Effect of carbamazepine and valproic acid monotherapy on thyroid function tests in epileptic patients

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ABSTRACT

Objectives: This study was conducted to assess the effect of carbamazepine (CBZ) and sodium valproate (VPA), as a monotherapy in epileptic patients, on thyroid function tests as assessed by serum total triiodothyronine (TT_3), total thyroxine (TT_4) and thyroid stimulating hormone(TSH).

Subjects and methods: Sixty three epileptic patients using monotherapy were included in the study. These included 44 patients using CBZ and 19 using VPA. A control group of 47 apparently healthy individuals were also included in the study for comparison. Measurement of TSH, TT_3 and TT_4 was done using Gamma counter.

Results: The results of this study revealed that patients on CBZ showed significantly decreased mean level of TT_4 in comparison with the control group ($P<0.01$), while mean TT_3 and TSH levels showed statistically insignificant differences from the control group ($P>0.05$). In the VPA group, mean TT_3, TT_4 and TSH values showed insignificant differences from the control group ($P>0.05$).

Conclusion: Unlike VPA, CBZ significantly decreases level of TT_4 without affecting TT_3 and TSH levels.

Keywords: Carbamazepine, sodium valproate, thyroid function tests.

الخلاصـــة

أهداف البحث: أجريت هذه الدراسة لمعرفة تأثير عقاري الكاربامازبين وفالبرويت الصوديوم كعلاج أحادي لمرضى الصرع على فحوصات وظائف الغدة الدرقية ،هرمون الثايرونين ثلاثي اليود، هرمون الثايروكسين والهرمون المحفز للدرقية.

المشاركون: أجريت الدراسة على 63 مريضاً مصاباً بالصرع ، 44 مريضاً منهم يستخدمون عقار الكاربامازبين كعلاج أحادي و19 منهم يستخدمون عقار فالبرويت الصوديوم كعلاج أحادي ، فضلاً عن 47 من الأصحاء الذين عدّوا كمجموعة سيطرة .

تم قياس مستويات هرمون الثايرونين ثلاثي اليود وهرمون الثايروكسين والهورمون المحفز للدرقية لأفراد عينة الدراسة باستخدام جهاز عداد كاما .

النتائج :أظهرت نتائج الدراسة وجود انخفاض معنوي في مستوى هرمون الثايروكسين لدى المرضى المستخدمين لعقار الكاربامازبين كعلاج احادي (ب ‹ 0.01) ، في حين لم يظهر فرق معنوي في مستويات هرموني الثايرونين ثلاثي اليود والهرمون المحفز للدرقية عن مجموعة السيطرة .

أما المرضى المستخدمين لعقار فالبرويت الصوديوم فلم يظهر لديهم أي فرق معنوي عن مجموعة السيطرة في مستويات الهرمونات الثلاثة المقاسة في الدراسة الحالية .

الاستنتاج: على عكس فالبرويت الصوديوم، أدى عقار كاربامازبين إلى انخفاض معنوي في مستوى هرمون الثايروكسين ولكن بدون أن يؤثر على مستوى الثايرونين ثلاثي اليود والهرمون المحفز للدرقية.

Thyroid diseases are usually presented as a spectrum of clinical and metabolic features of varying severity. Although primary diseases of the thyroid gland are the most common, secondary disorders due to hypothalamic-pituitary insufficiency can also give rise to dysfunctional states[1]. Many other factors, both exogenous and endogenous, may affect the thyroid function[2,3]. These include the pathways of thyroid hormone biosynthesis, secretion, transport in the circulation, and metabolism which offer numerous targets for drug interaction[4].

Euthyroid hypothyroxinaemia, describes a situation in which total or free thyroxine

concentrations are low but without evidence of thyroid dysfunction, usually with a normal TSH, This may be associated with medication or non-thyroidal illnesses like liver or renal disease, heart failure, and post-surgery [5].

