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BRAINSTEM AUDITORY EVOKED POTENTIALS IN EPILEPTICS ON DIFFERENT ANTI-EPILEPTIC DRUGS

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Abstract : The effects of anti-epileptic drugs (AEDs) on brainstem auditory evoked potentials (BAEPs) were studied on 32 female patients of epilepsy and 10 age-matched normal healthy females (NS). The patients were divided into 6 groups, those not receiving medication (drug free, DF) and those receiving AEDs: Phenytoin (PHT), Carbamazepine (CBZ), Phenobarbital (PB), a combination of PHT and PB and a combination of CBZ and PB. DF epileptics had shortened wave V absolute latency (AL) and I-V interpeak latency (IPL) as compared to NS. Phenytoin and CBZ monotherapy produced a prolongation of wave III AL (by PHT only), wave V AL, wave I-III IPL and I-V IPL, as compared to DF epileptics. Phenytoin monotherapy also prolonged wave III AL and I-III IPL, as compared to NS. When PB in the dosage of 30-60 mg/d was used in combination with PHT the above mentioned changes were not observed. These findings indicate altered neuronal conduction and/or synaptic transmission in epileptics. Anti-epileptic drugs in the dosages studied, with exception of PHT appear to lead towards "normalization" of BAEPs.

Key words : brainstem auditory evoked potentials epilepsy anti-epileptic drugs

INTRODUCTION

It is important that patients with epilepsy be administered anti-epileptic drug (AED) therapy such that it provides maximum benefit with least side effects. Other than application in clinical neurology, brainstem auditory evoked potentials (BAEPs) have emerged as a useful tool in characterising the electrophysiological phenomena of neural excitation, conduction and transmission across the auditory pathway (1) and hence may be used to study the functional effects of AEDs. Changes in BAEPs are reported following administration of AEDs in patients of epilepsy. These changes are observed even at therapeutic levels and in the absence of clinical signs of drug toxicity (2). Administration of phenytoin (PHT) and carbamazepine (CBZ) are reported to prolong the absolute latencies (ALs) and interpeak latencies (IPLs) of BAEPs (2, 3). Anti-epileptic drugs phenobarbital (PB) and clonazepam are also reported to prolong ALs of BAEP waves (4). On the other hand, one study (5) found no changes in BAEPs following CBZ monotherapy. There is also a paucity of studies on AEDs when given in combination. Most of the studies carried out so far have compared the patients of epilepsy receiving AEDs with normal healthy subjects, but not with epileptics not receiving medication.

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The present study was undertaken to evaluate the effect of PHT, CBZ and PB administered alone or in combination on BAEPs in patients of epilepsy. In order to assess whether epilepsy *per se* produces changes in BAEPs, epileptics not receiving medication (drug free) were included. Comparisons were made between patients receiving different AEDs with drug free epileptics and normal healthy subjects.

METHODS

BAEP data of 32 patients of epilepsy and 10 control subjects were analysed to study the effect of anti-epileptic drugs. The epileptic subjects were female patients 15-35 yrs old, attending the Neurology Clinic at Smt. S.K. Hospital, an exclusively female hospital. The control subjects were age-matched normal healthy female relatives of the patients from the same socio-economic background. An informed written consent was obtained from each subject prior to enrolment in the study. The clinical data of the subjects is shown in Table I. The subjects included in the study had no hearing deficit as reported after thorough ENT examination including audiometry. Epileptic subjects were on prescribed anti-epileptic medication for 6 months or longer and epilepsy was primary idiopathic (CT scan was normal). The subjects were categorized in the following groups :

Group A : Drug-free epileptics (DF) (n=5). These were patients yet to receive medication or those who had discontinued medication for atleast 15 days due to some reason.

Group B : Normal healthy subjects (NS); (n=10).

Group C : Subjects receiving PHT (n=5); 200-600 mg/d.

Group D : Subjects receiving CBZ (n=5); 200-800 ng/d.

Group E : Subjects receiving PB (n=7); 30-120 mg/d.

Group F : Subjects on a combined therapy of PHT and PB (n=5); PHT 300 mg/d and PB 30-60 mg/d.

Group G : Subjects on a combined therapy of CBZ and PB (n=5); CBZ 200-600 mg./d and PB 60-90 md/d.

