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Thyroid functions in children under long-term administration of antiepileptic drugs

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Objective In this study we investigated whether long-term administration of antiepileptic drugs effect thyroid functions.

Methods Serum free thyroxine (FT4), serum free triiodothyronin (FT3) and serum thyroid stimulating hormone (TSH) concentrations were measured in 93 epileptic patients receiving phenobarbital (30 cases) or phenytoin (9 cases) or carbamazepine (23 cases) or valproate (22 cases) or clonazepam (9 cases) who were admitted to Trakya University School of Medicine, Department of Pediatrics, between July 1992 and May 1994.

Results We found a significant reduction in FT4 levels receiving phenobarbital or phenytoin or carbamazepine or clonazepam compared to control group. FT3 and TSH levels were normal. However, in the valproat group there was not any significant difference in the levels of thyroid hormones between study and control groups. All patients were in euthyroid state, there were no clinical findings of hypothyroidism.

Conclusion These data suggest that phenobarbital, phenytoin, carbamazepine and clonazepam decrease serum FT4 , hovever while valproat does not.

Key words Thyroid, antiepileptic drugs.

Introduction

Antiepileptic drugs (AED) are widely used in childhood epilepsies and other convulsive conditions. Recently, the side effects of antiepileptic drugs to the endocrine system are being reported. Effects to the thyroid hormone balance are of primary importance in this regard (1-3)

The first study about the effects of antiepileptic drugs on thyroid gland is made in 1961 by Oppenheimer et al. They found a decrease in iodine bound to serum proteins and a disturbance in thyroxine secretion from thyroxine binding globulin (TBG) in adults taking phenytoin (3).

Since then, several studies have been reported about the toxic effects of antiepileptic drugs on thyroid gland (3-6). It's found that some antiepileptic drugs decrease thyroid functions certainly. For example, phenytoin and carbamazepine clearly decrease thyroid functions but do not change the euthyroid state. It has been reported that these drugs decrease the free serum thyroxine concentrations (FT4), but not change the serum free triiodothyronine (FT3) and throid stimulating hormone (TSH) levels (4-9).

The mechanisms of the effects of antiepileptic drugs on thyroid hormones have been studied intensively. Generally, phenobarbital, phenytoin and carbamazepine are called as "enzyme inducing antiepileptic drugs" because of their activating effects on hepatic microsomal enzyme system (3,4).

Among the studies searching the effects of antiepileptic drugs on thyroid hormones, the best and most different results are obtained with valproate which does not change the thyroid hormone levels. Some studies even revealed that valproate increases serum thyroxine levels (2,3,7).

In this study, thyroid functions were evaluated in 93 children receiving different antiepileptic drugs by measuring serum FT3, FT4 and TSH levels.

Material and Method

This study was carried out between July 1992 and May 1994 in 93 epileptic children who were followed in Trakya University School of Medicine Pediatric Outpatient Department. The children were taking following drugs; 30 children phenobarbital, 9 children phenytoin, 23 children carbamazepine, 22 children valproate and 9 children clonazepam. Blood samples were taken only after the patients received their drugs at least six months. In the study group no patient had a history of thyroid disfunction. They didn't use any other drug for a long time before the study. Non of the patients had any seizure in the last month prior to the examination. Patients receiving their drugs irregularly and those in their drug tempering period were excluded. All cases in study group were receiving monotherapy and the ones receiving politherapy were also excluded.

The control group included healthy children or children with simple upper respiratory tract infection in the outpatient department. They had no chronic diseases and did not receive any drugs during last two weeks. This group consisted of 50 cases; 26 males and 24 females.

Both in study and control groups, informed consent was taken from the family, and fasting blood samples were received early in the morning. The materials were examined by laborants who don't know the patients. Commercial products Amerlex-

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MAB FT3 and FT4 kits of Kodak Diagnostics Co. were used for FT3 and FT4. Also Hs TSH Coated Tube Assay of same company were used for TSH. Blood samples were examined with RIA method. Normal kit levels were accepted for FT4 as 0.85 - 1.86 ng/dl, for FT3 as 2.2-4.7 pg/ml and for TSH as 0.32-4.1 IU/ml.

Gender, age, kind of drugs, duration of administration and thyroid hormone values were loaded on a computer. Means, percentilles and significancy of every parameter were calculated using instant program called NCSS (Number Cruncher Statistical System). Student-t and Mann Whitney U tests were used in data analysis.

Results

There were 93 patients in the study group who received antiepileptic drugs at least for six months. 54 cases were male (58.1%) and 39 cases were female (41.9%).