Carbamazepine (CBZ) is one of the most important antiepileptic drugs. It is an iminostilbene of tricyclic structure related to imipramine and other antidepressants[6]. Thyroid function tests may be abnormal in patients receiving CBZ therapy[7]. Numerous studies have shown that serum thyroid hormones concentrations are decreased following treatment with CBZ but in the absence of clinical signs of hypothyroidism[8,9,10]. Valproate (VPA) medication in women with epilepsy is associated with certain metabolic and endocrine changes[11]. It may also affect steroid hormone metabolism in men with epilepsy[12]. However, reports on serum thyroid hormone levels in patients with epilepsy treated with VPA have been conflicting[8,9,10].

The aim of the current study is to assess the effects of CBZ and VPA, as monotherapy in epileptic patients, on serum total T_3 (TT_3), total T_4 (TT_4) and TSH.

Subjects and methods

This study was carried out during the period, from 15th Sept 2003 to 30th May 2004. Patients were received and interviewed with the main exclusion criteria from the study as follows:

1. Patients receiving other anti-epileptic drug or poly therapy.
2. Duration of therapy of less than 6 months
3. Signs or symptoms of liver disease, renal disease, thyroid disease or diabetes mellitus.
4. Abnormal neurological examination.
5. Long term use of any other drug.

Group 1: This group included 44 epilept patients on CBZ as a monotherapy for period ranging from 6 months-14 yea (mean ± SD 4.82 ± 3.19 years), wer included in this study. They were 18 male and 26 females with age of 28.43 ± 8.5 years, and ranging of 6-50 years. The mea CBZ daily dose was 559.09 ± 138.69 mg , and range of 400-800 mg/d.

Group 2: This group included 19 patient who were treated with sodium VPA as monotherapy for a period ranging from months -12 years (4.58 ± 3.32 year). The were 9 males and 10 females with mea age of 28.88 ± 7.37 years, and range of 1 40 years. The sodium VPA daily dose wa 588.88 ± 127.82 mg/d, ranged from 40 800 mg/d.

Group 3: This group included 4 apparently healthy persons, who had n chronic disease and did not receive an drugs during the last two weeks. They wer 22 males and 25 females with mean age 28.31 ± 8.54 year, and range of 14-4 years..

From all patients and controls, about 5 m of venous blood samples were collected plain tubes. Collection was done early the morning in the fasting state. Thyro function tests which include serum TT_3, T and TSH concentrations were measured b Radioimmunoassay using kits purchase from Immunotech (France)

The statistical methods were used for th analysis of data that includes determinatio of the mean, standard deviation (SD) an standard error (SE), unpaired student t-tes unpaired Z-test, analysis of varianc (ANOVA) and Pearson correlatio coefficient. The differences betwee observations were considered significant $P \leq 0.05$ [13]. The data are presented a mean ± SD.

Table (1): *Comparison of thyroid function tests between control and carbamazepine (CB treated groups.*

Parameter	Mean ± SD		z-value	p-value
	Control (n =47)	Patients on CBZ (n=44)		
TT_3 (nmol/L)	1.84 ± 0.44	1.86 ± 0.52	0.02	>0.05
TT_4 (nmol/L)	119.22± 18.07	101.49 ± 36.87	2.89	<0.01*
TSH (mIU/L)	2.24 ± 0.76	2.52 ± 1.42	0.004	>0.05

** Significant difference (p<0.01)*

Table (2): *Effect of carbamazepine dosage on thyroid function tests.*

Dosage (mg/day)	Mean ± SE		
	TT_3 (nmol/L)	TT_4 (nmol/L)	TSH (mIU/L)
400 (n = 16)	1.81 ± 0.16	111.61 ± 10.55	2.24 ± 0.38
600 (n = 21)	1.94 ± 0.49	100.28 ± 7.56	2.62 ± 0.32
800 (n = 7)	1.74 ± 0.36	81.96 ± 9.03	2.90 ± 0.41
F-value	0.47	1.64	0.61
p-value	>0.05	>0.05	>0.05

P>0.05: Non-significant difference

Table (3): *Comparison of thyroid function tests between males and females in carbamazepine (CBZ) treated group.*

