *children on PB, 20 (40%) children on PHT and 9 (19%) children on SVP and this difference was statistically significant ($p < 0.05$). Hyper activity was the major side effect of PB, observed in* 22% *of children.* ***Conclusion:*** *All 3 drugs were equally effective in controlling seizures. Side effects were minimal with SVP followed by PB. Though side effects were more frequent with PHT, most of them disappeared on adjusting drug dosage. Least expensive phenobarbitone may be preferred as the first drug of choice but, only for preschool children. SVP is advised for school going children.*

Key words: *Convulsions, Anticonvulsants, Phenobarbitone, Phenytoin, Sodium Valproate.*

CONVULSIONS are the commonest and most alarming of neurological problems in children. The reported prevalence of afebrile convulsions in children under 10 years is 5.2 to 8.1 per thousand (1). Generalized tonic-clonic seizures are the most common type of afebrile seizures occurring in childhood (2,3).

Children with seizure disorders require prolonged antiepileptic drugs (AED) for atleast 2 seizure free years(l). It is, therefore, important to identify a drug that controls seizures effectively with minimal side effects. In addition, cost is another important factor that influences the choice of the drug in developing countries. Carbamazepine, phenobarbitone (PB), phenytoin (PHT) and sodium valproate (SVP) are the preferred drugs for the management of generalized tonic-clonic convulsions. In this study, the efficacy of

PB, PHT and SVP was compared as these are less expensive than carbamazepine.

Subjects and Methods

This was a double-blind, randomized study carried out at the Institute of Child Health and Hospital for Children from March 1992 to March 1995. Consecutive cases of generalized tonic-clonic convulsions satisfying the following inclusion criteria were registered. The inclusion criteria were: *(i)* age between 4 and 12 years; *(ii)* history of more than one attack of afebrile convulsion; *(iii)* not associated with other type of seizures, *(iv)* cases should not have received AED previously; *(v)* otherwise neurologically normal child; and *(vi)* children who can come for regular follow up. Children with chronic medical illnesses, definite history of drug allergy, delayed developmental milestones, neurological abnormality or mental retardation were excluded.

After obtaining informed consent, 151 children were registered. A detailed history regarding duration of illness, frequency of seizures and precipitating factors were elicited. Since seizure frequency, type and epilepsy onset are known to influence the academic performance of epileptic children, these factors were taken into consideration to grade the severity of seizure (4-6). Arbitrarily, the severity was classified as: *(i)* mild when duration of illness was <24 months and total number of fits was <5; *(ii)* moderate when either duration of illness was <24 months but number of fits was >5 or duration of illness was >24 months but number of fits was <5: and *(iii)* severe when the duration was >24 months and number of fits was >5.

A complete clinical examination was carried out. Baseline laboratory investigations such as urine screening for albumin and sugar, WBC count, Hb estimation, platelet count, SGPT, SGOT, serum alkaline phosphatase and serum creatinine estimation were carried out for all patients. These were repeated once in 3 months during the study period. EEG was taken for all registered children to exclude children with secondary generalization.

By using computer generated random numbers, the children were randomized to receive either one of the 3 antiepileptic drugs in the following dosage: PB-3 to 5 mg/kg/day, PHT - 5 to 8 mg/kg/day, SVP - 15 to 50 mg/kg/day. The children were started with the minimal dose of the drug. In order to ensure complete blinding of the nature of the drug, each child was given one AED and placebos resembling the other 2 AEDs. Riboflavin tablets (30 mg) were given every day for each patient and they were instructed to take it along with the active drug. This was done to assess the compliance of the patient as riboflavin when excreted in the urine gives it a bright yellow florescence under a UV lamp(7).