The recordings were carried out in a quiet air-conditioned laboratory with the subjects resting in supine position. The active electrode (impedance below 5 kohms) was placed over the vertex (Cz), the reference over the ipsilateral earlobes (Al and A2 for left and right ears respectively), the grounding over the forehead (FPz). Monoaural auditory stimuli consisting of clicks of 100 μ secs duration, square wave pulses delivered through electrically shielded earphones (TDH-39PO1288 Telephonics 296 Doo-4) with 35 dB pure white noise contralateral masking. Stimuli were delivered at the rate of 11.4/sec, 75 dB above the click hearing threshold. The evoked electrical activity was amplified 10000 times with a band pass of 150-3000 Hz and averaged over 2000 sweep presentations using Nicolet Instruments (USA) Model Compact IV Evoked Potential System. Atleast 2 trials were obtained to ensure reproducibility of responses. The responses were displayed; the peaks of waves I, III and V were marked; the built-in computer calculated wave I, III and V ALs and I-III, III-V and I-V IPLs. BAEPs were plotted on an X-Y plotter (Hewlett Packard, USA). One-way ANOVA (paired comparison between means) was carried out to check for statistical significance of equality on different characteristics between various paired groupings, for e.g. NS vs each group, DF vs each group, etc. The results of 120 (6 C_2 x 8) paired comparisons were obtained. The level of significance was taken as $P<0.05$.

RESULTS

The tracings of BAEPs in different groups of subjects are shown in Fig. 1. Table II shows the ALs of BAEPs in different groups of subjects and Table III shows the IPLs in different groups.

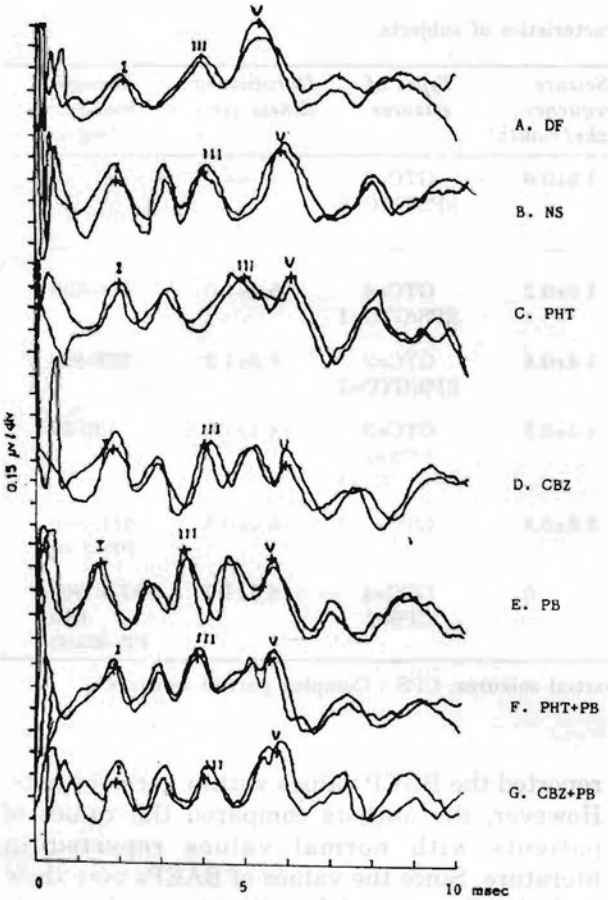

Fig. 1 : BAEP recordings taken from different groups. DF : drug free epileptics, NS : normal subjects, PHT : Phenytoin, CBZ : Carbamazepine, PB : Phenobarbital. Note the prolongation of wave III and V ALs and I-III and I-V IPLs by PHT as compared to DF and wave III AL and I-III IPL as compared to NS. CBZ also prolonged wave III and V ALs I-III and I-V IPLs as compared to DF.

DF : DF epileptics had reduced AL of wave V as compared to NS ($P<0.05$). IPL I-V was also reduced in DF as compared to NS ($P<0.05$). IPLs I-III and III-V were also reduced but the differences were not statistically significant.

PHT : Patients on PHT monotherapy showed significantly prolonged ALs of waves III and V ($P<0.05$ for both) as compared to DF epileptics and of wave III ($P<0.05$) as compared to NS. IPLs I-III and I-V were significantly prolonged by PHT when compared to DF ($P<0.01$ and $P<0.05$ respectively) and I-III IPL even when compared to NS ($P<0.05$).