Parameters	Mean ± SD		p-value
	Males (n=18)	Females (n=26)	
TT_3 (nmol/L)	1.81 ± 0.61	1.89 ± 0.46	> 0.05
TT_4 (nmol/L)	97.65 ± 38.44	104.14 ± 36.27	> 0.05
TSH (mIU/L)	2.81 ± 1.39	2.33 ± 1.43	> 0.05

P > 0.05 : Non-significant difference

Table (4): *Comparison of thyroid function tests between control and valproic acid (VPA) treated groups.*

Parameters	Mean ± SD		z-value	p-value
	Control (n =47)	Patients on VPA (n=19)		
TT_3 (nmol/L)	1.84 ± 0.44	2.03 ± 0.32	1.82	>0.05
TT_4 (nmol/L)	119.22 ± 8.07	125.49 ± 18.22	0.96	>0.05
TSH (mIU/L)	2.24 ± 0.76	2.10 ± 1.14	0.88	>0.05

P > 0.05 : Non-significant difference

Results

The results for serum TT_3, TT_4, and TSH were established in the control group 3. The values were 1.84 ± 0.44 (range 1.07-2.76) nmol/L for TT_3, 119.22 ± 18.07 (81.94-156.05) nmol/L for TT_4 and 2.24 ± 0.76 (1.01-3.91) mIU/L for TSH. No statistically significant difference in all these parameters of TFT was observed between males and females.

The TFT in patients on CBZ monotherapy was compared with that in the control subjects. Mean TT_4 concentration was significantly lower in epileptic patients on CBZ (101.49 ± 36.87 nmol/L) than in the control group (119.22 ± 18.07 nmol/L), ($p<0.01$). However, mean TT_3 and TSH values were not significantly different from those in the control group, Table 1. No significant effect was observed with regard to the daily CBZ dose and each of TT_3, TT_4 and TSH, Table 2. The duration of therapy showed also no significant correlation with TT_3, TT_4 and TSH with r values of -0.04, 0.06 and -0.28 respectively. Also, no effect of sex was observed on TT_3, TT_4 and TSH, Table 3.

In epileptic patients on VPA as a monotherapy, the mean values of TT_4, TT_3 and TSH were not significantly different from those in the control group, Table 4. Also no effect was observed with regard to the daily dose of VPA and TT_3, TT_4 and TSH, Table 5. The duration of therapy showed no significant correlations with TT_3, TT_4 and TSH with r values of 0.33, -0.02 and -0.12 respectively. No effect of sex was observed on TT_3, TT_4 and TSH, Table 6.

When comparing the different parameters of thyroid function between CBZ and VPA treated groups, only mean TT_4 was found to be significantly lower ($P<0.05$) in the CBZ treated patients (101.49 ± 36.87 nmol/L) than in VPA treated patients (125.49 ± 18.22 nmol/L). However, no statistically significant difference was found in TT_3 and TSH in both groups, Table 7.

Table (5): *Effect of valproic acid (VPA) dosage on thyroid function tests.*

Dosage (mg/day)	Mean ± SE		
	TT_3 (nmol/L)	TT_4 (nmol/L)	TSH (mIU/L)
400 (n = 5)	1.83 ± 0.19	141.38 ± 8.48	1.70 ± 0.56
600 (n = 11)	2.11 ± 0.09	121.50 ± 5.30	2.18 ± 0.40
800 (n = 3)	2.05 ± 0.05	113.70 ± 8.60	2.50 ± 0.40
F-value	1.18	2.659	0.36
p-value	>0.05	>0.05	>0.05

P > 0.05 : Non-significant difference

Table (6): *Comparison of thyroid function tests between males and females in valproic acid (VPA) treated group.*

Parameter	Mean ± SD		p-value
	Males (n=9)	Females (n=10)	
TT_3 (nmol/L)	1.99 ± 0.27	2.09 ± 0.39	> 0.05
TT_4 (nmol/L)	124.78 ± 20.10	126.41 ± 17.03	> 0.05
TSH (mIU/L)	1.90 ± 1.14	2.36 ± 1.17	> 0.05

