

Influence of Anticonvulsant Drugs on Thyroid Hormones in Epileptic Children

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Thyroid function tests were studied in epileptic children undergoing long-term anticonvulsive therapy with phenytoin, primidone or mephenytoin. Serum T_4 was decreased in all three treated groups, serum T_3 was diminished only in those treated with phenytoin or primidone. FT_4 was also significantly decreased while serum TSH and TBG were not affected in the treated patients. The effect of anticonvulsant drugs on thyroid hormone catabolism and peripheral conversion of T_4 seems to be important in these alterations.

In recent years several investigations have repeatedly documented that some anticonvulsants caused different alterations of thyroid hormone metabolism in adults [1, 5, 8, 9, 13, 14]. In this study we investigated the effects on the thyroid system of three anticonvulsive drugs commonly used in epileptic children.

Phenytoin was administered to 15 children over a period of 6 months to 11 (mean, 4 3/12) years. Eleven patients received primidone for 7 months to 7 6/12 (mean, 3 6/12) years, and seven patients were given mephenytoin for 6 months to 3 1/12 (mean, 2 1/12) years. The patients were selected by excluding those with goitre or a history of thyroid disease. The diagnosis of euthyroidism was established

PATIENTS AND METHODS

Four groups of children aged 3–12 years were investigated. Three of them consisted of patients with epilepsy. They received phenytoin, primidone or mephenytoin therapy; the fourth group was the control one. The composition of these groups is demonstrated in Table I.

TABLE I

Groups investigated in the study

Group	n	girls/boys
Phenytoin	15	8/7
Primidone	11	6/5
Mephenytoin	7	3/4
Control	11	6/5

Abbreviations

T_4	thyroxine
T_3	triiodothyronine
FT_4	free thyroxine
TSH	thyrotropic hormone
TBG	thyroxine binding globulin
r T_3	reverse triiodothyronine

by careful clinical investigation, and with no knowledge of the results of thyroid function tests. The patients receiving anti-convulsant medication were taking no other drug. The control group comprised children without epilepsy and thyroid disease.

Serum was separated immediately from blood samples drawn at 08 hours and stored at -20°C until analysis. Serum total T_4 and T_3 were determined by RIA (kits of the Isotope Institute of Hungarian Academy of Sciences). Serum free T_4 , TSH and TBG were measured with commercial RIA kits (Amerlex free T_4 RIA, Radiochemical Centre, Amersham; RIA-mat-TSH, Byk Mallinckrodt; TBG RIA, CEA Sorin). All assays were performed in duplicate, statistical analysis was done with the standard t test.

RESULTS

Figure 1 shows thyroid hormone concentrations in the different groups; individual values are indicated. In the treated groups, serum total T_4 level was lower than in the control group. Serum T_3 concentration was also lower in the groups

receiving phenytoin and primidone. In these two groups, the decrease in serum FT_4 concentration was significant. In children treated with mephenytoin, serum TSH and TBG were unaffected by anticonvulsants (Table II).

DISCUSSION

Phenytoin was the first anticonvulsant the decreasing effect of which on serum thyroid hormone concentrations was demonstrated with the protein bound iodine (PBI) method [11]. This observation was amply verified in later studies using the more specific competitive protein binding (CPB) and radioimmunoassay (RIA) methods for serum T_4 , and the same effect of other anticonvulsant drugs [6, 9, 10, 14], together with the decrease in serum total T_3 concentration was also demonstrated.

The exact mechanism of the alteration of serum thyroid hormone con-

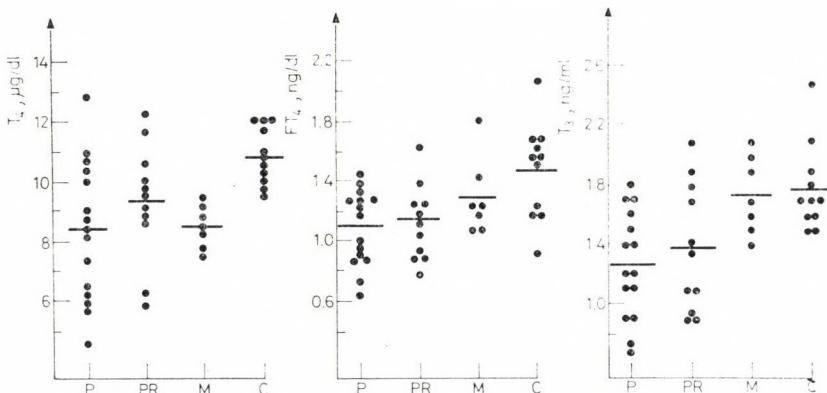


FIG. 1. Individual values of serum T_4 , FT_4 and T_3 in different groups. P = Phenytoin; PR = Primidone; M = Mephenytoin; C = Control

TABLE II

Serum T_4 , FT_4 , T_3 , TSH and TBG in children on long term treatment with various anticonvulsant drugs

Groups	(n)	T_4 $\mu\text{g/dl}$	FT_4 ng/dl	T_3 ng/ml	TSH $\mu\text{B/ml}$	TBG ng/ml
Phenytoin	(15)	8.42** ± 2.31	1.10** ± 0.24	1.25** ± 0.42	2.53+ ± 1.05	23.9+ ± 5.28
Primidone	(11)	9.37* ± 1.97	1.14** ± 0.27	1.38* ± 0.43	2.62+ ± 1.23	25.2+ ± 5.56
Mephenytoin	(7)	8.58*** ± 0.50	1.31+ ± 0.35	1.75+ ± 0.32	2.81+ ± 1.08	24.3+ ± 2.97
Control	(11)	10.98 ± 0.97	1.50 ± 0.31	1.78 ± 0.29	2.36 ± 1.12	24.5 ± 4.27

+ $p > 0.05$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

centrations in patients treated with anticonvulsants is not known. It was suggested that these drugs would decrease the level of thyroid hormone binding proteins [14, 15], but in our groups we could not find any difference in the TBG level. It was also assumed that the anticonvulsants decreased the thyroid hormone concentration by displacing them from their protein binding. Although the mechanism, an increase in the free/bound thyroid hormone ratio was observed in vitro [12], we could not find it in our patients.

An increased catabolism of thyroid hormones might also be the reason for the diminished serum thyroid hormone concentration. Acceleration of the T_4 clearance by phenytoin was observed [8] and converting enzyme activity in the rat liver was also stimulated [7]. T_4 catabolism is increased by phenytoin via stimulation of the hepatic microsomal system [8]. The increased conversion of T_4 to T_3 [3] may explain why serum T_3 and

T_4 decrease in a different manner. For example, in our patients treated with mephenytoin the decrease in T_4 was significant, while the decrease in T_3 was not significant. It seems that different anticonvulsants increase differently the activity of enzyme-caused degradation of thyroid hormones or catalyze the conversion of T_4 to T_3 .

Monodeiodination of T_4 in peripheral tissues produces not only T_3 but also a metabolically almost inactive reverse T_3 (rT_3) [2, 4]. The thyroid hormone status can thus be influenced by different effects of long-term anticonvulsant therapy on this dual pathway of T_4 metabolism. Still, significant differences in serum rT_3 concentration have never been found in patients treated with anticonvulsants [10].

It is worth mentioning that a decrease in thyroid hormone levels of patients receiving long-term anticonvulsant therapy was significant only statistically: all the patients were

euthyroid with a normal concentration of serum TSH. The test is therefore particularly valuable in patients receiving anticonvulsants when hypothyroidism is suspected.

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