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An Examination of the Effects of Phenobarbital on Thyroid Function Tests in Childhood Epilepsy

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Abstract ***Aim:*** The aim of this study was to evaluate changes in thyroid function tests in a group of epileptic children taking phenobarbital. ***Materials and Methods:*** Patients' demographic data and free thyroxine (FT4), free triiodothyronine (FT3) and thyroid-stimulating hormone (TSH) levels during at least 12 months of treatment were recorded. Forty-eight children using phenobarbital and 45 healthy children were enrolled. ***Results:*** In the phenobarbital group, FT3 level was 4.14±0.1 pg/mL, FT4 1.22±0.01 ng/dL and TSH 2.88±0.21 mIU/L. In the control group, FT3 level was 4.28±0.08 pg/mL, FT4 1.34±0.02 ng/dL and TSH 2.28±0.19 mIU/L. The rates of subclinical hypothyroidism between the two groups were not show statistically significant difference (p=0.16). ***Conclusion:*** The use of phenobarbital in the treatment of childhood epilepsy does not appear to increase the risk of thyroid dysfunction.

Key words Child; Epilepsy; Phenobarbital; Thyroid function test

Introduction

Phenobarbital (PB), one of the classic antiepileptic drugs (AEDs), has recently become less popular due to its adverse effects, especially cognitive and behavioural side-effects. Despite the development of a new generation of AEDs with fewer side-effects, PB is still widely used, however, especially in developing countries, because of its low cost.[1]

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The antiepileptic activity of PB is based on enhancement of γ-aminobutyric acid (GABA)-mediated transmission. It has long been recognised that PB acts by potentiating the action of GABA on $GABA_A$ receptors, and at higher concentrations by activating the receptors directly.[2]

Both seizures and AEDs may induce disturbances in the hormonal system. Since the majority of AEDs antagonise glutamate receptors and/or block voltage-dependent calcium and sodium channels and enhance GABAergic transmission, similar neurochemical mechanisms may be expected to be involved in the interaction of these drugs with synthesis of hypothalamic hormones, such as thyrotropin-releasing hormone. Moreover, PB may affect hormone metabolism by stimulating cytochrome P450 isoenzymes.[3,4]

PB reduces the level of serum thyroid hormone and increases the activities of hepatic drug metabolising enzymes in rats, mice and dogs.[5-7] PB also increases levels of serum thyroid stimulating hormone (TSH) and thyroid gland growth in rats.[6] Enhancement of thyroid hormone metabolism has been proposed as a possible mechanism for the PB induced increase in the level of TSH.[8] This effect of PB on thyroid hormones shown in animal studies has not been clearly demonstrated in human studies, however, especially in childhood.[9,10] In this study, we investigated

the serum levels of free thyroxine (FT4), free triiodothyronine (FT3) and TSH in epileptic children during chronic treatment with phenobarbital compared to healthy children.

Materials and Methods

This study was performed at the Pediatric Neurology and Endocrinology Division of the Department of Pediatrics at the Ataturk University Faculty of Medicine, Erzurum, Turkey. Permission was obtained from the parents of all children included. The study was approved by the local Ethical Committee.

Study Design and Participants

The study group consisted of 48 children monitored for epilepsy and 45 healthy children. The children in the study group suffered from different types of idiopathic epilepsy in childhood, including those classified as idiopathic generalised epilepsies and idiopathic focal epilepsies, excluding epileptic encephalopathies. The diagnosis of epilepsy was based on electroencephalography and clinical features. None of the patients received any medication and AED other than PB. PB was prescribed at the normal dosages in two daily doses. Children were deemed eligible for inclusion if they were aged 1 to 4 years, had received PB monotherapy for 12 or more months and had been seizure-free for 6 months or more. These periods were selected based on data from previous similar studies.[11,12]

The study and control groups had similar demographic characteristics. Age and sex matched children were selected as controls. The children in the control group from the same geographical area and were admitted to the paediatric out-patient clinic for reasons other than chronic systemic disease such as endocrine and neurologic disorders. Controls were similar to patients except for epilepsy and PB therapy. We reviewed the records of all patients and looked at the following details: age of onset, length of drug use, drug dosage and laboratory parameters, including FT3, FT4 and TSH.

In accordance with laboratory reference values, normal serum values were determined at 0.35-4.94 mIU/L for TSH, 0.93-1.7 ng/dL for FT4 and 1.8-4.6 pg/mL for FT3. While TSH levels were higher than 4.94 mIU/L in cases with subclinical hypothyroidism, FT4 values remained within normal limits.

The exclusion criteria were use of any medications known to interfere with liver or renal functions and thyroid functions, endocrine disorders, abnormal neurological examination and cerebral computed tomography and/or magnetic resonance imaging scans and non-therapeutic levels of phenobarbital level measured.

Biochemical Analysis

Blood samples were collected from patients at least 12 months after diagnosis and start of PB treatment. All blood samples were stored at -20°C until analysis. All tests were performed according to the manufacturer's instructions.