P > 0.05 : Non-significant difference

Table (7): *Comparison of thyroid function tests between carbamazepine (CBZ) and valproic acid (VPA) treated groups.*

Parameter	Mean ± SD		z-value	p-value
	Patients on CBZ (n=44)	Patients on VPA (n=19)		
TT_3 (nmol/L)	1.86 ± 0.52	2.03 ± 0.32	1.49	>0.05
TT_4 (nmol/L)	101.49 ± 36.87	125.49 ± 18.22	2.57	<0.05*
TSH (mIU/L)	2.52 ± 1.42	2.10 ± 1.14	0.911	>0.05

** P < 0.05 : Significant difference*

Table (8): *Results of other authors regarding the effects of CBZ and VPA on thyroid function tests.*

1.	CBZ	Caksen et al [14]	TT4 and free T4 : low	T3 and TSH unaffected
2.	CBZ	Yuksel et al [15]	TT4, free T4 and free T3 : low	TT3 and TSH : unaffected
3.	CBZ	Strandjord et al [16]	TT4, free T4 index and TT3: low	TSH : unaffected
4.	CBZ	Conran et al [24]	TT4: reduced	Free T4, T3 and TSH : unaffected
5.	VPA	Bentsen et al [8]	TT4, free T4 and TT3 : reduced	
6.	CBZ	Verrotti et al [21]	TT4 and Free T4 : lower	TT3, free T3 and TSH : unaffected
	VPA			TT4 ,free T4,TT3, free T3 and TSH : unaffected
7.	VPA	Eiris-punal et al [10]	TT4, free T4 and TT3:Lower TSH : higher	
8.	VPA	Caksan et al [22]		TT3, T4 and TSH: unaffected
9.	CBZ	Vainionpaa et al [23]	TT4 and free T4 : reduced	TSH : unaffected
	VPA		TSH : increased	TT4 and free T4: unaffected

Discussion

The present study revealed a reduced mean TT_4 levels in patients using CBZ monotherapy, while TT_3 and TSH levels were not different from the controls. These results agreed with the results of Caksen *et al.* [14], who evaluated the effects of CBZ as a long term monotherapy on thyroid function in 18 epileptic children, with a duration of 10 months-5 years, They reported that total and free T_4 levels were significantly lower than in the control group, while T_3 and TSH levels did not differ from the controls, table 8. Yuksel *et al.* [15] also noted that after CBZ monotherapy, serum levels of TT_4, free T_4 and free T_3 were found to be low, but serum TT_3 and TSH were unaffected. Strandjord *et al.* [16] studied the influence of CBZ on serum T_4 and T_3 in 42 epileptic patients. He observed that TT_4, free T_4 index and TT_3 were significantly lower than in the controls, while TSH did not differ between patients and controls.

Low serum TT_4 with normal TSH levels are commonly associated with medications [5], such as anticonvulsants, that have been implicated to cause thyroid disorders. It has been known since 1961, that phenytoin has a significant effect on the levels of thyroid hormones [17]. In his study, Hansen *et al.* [18] evaluated the effects of diphenylhydantoin on thyroid function in 26 epileptic patients. His data revealed a decrease in serum TT_4, free T_4 index and TT_3 to 75% of control values, while TSH was significantly increased. Serum total and free thyroid hormone concentrations were estimated in 42 epileptic patients taking (phenytoin, phenobarbitone and carbamazepine) either alone or in combination. It was found that there was a significant reduction in TT_4, free T_4 and free T_3, in the treated group compared with the controls [19,20].