Follow-Up

The patients were evaluated once a month. One of the investigators who was blind to the nature of the drug was assessing the patient throughout the study for both recurrence and side effects. Another investigator was controlling the drug dosage depending on the serum AED levels. The serum drug levels were initially estimated 1 month after starting the drug and the dosage of the drug was adjusted depending on the results. Subsequently it was done at the end of the study period or earlier if the child developed convulsions or significant side-effects warranting alteration in dosage of medication.

During each follow-up visit, seizure recurrence, if any was noted. If seizures occurred when the serum AED level was within the therapeutic range, the dose was

increased to the maximum. When seizures were not controlled even after reaching the maximum dosage of the drug, it was considered as drug failure.

Assessment of Side Effects

Each child was examined clinically for the possible side effects of all the 3 drugs. The side effects noticed in the patients were categorized as: *(a)* severe when they necessitated drug stoppage; *(b)* moderate when dose adjustment was required; and *(c)* mild when they were tolerable requiring neither drug adjustment nor drug stoppage.

If seizures were controlled, but unacceptable side effects appeared, the dose was reduced. If the lowered dose still produced unacceptable side effects or resulted in recurrence of seizures, the drug was withheld.

Compliance was assessed by pill counting and by screening the urine for fluorescence under UV lamp.

Fischer's exact test and Chi square test were used to compare the proportions of children with side effects and recurrence among the three groups.

Results

Of the 151 children, 51 children were randomized to receive phenobarbitone, 52 to receive phenytoin and 48 to receive sodium valproate. Age, sex and other risk factors for recurrence of convulsions were equally distributed among the three groups *(Table I).* Compliance of children among the three groups was comparable.

Out of 151 children, 127 children were followed up completely. The minimum follow-up period was 22 months and the maximum was 36 with mean duration of 29 months (SD 3.8 months). The target follow-up period was 2 years and it was achieved in 84% of cases. Twenty four (16%) children dropped out after a varying period of follow-up *(Table I).*

During the study period, 16 (95% CI 19-45) in PB group, 14 (95% CI 16-41) in PHT group and 10 (95% CI 10-34) in SVP group developed at least one attack of convulsion. Out of these 40 children, 32 developed convulsions either because their serum AED levels were low or they were irregular in taking the drug. Adjusting drug dosage and establishing better compliance resulted in this group remaining seizure free till the end of the study. The remaining 8 developed recurrence while on regular AED therapy and their serum AED levels were within the therapeutic range. Of these 8, 3 children were in PB group, 3 in PHT group and 2 in SVP group.

In the PB group, 17 children developed side effects. Of these, 14 developed the side effects while their serum AED levels were within the therapeutic range *(Table II).* Hyperactivity was observed in 11 (22%), temper tantrums in 11 (22%) and poor school performance in 8 (16%).

In the PHT group, out of 33 children with side effects, 15 showed the side effects when their serum AED levels were within normal limits *(Table II).* Gingival hypertrophy was observed in 30 (58%), ataxia in 13 (25%) and sedation in 12 (23%). All children with perceptible ataxia, nystagmus and confusion had elevated serum AED levels and side effects disappeared after dose adjustment. One child with high serum AED level developed profuse nausea and vomiting requiring hospitalization for fluid therapy. This child did not have ataxia or nystagmus but showed mild gingival hypertrophy.

In the SVP group, out of 15 children with side effects, the serum AED level was normal in 10 *(Table II).* Hyperactivity was

TABLE I–*Demographic Data of the Study Population*

Parameter	PB (n=51)		PHT (n=52)		SVP (n=48)	
	No.	%	No.	%	No.	%
1. Age (yrs)						
4 — 6	14	27	17	33	17	35
6 — 10	30	59	28	54	21	44
> 10	7	14	7	13	10	21
2. Sex						
Male	29	57	26	50	26	54
Female	22	43	26	50	22	46
3. Maternal Education						
(*a*) Never went to school	24	47	14	27	18	38
(*b*) Elementary Education	18	35	22	42	21	43
(*c*) High School	9	18	16	31	9	19
4. Family history						
(*a*) Febrile fits	2	4	2	4	3	6
(*b*) Epilepsy	7	14	8	15	7	15
(*c*) Both	0		2	4	0	
5. Past H/O febrile fits in patients						
(*a*) Present	10	20	15	29	9	19
(*b*) Absent	41	80	37	61	39	81
6. Severity of illness						
(*a*) Mild	41	80	42	81	39	80
(*b*) Moderate	7	14	9	17	8	18
(*c*) Severe	3	6	1	2	1	2
7. Drop out	8	16	6	12	10	20