This assay is based on the bacterial enzyme β-galactosidase, which has been genetically engineered into two inactive fragments. These fragments spontaneously reassociate to form fully active enzyme that, in the assay format, cleaves a substrate, generating a colour change that can be measured spectrophotometrically. In the assay, analyte in the sample competes with analyte conjugated to one inactive fragment of β-galactosidase for antibody binding site. If analyte is present in the sample, it binds to antibody, leaving the inactive enzyme fragments free to form active enzyme. If analyte is not present in the sample, antibody binds to analyte conjugated on the inactive fragment, inhibiting the reassociation of inactive β-galactosidase fragments, and no active enzyme will be formed. The amount of active enzyme formed and resultant absorbance change are directly proportional to the amount of drug present in the sample). Serum FT3 (pg/mL), FT4 (ng/dL), TSH (mIU/L) were determined in serum using an electrochemiluminescence immunoassay kit (Roche Diagnostics GmbH, Mannheim, D-68298, Germany).

Statistical Analysis

Data were subjected to Pearson's chi-square and independent sample T tests using SPSS 18.0 (Armonk, NY, United States of America) software. Significance was set at p less than or equal to 0.05. The results are expressed as mean ± Standard error mean.

Results

Mean age and gender of the PB and control group subjects and mean duration of drug use and dosage are shown in Table 1. There was no statistically significant difference between the PB and control groups in terms of gender or age ($p>0.05$).

In the PB group, mean PB level was 17±0.7 µg/mL, FT3 level was 4.14±0.1 pg/mL, FT4 1.22±0.01 ng/dL and TSH 2.88±0.21 mIU/L. In the control group FT3 was

4.28±0.08 pg/mL, FT4 1.34±0.02 ng/dL and TSH 2.28± 0.19 mIU/L. FT4 levels were statistically significantly different between the PB and control groups (p=0.003). FT3 and TSH levels were not statistically significantly different between the groups (p>0.05) (Figure 1).

Subclinical hypothyroidism was determined in six children in the PB group and two in the control group. Rates of subclinical hypothyroidism were not statistically significantly different between the groups (p>0.05).

Discussion

This study investigated the effects on thyroid function of single-drug treatment with PB, which is still widely used in the early years of life. We found that PB caused a reduction in FT4 levels and a small, but not significant, increase in the mean level of TSH. The changes are typically less marked than those in children treated with microsomal enzyme-induced drugs such as diphenylhydantoin and carbamazepine.[10,13-15] These data suggest that PB differs from these drugs, although it has a similar mechanism of enzyme induction.[16]

Animal studies have shown that PB significantly affects serum TSH and FT4 levels.[16,17] In human studies, PB has been reported to cause a significant reduction in levels of FT4, but no change in the level of TSH.[15,18-20] Castro-Gago et al reported that the minor effects of PB on thyroid function tests probably reflect the absence of effects on thyrotropin.[10] Various hypotheses have been proposed regarding the mechanism involved in the decrease in serum FT4 levels caused by PB in animal studies.[8,21] McClain et al suggested that the induction of thyroxine glucuronyl transferase appears to play an important role in the increased metabolism and excretion of thyroxine in rats receiving PB.[8] We concluded that this may be due to the difference in PB effects on thyroid hormones between human and animal studies, a higher dose of PB being given in animal studies.

There are various limitations to this study. One is the low patient numbers. Secondly, although patients were selected from the same geographical region, they could not be completely matched in terms of all parameters. Thirdly, blood specimens were collected only once, again for ethical reasons. Fourthly, the inclusion of healthy subjects as the control group was unable to exclude the uncertain effect regarding thyroid functioning in epileptic patients. Fifthly, duration of PB use was short.

In conclusion, the administration of PB in childhood does not appear to increase the risk of thyroid dysfunction. It seems the effect of PB in thyroid function is minimal and subclinical. However, further long-term studies involving greater patient numbers are needed for any recommendation to routine monitoring of thyroid function tests in these patients. We also think that more detailed studies should be performed to examine the correlation between subclinical hypothyroidism and PB in childhood epilepsy treatment.

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Table 1 Comparison of the phenobarbital group versus the control group

	Control group n=45	Phenobarbital group n=48	P value
Male	30	33	0.83
Female	15	15	
Age (years)	2.46±0.14	2.53±0.13	0.602
Mean duration of drug use (months)	–	17.8±1.32	–
Mean drug dosage (Mg per Kg)	–	4.21±0.08	–

Note: P<0.005 was significant

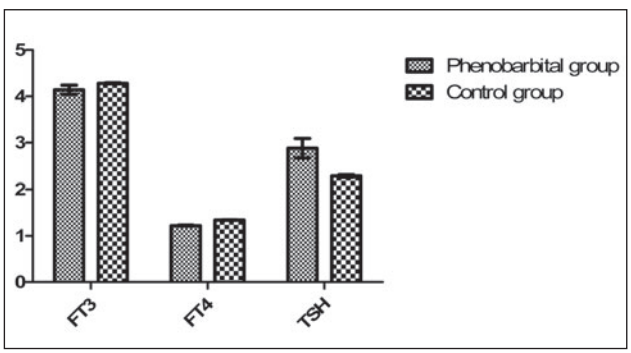

Figure 1 Comparison of thyroid function tests in phenobarbital group versus control group. Notes: FT4, Free throxine (ng/dL); FT3, free triiodothyroxine (pg/mL); and TSH, thyroid-stimulating hormone (mIU/L). Results are the means ± Standart error of the mean.

Declaration Interest

All authors declare that they have no conflicts of interest.

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