The current study involved also epileptic patients on VPA monotherapy. Serum levels of TT_4,TT_3 and TSH were found to be not different from the controls. Bentsen *et al.* [8], reported that VPA as a monotherapy causes a reduction in TT_4, free T_4 and TT_3 levels. Verrotti *et al.* [21] on evaluating the effects of CBZ or VPA in 37 epileptic children reported that TT_4 and free T_4 levels were significantly lower in patients treated with CBZ and in those treated with CBZ plus VPA in comparison with controls. Serum TT_4 and free T_4 concentrations were unaffected by VPA monotherapy. Serum TT_3 and free T_3 as well as TSH concentrations were similar in the three groups of studied patients. Eiris-punal *et al.* [10], recorded lower mean TT_4, free T_4, TT_3 and higher mean TSH in epileptic children on VPA therapy as compared with controls. Caksan *et al.* [22], in their study, evaluated the effects of chronic VPA therapy on thyroid function in 31 epileptic children, with a duration of therapy of 1-5 years. their finding revealed that mean levels of T_3, T_4 and TSH were not different from the control and they suggested that VPA has no effect on thyroid function in childhood epilepsy. A recent work done by Vainionpaä *et al.* [23] involving 78 girls on antiepileptic monotherapy, of whom 41 on VPA, 19 on CBZ and 18 on oxcarbazepine (10-keto analogue of CBZ) as well 54 healthy age-matched controls, studying effects of such antiepileptics on thyroid function. The study indicated that both CBZ and oxcarbazepine reduces TT_4 and free T_4, despite the fact that CBZ and oxcarbazapine have different metabolic pathways in the liver (CBZ by

oxidation and oxcarbazapine by reduction). However, TSH levels were not different from the controls. While VPA was associated with a normal serum TT_4, free T_4 and increased TSH levels as compared to the controls. Finding a normal TSH levels in this study is in consistence with the study conducted by Conran *et al.* [24], who investigated the hypothalamic-pituitary axis (HPA) function in children and adolescents receiving long term monotherapy with either CBZ or VPA. They found a significant reduction in TT_4 in the CBZ group, while free T_4, T_3 and TSH response to thyrotropin-releasing hormone were similar in both groups. They concluded that HPA function in children and adolescents is not compromised by long-term monotherapy with CBZ or VPA In their study, Thomas *et al.* [25] found no correlation between neuropsychological impairment among epileptic patients and the levels of thyroid hormones.

Carbamazepine is considered a drug of first choice for the treatment of partial and secondarily generalized seizures[26] Valproate also has been found to be an effective antiepileptic drug in many types of epilepsy [27]. Although these two antiepileptic drugs are well tolerated, many effects on endocrine function have been reported in the literatures [28, 29]. Carbamazepine is a well-known stimulant of the microsomal enzymes system of the liver-metabolizing thyroid hormones [30], whereas VPA does not seem to have similar enzyme-inducing effect [31]. It has been postulated that serum TT_4 levels are low in epileptics receiving CBZ because of the accelerated metabolism of thyroid hormones in the liver [32]. Furthermore, an increased peripheral conversion of T_4 to T_3 during CBZ therapy also has been suggested as an explanation for the slightly changed or unchanged T_3 levels[33]. Interestingly, Eravci *et al.* [34], demonstrated that CBZ induces significant changes in 5` D–II and 5` D–III activities in up to 10 regions of the rat brain; these changes in deiodinase activities, perhaps present in the peripheral tissues as well, could have a role in the explanation of our results. Also, although serum TT_4 were reduced, such patients do not require thyroxine supplementation, as it is the level of thyrotropin which is important in thyroid disorders, and its normal level excludes primary involvement of thyroid gland by a disease process[35]. TT_4 shows an apparent lower level as the dose of carbamazepine increases, this did not show a statistically significant relation probably because of the small number of patients in the subgroups.

De Luca *et al.* [36], suggesting that hypothyroidism in patients with partial epilepsy to whom CBZ had been administered requires a higher L-T_4 substitutive regimen. We suggest according to the result of this study that CBZ is a good choice to treat an epileptic patient complaining from hyperthyroidism.

In conclusion, in epileptic patients with thyroid disease, probably VPA may be more suitable than CBZ for the potential influence of the latter on TT_4.

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