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EFFECTS OF ANTICONVULSANT DRUGS ON THYROID HORMONES IN EPILEPTIC CHILDREN*

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Serum total and free thyroid hormones, reverse T3 (rT3), thyroxin binding globulin (TBG) and thyroid stimulating hormone (TSH) concentrations were measured in 35 epileptic patients receiving anticonvulsants (phenobarbitone, phenytoin). There was a significant reduction found in total thyroxine (TT4), free thyroxine (FT4), total triiodothyronine (TT3), free triiodothyronine (FT3) and rT3 in the group treated with, phenytoin. The thyroid hormone levels were within normal limits in the group receiving phenobarbitone. *Key words: anticonvulsant drugs, thyroid functions.*

It is widely known that long-term administration of anticonvulsant drugs affects blood thyroid hormone levels[1]. Despite a reduction in serum TT4 and FT4 concentrations, most studies have emphasized that patients receiving anticonvulsants appear to be clinically euthyroid with normal reference TSH levels[2].

In 1961, studies revealed a decrease in protein-bound iodine in adults undergoing phenytoin therapy, which was attributed to the displacement of T4 from its binding to TBG[3,4]. More recent investigations have demonstrated that adults treated with phenytoin also have decreased TT4, FT4 and T3 levels[3].

The long-term use of phenobarbitone has been shown to produce a drop in the serum T4 concentration which coincides temporarily with hepatic enzyme induction[5].

The aim of this study was to determine the effect on thyroid function of long-term anticonvulsant treatment with phenytoin and phenobarbitone, placing particular emphasis on the direct measurement of serum TT4, FT4, TT3, rT3, TBG and TSH concentrations.

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Material and Methods

This study was conducted in epileptic children who were receiving anticonvulsant therapy for a mean period of 2-3 years.

We examined two groups, one consisting of 20 patients who received only phenobarbitone and the other, consisting of 15 patients, who were only receiving phenytoin. The age distribution of the patients receiving phenobarbitone ranged between 2.5-8 years (mean 6.9 years). Fifteen healthy children, whose ages were between 4-12 years (mean 8 years), were the control subjects. (Table I).

Table I: Mean Serum Concentrations and Period of Treatment With Anticonvulsant Drugs

	Phenobarbitone		Phenytoin
Serum concentration of drug (μ g/ml)	23.64 ± 7.3 (11.26 – 34.64)		10.62 ± 4.6 (8.78 – 14)
Period of drug use (yrs.)	2.3 ± 1.2 (1.4 – 4.5)	$p > 0.05$	2.5 ± 1.8 (1.5 – 6) ($p > 0.05$)

All patients were examined by a pediatric endocrinologist, and except for short stature and delayed skeletal maturation, none of them showed clinical findings of hypothyroidism.

The serum TT3, TT4, FT3, FT4, TSH, rT3 and TBG levels were measured in all patients by the radioimmunoassay technique using commercially available kits (Diagnostic Product Corporation for TT3, TT4, FT3, FT4; IRMA for TSH, Biodata for rT3 and GMBH for TBG).

Serum phenobarbitone and phenytoin levels were measured in all patients by the radioimmunoassay technique of Baxter.

The results were analyzed statistically using Student's *t* test.

Results

In group I (patients on phenytoin), TT_4 levels were lower when compared with the control group, and the difference was statistically significant ($p < 0.01$). In group II (patients on phenobarbitone), TT_4 levels did not differ and when compared with the control group, the difference was not statistically significant ($p > 0.05$). The difference in TT_4 levels was also statistically significant in groups I and II ($p < 0.01$). FT_4, TT_3, FT_3, and rT_3 levels were lower in group I when compared with group II and the control group, and the difference was statistically

significant ($p < 0.05$). Between group II and the control group, there was no difference with regard to these hormones ($p > 0.05$). There were also no significant variations in the TSH levels of the three groups ($p > 0.05$). In groups I and II, the TSH levels were found to be within normal ranges. The TBG levels were found to be lower in group I when compared with group II and the control group and the results were statistically significant ($p < 0.01$) (Table II). Although, there was a significant decrease in the thyroid functions of group I, no clinical signs of hypothyroidism were detected.

Table II: Mean Serum Concentrations of TT_4, TT_3, FT_4, FT_3, rT_3, TSH and TBG in Serum During Anticonvulsant Therapy in Epileptic Children and Controls.

