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The impact on cognition by phenobarbital in epilepsy treatment

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Abstract

Despite the development of successive generations of antiepileptic drugs, phenobarbital has retained a unique position in the therapeutic armamentarium and is still the most widely prescribed treatment for epilepsy worldwide. Although serious systemic side effects of phenobarbital are uncommon, its potential neurotoxicity remains a major concern. This is particularly so in the developed world. These neurotoxic effects include sedation, behavioral problems (in particular, hyperactivity), impaired cognition, depressed mood and affect. We conducted a case control study to evaluate the cognitive effects of phenobarbital treatment in epilepsy patients in rural China. The study patients were treated with phenobarbital monotherapy. Neuropsychological tests including Mini-Mental State Examination, Auditory Verbal Learning Test, Digit Span Test, Verbal Fluency Test, and Digit Cancellation Test were performed at baseline and during follow up. We did not find any significant change in the cognitive function, expect for improvement in verbal fluency test among patients whose seizures control improved with phenobarbital. We concluded that there was no cognition impairment from treatment with phenobarbital in patients with epilepsy. On the other hand, language function of patients may improve due to the beneficial effect of seizure control. Phenobarbital remains useful to treat epilepsy particularly in the developing countries.

INTRODUCTION

Epilepsy is among the most common serious brain disorders worldwide. It has been estimated that up to 85% of the 50 million epilepsy patients living in the developing world do not receive any antiepileptic drug (AED) treatment.[1] Phenobarbital (phenobarbitone; PB) was synthesized in 1911. It has retained a unique position in the therapeutic armamentarium and is still the most widely prescribed treatment for epilepsy worldwide.[2] Its potential neurotoxicity remains a topic of major concern, such as sedation, behavioral problems, impaired cognition and depressed mood and affect, particularly in the developed world.[3]

One of the studies to address this issue is that from Chen *et al*. from Taiwan.[4] This was a randomized parallel group design study comparing the cognitive functions of patients on different AEDs. The subjects were 73 newly diagnosed children with epilepsy. Among them, 25 patients were treated with carbamazepine, 23 treated with PB and 25 treated with valproate. The mean steady-state blood levels of AEDs in each group was within therapeutic range during treatment. There was also no significant difference in seizure control among the three treatment groups. The study found that there was no significant differences in mean IQ score among the three groups at any stage. However, there was a significant negative relation between P300 latencies were increased in the children receiving PB, but not in children receiving carbamazepine and valproate.

An earlier study from California evaluated the cognitive effect of PB treatment on 25 children with febrile convulsion receiving PB for a mean of 35 months, versus 25 other children with febrile convulsion, not receiving PB, matched for sex, age at the time of testing, race and socioeconomic status. All the subjects were tested by Wechsler Preschool and Primary Scale of Intelligence; the Matching Familiar Figures Test; and the Children's Embedded Figures Test. There were no significant differences in test results between the two groups.[5]

Recently there has been increasing concern on the effect of prenatal exposure to AEDs on mental development of children. A double-blind study[6] compared 114 adults men who were exposed to PB in utero with 163 controls who were not exposed to PB during gestation. The two groups were matched on a wide spectrum of maternal variables. This study showed that men exposed prenatally to PB had significantly lower verbal intelligence scores.

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COGITIVE EFFECTS OF PHENOBARBITAL TREATMENT IN RURAL CHINA

During 2008-2009, we conducted a study aimed to evaluate the cognitive effects of PB treatment in epilepsy patients in rural China. One hundred and forty four patients with generalized tonic clonic seizures (GTCS) and 144 normal controls were recruited from five study sites. For the study patients, neurologists reviewed the history and performed physical examinations to establish the diagnosis of epilepsy. Patients were enrolled if they fulfilled the following inclusion criteria: 1) ≥16 years of age; 2) primary or secondary GTCS; 3) newly diagnosed or receiving non-conventional treatment only; 4) mini-mental state examination (MMSE) score >22, and Hamilton depression rating scale (HAMD) <7. The exclusion criteria were: 1) <16 years of age; 2) symptomatic epilepsy secondary to known neurological disorder (cerebrovascular disease, injury, tumor, etc); 3) seizure types other than GTCS; 4) seizures well controlled by standard AEDs; 5) MMSE score ≤22, and HAMD scale >7; 6) presence of a progressive neurological condition; 7) presence of cardiac, hepatic, or renal disorders, or severe hypertension; status epilepticus alone; current adequate medical treatment; or an active psychiatric condition that would impact interpretation of neurological assessment. Controls were recruited among healthy individuals without any neurological and other chronic disease, who were living in the same village and matched age, sex and education level with the epilepsy cases. Patients entering the study were treated with PB monotherapy. Starting doses were 60 mg, taken once daily at night, and the usual maintenance dose was 120–180 mg daily. The maintenance doses were those that controlled the seizures and were well tolerated.

At baseline and 12 months of follow-up, cases and controls were evaluated with a battery of neuropsychologic tests, which comprised of MMSE, HAMD, Digit Span Test, Verbal Fluency Test (VFT), Auditory Verbal Learning Test and Digit Cancellation Test. Efficacy of PB treatment was evaluated at the end of follow-up.

In both the patient and control groups, 93 (64.6%) were males. The average age of the patients was 36 years old and their average education years were 7.4. There was no significant difference in the BMI between patient and control groups (22.2±2.7 *vs*. 22.7±2.7, p=0.104).

Among the study patients, 141 (97.9%) had primary GTCS, 3 (2.1%) had focal with secondary GTCS. One hundred and three patients (71.5%) were previously not receiving conventional AEDs.

At 12 month follow-up, 136 (94%) epilepsy patients and 137 (95%) controls completed the cognitive function assessment. At each visit during follow-up period, we found some improvement of cognition assessments of both groups, but with no statistical significance, expect for verbal fluency test. The mean score of VFT of patients at 12 months (21.5 ±5.5) was significantly higher when compared to the mean score at the baseline (19.6±6.0, P<0.001). By multivariate analysis, it was found that PB efficacy was the most important factor of the score changes of cognitive function, with significant increase of VFT scores found in subgroup with PB efficacy over 75%. Among all the neuropsychological tests, there was significant difference between patient and control groups only for VFT.

In conclusion, there was no cognition impairment from treatment with PB in patients with GTCS. On the other hand, language function of patients with GTCS may improve due to the beneficial effect of seizure control. Therefore, PB should remain in the therapeutic armamentarium to treat epilepsy particularly in the developing countries.

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