Abstract

To determine the effects of Phenobarbital (PBT) monotherapy on thyroid function tests including total T\textsubscript{4}, total T\textsubscript{3}, and TSH in epileptic children whose age ranged between 7-15 years.

The study was conducted in the department of pharmacology, college of medicine, university of Mosul, during a period of 9 months commencing from January-2005.

The patients’ group consist of 19 patients on PBT monotherapy together with a control group. Serum total T\textsubscript{4}, total T\textsubscript{3}, and TSH concentrations in epileptic children on PBT monotherapy were compared with those in control group by using unpaired “t” test.

We found a statistically significant reduction in total T\textsubscript{4} levels in patients receiving PBT compared with the control group, while Total T\textsubscript{3} and TSH levels were indifferent statistically. All patients were in euthyroid state, there were no clinical findings of hypothyroidism.

These data suggest that PBT monotherapy decreases serum total T\textsubscript{4} levels significantly(P<0.001), while total T\textsubscript{3} and TSH levels remained unaffected.

Introduction

A number of drugs may adversely affect thyroid function, either by increasing or decreasing its function or activity[1]. The pathways of thyroid hormone synthesis, secretion, transport in the circulation, and metabolism offer numerous targets for drug interaction [2]. Antiepileptic drugs(AED) are widely used in childhood epilepsies and other convulsive conditions. Recently, the side effects of AED to the endocrine system are being reported. Effects on thyroid hormone
balance are of primary importance in this regard[3]. Since anticonvulsants are used over along period, potential adverse effects should be adequately investigated. However only a few studies of thyroid function in children on long term anticonvulsant therapy have been conducted, and, in particular, the effects of chronic administration of a single anticonvulsant on thyroid functions have not been clarified[4]. PBT is a well known stimulant of the microsomal enzymes system of the liver metabolizing thyroid hormones. The effects of long term monotherapy with Phenobarbital(PBT) on the thyroid function were evaluated in a selected group of children and adolescent patients with epilepsy. Some studies have shown that PBT increases the peripheral clearance of T4 and T3 and decreases serum T4 and T3 concentrations in rats, but TSH remains unchanged [5]. Other studies showed that PBT therapy decreases serum T4 concentration without producing clinical signs of hypothyroidism while serum TSH concentrations were not affected [3,4,6,7].

The aim of the present study was to assess the effects of PBT as a monotherapy in epileptic children on total T3, T4 and TSH concentrations.

Subjects, materials and methods

A. patients

This study was conducted between Jan. and Sept. 2005. Patients with epilepsy were referred from specialists in the field of pediatrics and those who fulfilled the criteria were included in this study.

Criteria:
1. Epileptic patients on PBT monotherapy.
2. Duration of therapy not less than 1 year.
3. They didn’t use any other drug for a long time before the study.
4. Patients free from other organic diseases especially, hepatic, renal, thyroid or diabetes mellitus.
5. No abnormalities on neurological examination.

Nineteen epileptic patients were finally selected and included in this study with an age ranged between 7 and 15 years (mean 11.89 ± 2.35 years). They were 16 males and 3 females. Patients were on PBT in mean daily dose of 135.78 ± 41.67 mg ( ranged between 60 and 180 mg/d), with a mean duration of therapy of 3.63 ± 2.08 years ( ranged between 1 and 7 years).

B. Control

Twenty one apparently healthy subjects, who did not receive any medication for the past 2 weeks taken as a control group. They were 19 males and 2 females with a mean age of 11.80 ± 2.44 year ( ranged between 7 and 16 years).

Materials and method

From both patients and control a 5 ml fasting venous blood samples were taken early in the morning , and sera were taken for the assay of total T4, total T3 and TSH ( using kit Immunotech-France) with the aid of Gamma counter.

Statistical analysis

Standard statistical methods to determine the mean and standard deviation of the values. Unpaired t-test was used to compare measured total T3, T4 and TSH between control and patients group. Differences considered significant at p≤ 0.05[8].

Results

By comparing measured total T3, T4 and TSH between control and patients group, there was a significantly lower total T4 in the patients group (p<0.001) ,while there was no significant differences between control and
patients group with regard to total T₃ and TSH. (table 1).

**Table 1** Comparison of measured thyroid hormones between control and cases.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
<th>Cases(N₀=19)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₃₃ (nmol/L)</td>
<td>2.82 ± 0.31</td>
<td>2.80 ± 0.29</td>
<td>0.26</td>
<td>&gt;0.05 (NS)</td>
</tr>
<tr>
<td>T₄₄ (nmol/L)</td>
<td>138.19 ± 11.83</td>
<td>91.05 ± 11.38</td>
<td>12.82</td>
<td>&lt;0.001(S)</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>1.71 ± 0.31</td>
<td>1.74 ± 0.30</td>
<td>0.38</td>
<td>&gt;0.05 (NS)</td>
</tr>
</tbody>
</table>

NS= Not significant.  
S= significant.

**Discussion**

The present study involved 19 epileptic patients on Phenobarbital (PBT) monotherapy, their thyroid function tests revealed a statistically significant reduction in the serum level of total T₄ with statistically insignificant differences in the serum levels of total T₃ and TSH in comparison with an age and sex matched apparently healthy control. Theodoropoulos and Zolman (1989), reported that PBT therapy increases the peripheral clearance of T₄ and T₃ and decrease serum T₄ and T₃ concentration while TSH remains unchanged in rats[5], while in dogs Daminet et al., (1999) found that PBT therapy in euthyroid dogs did not affect total T₄, total T₃ and TSH levels[9].

With regards to human research, Tanaka et al.,(1987) studied thyroid functions in 287 epileptic children on long term anticonvulsants of which 63 of them on PBT monotherapy. He concluded that total T₃ and T₄ concentration were decreased after more than 6 years of therapy with PBT[4]. Kirimi et al.,(1999) also by assessing thyroid functions in epileptic patients on long term anticonvulsant monotherapy (phenobarbital, phenytoin, carbamazepine, clonazepam and valproate), found that PBT, phenytoin, carbamazepine and clonazepam depress serum free T₄ level while valproate hase no effects on thyroid functions[3].

Our finding could be related to the effect of the disease (epilepsy) or to the drug, Thomas et al.,(1998) found no correlation between neuropsychological impairment among epileptic patients and levels of thyroid hormone[10]. Euthyroid hypothyroxinemia describes a situation in which total or free T₄ concentrations are low without evidence of thyroid dysfunction usually with normal TSH, this may be associated with medication or a non-thyroidal illnesses as liver or renal disease[11].several assay techniques have been developed to measure free hormone concentrations. These methods produce results that show good agreement in most ambulant patients, however, in patients with non-thyroidal illnesses, results may not always correlate well with one another due to various assay artifacts[1].PBT is a well known stimulant of the microsomal enzymes system of the liver metabolizing thyroid hormones. It has been postulated that serum T₄ levels are low in epileptic patients on PBT therapy because of accelerated metabolism of thyroid hormones in the liver [12,13,14]. Furthermore, an increased peripheral conversion of T₄ to T₃
during PBT therapy also has been suggested as an explanation of unchanged $T_3$ levels[15]. In our study a normal TSH level is in consistence with the finding of Gaskill et al. (2000) who found that TSH and TSH stimulating test were normal in dogs receiving PBT for 1 year, and attributed the result to appropriately functioning hypothalamic pituitary thyroid axis[6].

**Conclusion**

We conclude that thyroid functions should be examined in children given long-term treatment with PBT since thyroid hormones influence brain development in childhood.

**References**