CBZ : Patients on CBZ monotherapy had significantly prolonged ALs of waves III (left ear recording) and V ($P<0.05$ for both) as compared to DF epileptics. IPLs I-III and I-V were also significantly prolonged as compared to DF epileptics ($P<0.05$ for both). There were no statistically significant differences in ALs and IPLs as compared to NS.

PB, PHT + PB and CBZ + PB : Patients in these groups showed no significant changes in ALs and IPLs except for a prolongation of wave V AL as compared to DF epileptics ($P<0.05$).

Comparison of AED Groups : PHT monotherapy prolonged wave III AL as compared to PHT+PB ($P<0.05$). Wave V AL was also prolonged by PHT monotherapy as compared to PHT + PB but the difference was not statistically significant. PHT monotherapy prolonged I-III IPL as compared to PB ($P<0.05$), PHT+PB ($P<0.01$), CBZ+PB ($P<0.05$). I-V IPL was also prolonged by PHT as compared to PHT +PB. CBZ monotherapy significantly prolonged I-III IPL as compared to PB ($P< 0.05$) and PHT+PB ($P<0.05$).

DISCUSSION

We found that patients not receiving medication had reduced wave V AL and I-V IPL as compared to normal healthy subjects. Phenytoin and CBZ prolonged the wave III (PHT only) and V ALs and I-III and I-V IPLs as compared to DF epileptics. Phenytoin monotherapy also produced a prolonged wave III AL and I-III IPL as compared to normal subjects.

It is well known that the epileptogenicity is modulated by mechanisms that alter neuronal excitability and synchronisation involving both synaptic and nonsynaptic events (6). An altered synaptic transmission and/or neuronal conduction may lead to reduced wave V AL and I-V IPL in DF epileptics. There is only one published study (7) which has reported any data on epileptics without medication. This study

TABLE I : Clinical characteristics of subjects.

	Group	n	Age (yrs)	Seizure frequency (attacks/month)	Types of seizures	Duration of illness (yrs)	Dosage of medication (mg/d)
A.	Drug free epileptics (DF)	5	22.0±2.8	1.8±0.6	GTC=3 SPS/GTC=2	—	—
B.	Normal Subjects (NS)	10	25.9±1.7	—	—	—	—
C.	Phenytoin monotherapy (PHT)	5	26.4±2.7	1.6±0.2	GTC=4 SPS/GTC=1	5.1±1.0	200-600
D.	Carbamazepine monotherapy (CBZ)	5	21.7±2.6	1.4±0.4	GTC=3 SPS/GTC=2	3.8±1.2	200-800
E.	Phenobarbital monotherapy (PB)	7	20.9±2.8	1.3±0.3	GTC=3 SPS=3 SPS/GTC=1	4.1±1.6	30-20
F.	Phenytoin + Phenobarbital (PHT+PB)	5	24.5±2.6	3.8±0.8	GTC=5	5.0±0.9	PHT=300 PB=3-90
G.	Carbamazepine Phenobarbital (CBZ+PB)	5	23.1±1.9	2.8±1.0	GTC=4 CPS=1	6.0±1.7	CBZ = 200-600, PB=60-90

GTC : Generalised tonic clonic seizures; SPS : Simple partial seizures; CPS : Complex partial seizures; SPS/GTC : Partial with secondary generalisation.

TABLE II : Absolute latencies of BAEPs in different groups of subjects.
(Values are from right side stimulation)

Group	n	Absolute latencies (msec) Mean ± SE		
		I	III	V
A. Drug free epileptics (DF)	5	1.88 ± 0.09	3.74 ± 0.12	5.31* ± 0.07
B. Normal Subjects (NS)	10	1.75 ± 0.04	3.77 ± 0.05	5.63 ± 0.07
C. Phenytoin monotherapy (PHT)	5	1.71 ± 0.05	4.17*• ± 0.30	5.76* ± 0.17
D. Carbamazepine monotherapy (CBZ)	5	1.67 ± 0.09	3.96 ± 0.12	5.68* ± 0.07
E. Phenobarbital monotherapy (PB)	7	1.88 ± 0.14	3.23 ± 0.07	5.66* ± 0.09
F. Phenytoin + Phenobarbital (PHT + PB)	5	1.88 ± 0.11	3.70 ± 0.17	5.66* ± 0.17
G. Carbamazepine + Phenobarbital (CBZ + PB)	5	1.89 ± 0.05	3.96 ± 0.08	5.71* ± 0.13

*P<0.05 vs DF, •P<0.05 vs NS. Wave III AL was also prolonged by PHT in comparison to PHT + PB (One way ANOVA).

reported the BAEP values within normal limits. However, the authors compared the values of patients with normal values reported in literature. Since the values of BAEPs may show variation from one laboratory to another, it is pertinent to study normal subjects in one's own laboratory as has been done in the present study.