Thirty cases 17 males (57%) and 13 females (43%), (mean age 5.31 ± 3.31 years) received phenobarbital for 21.33 ± 18.51 months. In comparison with the control group, there was no significant differences in age, serum FT3 and TSH levels. But serum FT4 levels were significantly decreased ($p<0.01$). Nine patients 5 males (55.6%) and 4 females (44.1%), (mean age 5.38 ± 2.87 years) received phenytoin for 14.88 ± 11.86 months. There was no difference in age, serum FT3 and TSH values, but serum FT4 levels were significantly decreased compared with the controls ($p<0.01$).

There were 23 patients in carbamazepine group 18 males (78.3%) and 5 females (21.7%), (mean age 7.54 ± 3.33 years, mean duration 17.82 ± 16.11 months). In comparison with the control group, patients receiving carbamazepine had no difference in serum FT3 and TSH levels. Their ages were significantly high ($p<0.03$), this was accepted as a co-incidence, because cases were gathered randomly. However serum FT4 levels were significantly low in carbamazepine group ($p<0.01$). Number, age, duration, serum FT3, FT4 and TSH values of patients receiving phenobarbital, phenytoin, carbamazepine were given on table I.

Twenty-two cases receiving valproate; 10 males (45.4%), 12 females (54.6), (mean age 7.02 ± 3.68) were treated for 15.8 ± 14.88 months. In comparison with the control group, patients did not have any differences in age, serum FT3, FT4 and TSH values. Contrary to the other groups, their serum FT4 levels were not different compared to the controls. Nine cases 3 males (33.3 %), 6 females (66.7%), (mean age 2.45 ± 2.31 years and mean duration 11 ± 6.12 months) receiving clonazepam had significantly low mean age, because of the five infants with West syndrome. Although there were no differences in serum FT3 and TSH levels, their FT4 levels were significantly low compared with the control group ($p<0.01$). The data of patients receiving valproate, clonazepam and the control group are given in table II.

Discussion

The effects of AED on thyroid functions are known for a long time. In spite of the new information which accumulated in the eighties and

Table I. Number, mean age, mean duration, serum FT3, FT4 and TSH values of patients receiving phenobarbital, phenytoin and carbamazepine

	Phenobarbital	Phenytoin	Carbamazepine
Number	30	9	23
Mean age (year)	5.31 ± 3.31	5.38 ± 2.78	5.54±3.33*
Mean duration (mo)	21.33 ± 18.51	14.88 ± 11.86	17.82 ± 16.11
FT3 (pg/ml)	3.49 ± 0.80	3.63 ± 1.63	3.36 ± 1.08
FT4 (ng/dl)	1.08±0.24**	0.99±0.14**	0.99±0.17**
TSH (IU/ml)	2.76 ± 1.29	2.98 ± 1.39	2.58 ± 1

*Compared with control group ($p=0.03$), **Compared with control group ($p<0.01$).

Table II. Number, mean age, mean duration, serum FT3, FT4 and TSH values of patients receiving valproate, clonazepam and also control group.

	Valproate	Clonazepam	Control group
Number	22	9	50
Mean age (year)	7.02 ± 3.68	2.45±2.31*	5.72 ± 3.88
Mean duration (mo)	15.80 ± 14.88	11 ± 6.12	-
FT3 (pg/ml)	3.53 ± 0.78	3.78 ± 1.01	3.36 ± 0.90
FT4 (ng/dl)	1.48 ± 0.27	0.99±0.34*	0.52 ± 0.27
TSH (IU/ml)	2.54 ± 1.24	3.35 ± 1.35	2.52 ± 1

*Compared with control group ($p<0.01$).

nineties, not a common conclusion has existed yet. In human body, only free potions part of thyroid hormones are functional. In the examinations of thyroid functions, FT4, FT3 and TSH levels are used by most of the investigators (2,3,6-11).

Phenobarbital effects on thyroid functions are like phenytoin and carbamazepine. There is no consensus among the investigators how phenobarbital effects the thyroid functions. Phenobarbital is one of the drugs inducing hepatic mikrosomal enzyme system. That is why it is believed that they are showing their effects on thyroid hormones by the way of this mechanism (4,7,12). Rousso et al. (4) investigated serum T4, FT4 indeks (T4 uptake x total T4) and TSH levels in 110 children under long-term phenobarbital, phenytoin and carbamazepine administration; and they found in phenobarbital receiving cases low serum T4 levels and FT4 indeks but no change in TSH concentrations. Haidukewitych and Rodin (7) found significantly low serum T4 and FT4 index in 58 cases receiving phenobarbital but reported that patients maintained their euthyroidic state. Deda et al. (6) reported in their study, 20 children receiving phenobarbital and 15 ones receiving phenytoin There were no significant difference in serum FT4, FT3 and TSH levels compared with the control group.Yüksel et al. (12) reported ten pediatric cases receiving phenobarbital, significant decreased in serum FT4 and FT3 levels compared with control group.