	Phenytoin Group I n = 15		Phenobarbitone Group II n = 20		Control n = 15
TT_4 nmol/1 (58 – 61)	62 ± 21.10[E] (46 – 80)	$p < 0.01$	105 ± 16.23 (66 – 105)	$p > 0.05$	137 ± 11.90 (95 – 146)
TT_3 nmol/1 (1.32 – 2.87)	1.30 ± 0.77[*] (1.02 – 1.33)	$p < 0.05$	2.34 ± 0.47 (1.7 – 2.7)	$p > 0.05$	2.45 ± 0.57 (2.2 – 2.9)
FT4 pmol/1 (10.3 – 18.9)	10.28 ± 4.3[*] (7.2 – 12.6)	$p < 0.05$	16.68 ± 5.9 (9.8 – 16.7)	$p > 0.05$	15.57 ± 4.6 (15 – 17.6)
FT3 pmol/1 (2.14 – 5.34)	2.25 ± 1.95[*] (1.95 – 4.1)	$p < 0.05$	4.85 ± 1.7 (2.05 – 6.1)	$p > 0.05$	0.42 ± 0.12 (2.5 – 6.6)
rT3 nmol/1 (0.20 – 0.56)	0.26 ± 0.96[*] (0.17 – 0.22)	$p < 0.05$	0.48 ± 0.77 (0.25 – 0.45)	$p > 0.05$	0.42 ± 0.12 (0.27 – 0.49)
TSH µu/1 (0.3 – 4.5)	2.08 ± 1.38[*] (1.05 – 3.8)	$p < 0.05$	2.29 ± 1.05 (1.5 – 2.9)	$p > 0.05$	2.02 ± 0.7 (1.7 – 2.2)
TBG mg/1 (14.7 – 36.3)	18.10 ± 7.5[E] (10.5 – 19.2)	$p < 0.01$	31.75 ± 6.6 (26.4 – 32.9)	$p > 0.01$	29.5 ± 4.4 (27.8 – 34.5)

E Compared with control ($p < 0.01$)
* Compared with control ($p < 0.05$)
* Compared with control ($p > 0.05$)

There was no difference seen in the duration of the anticonvulsant therapy between groups I and II (Table I).

When we attempted to make a correlation between the concentration of anticonvulsants and thyroid functions, we found that in the patients on phenytoin there was a negative correlation between TBG levels and phenytoin serum concentration ($r = 0.55$) ($p < 0.01$) (Fig. 1), while there was no correlation found between the duration of the anticonvulsant therapy and the levels of thyroid hormones. However, there was a negative correlation found between FT_4 levels and serum phenytoin concentrations ($r = 0.62$) ($p < 0.01$) (Fig. 2).

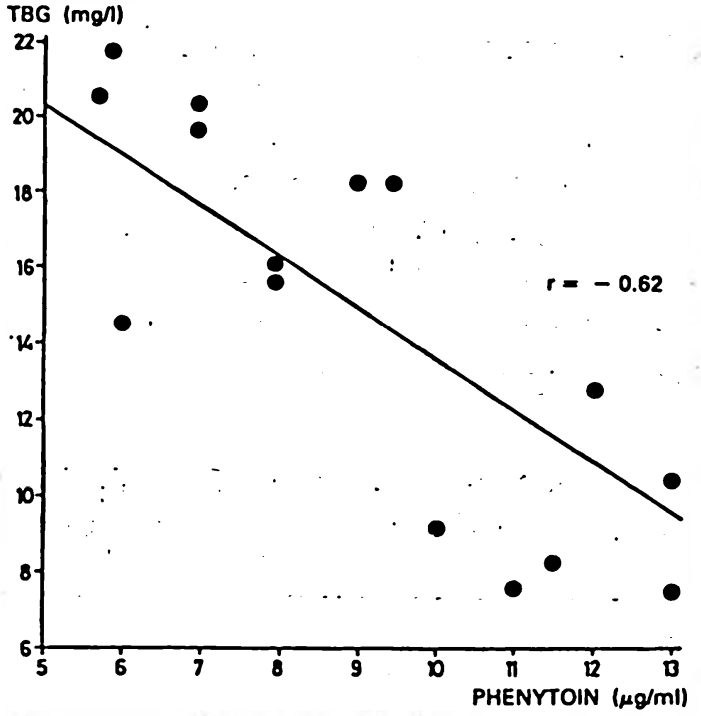

Fig. 1: Correlation between serum levels of TBG and phenytoin (r:-0.62) ($p < 0.01$)