Phenytoin and CBZ monotherapy was associated with prolonged wave III AL (PHT only), wave V AL, I-III and I-V IPLs as compared to DF patients of epilepsy. These findings are in agreement with previous reports on the effect of PHT (4) and CBZ (3). Phenytoin also produced prolongation in wave III AL and I-III IPL in comparison with normal healthy subjects. This is in agreement with previous studies of Chan et al (2) and Green et al (5). Both these studies used normal subjects for comparisons.

Phenytoin concentrates selectively at specific binding sites at the cerebellum and brainstem (8, 9). Considering the generation of BAEP waves as follows: Wave I from the auditory nerve,

TABLE III : Interpeak latencies of BAEPs in epileptics on different group of subjects.
(Values are from right side stimulation)

Group	n	Interpeak latencies (msec) Mean ± SE		
		I-III	III-V	I-V
A. Drug free epileptics (DF)	5	1.83 ± 0.08	1.65 ± 0.10	3.48* ± 0.13
B. Normal Subjects (NS)	10	2.02 ± 0.03	1.86 ± 0.04	3.88 ± 0.06
C. Phenytoin monotherapy (PHT)	5	2.46**+ ± 0.27	1.59 ± 0.19	4.05* ± 0.16
D. Carbamazepine monotherapy (CBZ)	5	2.29* ± 0.12	1.73 ± 0.10	4.02* ± 0.08
E. Phenobarbital monotherapy (PB)	7	1.93 ± 0.11	1.84 ± 0.11	3.78 ± 0.20
F. Phenytoin + Phenobarbital (PHT + PB)	5	1.82 ± 0.14	1.76 ± 0.15	3.58 ± 0.18
G. Carbamazepine + Phenobarbital (CBZ + PB)	5	2.08 ± 0.04	1.60 ± 0.16	3.58 ± 0.09

*P<0.05 and **P<0.01 vs DF, +P<0.05 vs NS. I-III IPL was prolonged by PHT as compared to PB (P<0.05), PHT+PB (P<0.01) and CBZ+PB (P<0.05), and by CBZ in comparison to PB (P<0.05) and PHT+PB (P<0.05). I-V is prolonged by PHT and CBZ as compared to PHT+PB (P<0.05) (one way ANOVA).

Wave II from the entry point of the auditory nerve at the brainstem on the cochlear nucleus, waves III, IV and V in the brainstem along the ascending auditory pathway between the cochlear nucleus and inferior colliculus (10), it appears that PHT and CBZ may produce a slower conduction between the cochlear nucleus and inferior colliculus. This is indicated by the observed prolongation in wave III and V ALs and I-III and I-V IPLs. A slower conduction velocity, due to effects on axon membranes, synaptic transmission and neuronal integration may prolong the central conduction (11-13). The slowed conduction may reflect a general membrane stabilising effect of the AEDs (3).

Phenobarbital monotherapy did not produce any BAEP changes except for a prolongation of wave V AL. This finding is in agreement with previous reports (14) indicating that much higher dosages than used in the present study are needed to obtain BAEP changes in animals and man. Phenobarbital (in the dosage of 30-60 mg/d) when used in combination with PHT also gave the same results. On comparison of the drug groups with each other, PHT and CBZ were found to produce greater prolongation of wave III AL (PHT only), I-III and I-V IPLs as compared to PB monotherapy and PHT and PB combination. The interaction of PB with PHT is difficult to explain. The effect observed could be due to a "protective effect" of PB on the alteration of BAEPs by PHT as suggested by a previous study (15).

Epilepsy *per se* may produce alterations in BAEPs. Anti-epileptic drugs studied alone or in combination in the mentioned dosages appear to lead to "normalization" of BAEPs with the exception of PHT monotherapy which produces alterations of BAEPs as compared to normal subjects.

The present study emphasises the application of BAEPs in the evaluation of AED therapy. The test may give better information about the functional effects of AEDs than blood levels which may not be an appropriate indicator of the effective levels at the CNS.

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