In our study 30 cases with mean age 5.31 years receiving phenobarbital for a mean duration of 21.33 months, we obtained significant low serum FT4 levels ($p<0.01$); howewer no significant difference in serum FT3 and TSH levels compared with the control group.

Phenytoin is the drug which effects on thyroid function is investigated thoroughly. It's one of the antiepileptic drugs known which most powerfully induce hepatic microsomal enzymes (13-21). Isojarvi et al. (2) reported in their studies with cases receiving phenytoin and carbamazepine significant low T4 and FT4 but no change in T3 and TSH levels. They also reported in 1992 in a study with 26 phenytoin receiving patients significant low serum T4 and FT4 but no change in serum T3 and TSH levels (3). Rousso et al. (4) reported children receiving phenytoin significant low serum T4 and serum FT4 but significant high serum TSH levels. Deda et al. (6) examined 15 children receiving phenytoin. Cases with mean 2.5 years drug receiving period had low serum T4, FT4, T3 and FT3 levels. But TSH levels were not significantly different from control group. Haidukewitych and Rodin (7) reported 165 cases receiving phenytoin significant low serum T4 level and FT4 index. Larkin at al. (7) reported 13 cases receiving phenytoin significant low serum T4 and FT4 but normal serum TSH levels. H. Fischel and G. Knöpfle (9) reported in 1978 in a detailed study with 25 children receiving phenytoin, significant low serum T4,T3 and FT4 but no change in TSH levels. Ericsson et al. (13) also reported in their study with children of mean age 16 years, the same results Suzuki et al. (11) reported in 32 cases receiving phenytoin for mean 81 months duration, significant low serum FT4 but no change in TSH levels.

In our study 9 children with mean age 5.38 years receiving for mean 14.88 months, significant low FT4 ($p<0.01$) but no change in serum FT3 and TSH levels compared with control group.

Effects of carbamazepine are similar to phenytoin because of carbamazepine is one of the hepatic microsomal enzyme inducing drugs (22). Isojarvi et al. (2) reported their cases receiving carbamazepine with significant low serum T4 and FT4 but unchanged serum T3 and FT3 levels. They reported also in 1992, 24 carbamazepine receiving patients with significant low T4and FT4 but unchanged T3 and TSH levels (3). Rousso et al. (4) reported children receiving carbamazepine significant low serum T4 and FT4 but significant high serum TSH levels. Strandjord et al. (5) reported 42 cases the serum T4, FT4 and T3 levels significantly decreased after receving 8-24 months carbamazepine compared with control group. They also followed 12 patients for1-5 months and found that their serum T4 concentrations significantly decreased, but their serum T3 and TSH concentrations didn't change in comparison with the pre-treatment levels. Yüksel et al. (12) reported 11 pediatric cases receiving carbamazepine, significant decreased in serum FT4 and FT3 levels compared with control group. Isojarvi et al. (2) reported in their studies with 40 cases receiving carbamazepine significant low T4 and FT4 but no change in T3 and TSH levels.

In our study 23 cases with mean age 7.54 years receiving carbamazepine for a mean duration of 17.82 months, we obtained significant low serum FT4 levels ($p<0.01$); howewer no significant difference in serum FT3 and TSH levels compared with the control group.

Among the studies about the effects of antiepileptic drugs on thyroid hormones, the best and most different results are obtained with valproate. It has been concluded that valproate does not change the thyroid hormone levels, because it is not an inducing drug (2,3,7). Isojarvi et al. (2,3) reported that there was no significant difference between valproate and control groups. Ericsson et al. (13) reported high serum T3 and T4 but normal TSH

levels. Haidukewitych and Rodin (7) reported 69 patients and found normal T4, T4 index levels. In another study by Yüksel et al. (12) there were no differences about thyroid hormones. In our study there were 22 children (mean age 7.02 years and mean duration 15.8 months). We found no defference about thyroid hormones compared with the control group.

We studied 9 patients receiving clonazepam. But there were not handled any study about this drug because of it has small indication for use, recently. However, in our patients, values of FT4 were significantly low ($p<0.01$). Also TSH levels had borderline low value compared with control group ($p= 0.051$). Clonazepam is one of the drugs which has not enyzme inducing effects. Therefore, other mechanisms should be operative in decreasing serum FT4 and may be TSH. We wonder if, are there any effects to central nervous system and TSH of this drug? We need more patients about this subject.

Finally, our data suggest that phenobarbital, phenytoin, carbamazepine and clonazepam decrease serum FT4 levels, while valproat does not. All patients were in euthyroid state and there were no clinical findings of hypothroidism.

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