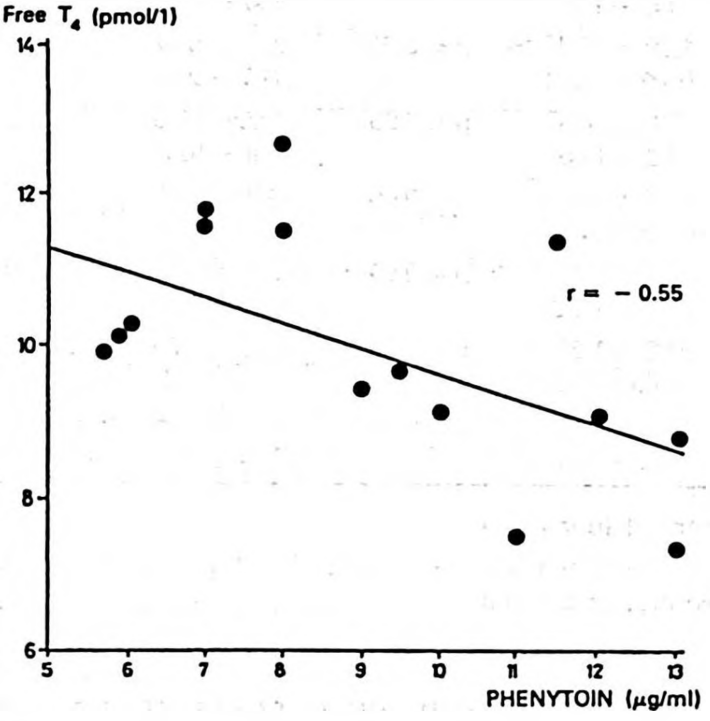

Fig. 2: Correlation between serum levels of phenytoin and FT_4 (r:-0.55) ($p < 0.01$)

Discussion

Anticonvulsants are known to induce the hepatic microsomal enzyme system resulting in the catabolization of thyroid hormones. During chronic use of phenobarbitone, deiodinating activity increases in the hepatic microsomes and the degradation of the thyroid hormones is aggravated. At the same time, phenobarbitone has an activating effect of up to 100 percent on the fecal clearance of T4[1]. On the other hand, during chronic use of phenobarbitone, T4

levels may remain compensatorily within normal limits. It was shown previously that phenobarbitone had no significant effect on thyroid functions[2]. In our study, the TT4 and FT4 levels in the group on phenobarbitone were not significantly different than those in the control group (Table II).

It has been reported that the use of phenytoin alone or in combination with carbamazepine results in a significant decrease in thyroid functions[3-5]. Results of other studies indicate that despite the decrease in TT4, and FT4 levels, TT3 and FT3 levels have been found to be normal in patients taking phenytoin[6]. This result was believed to be related to the sufficient conversion of peripheral T4 → T3 in spite of an increased catabolism of T4[7]. In some studies, as a result of the increased peripheral utilization and clearance of thyroid hormones related to phenytoin, a decrease was detected in FT4, FT3 and rT3 levels[2].

In our study, TT4, FT4, TT3, FT3 and rT3 levels revealed a statistically significant decrease in group I when compared with the control group and group II (Table II).

Despite the decreasing effect of anticonvulsants on thyroid hormone levels, most patients in the euthyroid state have normal TSH levels[8]. Some investigators have found high TSH levels in patients taking phenytoin[9]. An insufficient increase in TSH levels, in spite of the drop in T4 and T3 levels, has not been clearly explained. But normal TSH values reveal that the intrapituitary conversion of T4 to T3 is normal.

Surks et al[10] showed that phenytoin caused insufficient TRH → TSH stimulation. In our study, serum TSH levels were within normal limits in groups I and II.

It is known that phenytoin decreases TBG by an unknown mechanism. Although, the affinity of phenytoin to TBG in serum is less than T4, once the concentration of phenytoin reaches a certain level in serum, it is bound to TBG[8]. In our study, the TBG levels were found to be reduced in group I, and there was a negative correlation found between phenytoin serum concentrations (Fig. 1). This finding shows that the depressant effect of phenytoin on TBG is not related to the duration of therapy, but correlated with the serum concentrations of phenytoin. The same correlation is also seen in FT4 levels (Fig. 2). We found that serum thyroid hormone levels of the patients on phenobarbitone did not differ significantly, but that they had decreased significantly in the patients receiving phenytoin therapy. This decrease was mainly due to the serum concentration of phenytoin rather than to the duration of therapy.

There are some reports indicating that anticonvulsants not only affect thyroid hormones subclinically, but also cause clinical hypothyroidism[11]. In conclusion, we recommend that thyroid functions be monitored in patients receiving anti-convulsant therapy.

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