observed in 6 (13%) children and school performance was impaired in 4 (8%) children. One child developed a severe form of skin allergy 18 months after start of therapy requiring discontinuation of drug. Initially, the rashes were maculopapular with severe itching. They subsided after a month, but hyperpigmented patches appeared in their place.

More than one side effect was observed in 16 (32%) children of PB group, 20 (40%) of PHT group and 9 (19%) children in SVP group and the difference observed was statistically significant ($p < 0.05$).

Periodic evaluation of hematological parameters and urine screening for albumin and sugar were normal in all 3 groups. However, serum alkaline phosphatase

TABLE II– *Side Effects and Serum Blood Levels (μg/ml)*

Serum drug levels	Severity of side effect			
	Mild	Moderate	Severe	Nil
1. *PB*				
> 30	3	0	0	2
15-30	14	0	0	24
2. *PHT*				
> 20	5	12	0	6
10-20	15	0	1	7
3. *SVP*				
> 100	4	0	0	6
50-100	10	0	1	17

levels were elevated beyond the normal range in 1 child in PB group, 4 in PHT and 6 in SVP group. The serum alkaline phosphatase values in the SVP group were not significantly elevated compared to those in the other groups. The EEG of 22% of children showed abnormal epileptiform activity.

Discussion

In this study, the proportion of children with recurrence was equal in all three groups. Vining observed that the recurrence of convulsions was equal in PB and SVP groups as in the present study(8). In adults, Mattson observed that PB was as successful as PHT or carbamazepine in controlling generalized tonic-clonic seizures(9).

Behavior disturbances due to PB therapy have been reported in 9-75% cases (10-12). In this study, 22% of children on PB and 13% of children on SVP showed behavior problems. Vining *et al.* reported behavior problems as observed by mother to be 33% with SVP and 43% with PB(8). No child in PB group showed signs of depression in the present study whereas other workers have observed features of depression to be more frequent with PB therapy(13,14).

School performance was taken as a measure of cognitive functions as a whole. School performance deteriorated during the study period in 8 (16%) in PB group, 6 (12%) in PHT group and 4 (8%) in SVP group. It has been shown that cognitive functions are affected by PB and PHT(12,15-18) while SVP has minimum adverse effects on cognitive functions(19).

The reported incidence of gingival hypertrophy is 20%, whereas it was observed in 58% of the children on PHT in the present study(20). A severe form of skin allergy was observed in one child on SVP. The skin reaction was so dramatic and extensive that it clinically closely resembled Steven Johnson's syndrome but did not involve the cornea and the rashes subsided within a month after drug withdrawal. Though serious skin allergy and Steven Johnson's syndrome are more common with phenytoin therapy, they can also occur with other antiepileptic drugs.

In the management of generalized tonic-clonic convulsions, all three drugs were equally effective in controlling seizure recurrence, but the side effects varied. Therefore, side effects become the important factor that will determine the choice of AED for long term management. This study revealed SVP to be the drug with least side effects followed by PB. Though side effects were more frequent with PHT after a period of therapy, they disappeared after dose adjustment. Non linear elimination of PHT resulted in high blood levels of the drug and was responsible for the side effects(21). This feature necessitates constant supervision of serum drug levels when PHT is used.

In conclusion, since PB is cost effective, this may be used in pre-school children whereas SVP may be preferred in children in the school going age group.

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