Effects of Carbamazepine on sex hormonal levels in male epileptic patients

Hani M.M.S Al-Mohtar*, Imad A.J. Thanoon**

Department of Pharmacology, Colleges of *Pharmacy, **Medicine
University of Mosul

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ABSTRACT

Objective: To assess the effects of carbamazepine monotherapy on male sex hormonal levels (testosterone, lutenizing hormone (LH), follicular stimulating hormone (FSH), prolactin and estradiol) in epileptic male patients taking in consideration duration of therapy, daily dose and age of the patient.

Design: Case-control study.

Setting: Patients were received in the department of pharmacology, college of Medicine, University of Mosul. Measurements of hormonal levels were done in Hospital of Nuclear Medicine in Mosul city, from Oct 2004 to May 2005.

Patients and Methods: Forty three male epileptic patients, with certain criteria , were included in this study , they were on carbamazepine monotherapy . Forty apparently healthy male subjects were also included and taken as a control group . For both patients and controls , assessment of serum testosterone, LH, FSH, prolactin and estradiol were done using especial commercial kits with the aid of a Gamma Counter.

Results: This study revealed a significant increase in the serum level of estradiol in comparsion with the controls. Other parameters (testosterone, LH, FSH and prolactin) showed no significant differences in comparison with the controls. No effect have been found for age of patient , duration of therapy or daily dosage, on the measured parameters .

Conclusion: Carbamazepine administration is associated with significant changes in estradiol levels with insignificant changes in testosterone, LH, FSH, and prolactin in patients on carbamazepine medication, which may require especial attention to this point.

الخلاصة

أهداف البحث: دراسة تأثير عقار الكاربامزبين كعلاج أحادي على مستوى الهرمونات الذكرية (التستوستيرون، الهرمون الحافز للحويصلات ، الهرمون المحفز للخلايا البنيه، هرمون البرولاكتين وهرمون الاسترادايول) عند مرضى الصرع من الذكور اخذين بنظر الاعتبار عمر المريض مدة العلاج والجرعة اليومية للعقار .

التصميم: دراسة عينية – مقارنة

مكان إجراء البحث والإطار الزمني: تم استقبال المرضى في فرع الأدوية – كلية الطب – جامعة الموصل ومستشفى الطب الذري لقياس مستوى الهرمونات للفترة من تشرين الأول ٢٠٠٤ لغاية ايار من سنة ٢٠٠٥م.

المرضى والطرق المتبعة: ضمت هذه الدراسة ٤٣ مريضا من الذكور المصابين بالصرع ، كما ضمت ٤٠ شخصا من الذكور الاصحاء كمجموعة ضبط. تم قياس مستوى هورمون التستوستيرون ، الهرمون الحافز للحويصلات ، الهرمون المحفز للخلايا البنية هرمون البرولاكتين وهرمون الاسترادايول باستخدام كتات خاصة . تم القياس حسب الارشادات الواردة مع كل كت وباستخدام جهاز عداد كاما .

النتائج: أظهرت نتائج هذه الدراسة وجود ارتفاع معنوي في مستوى هرمون الاستراديول لدى المرضى بالمقارنة مع مجموعة السيطرة في حين لم يظهر فرق معنوي في مستوى باقي الهرمونات . كما لم تكن هنالك تاثيرات لعمر المريض ، فترة العلاج او الجرعة الدوائية على مستوى الهرمونات عند المرضى.

الاستنتاج: كان استخدام الكاربامزبين مصحوبا بتأثيرات على مستوى الاسترادايول عند مرضى الصرع من الذكور. عليه فان المرضى الذين يناولون أدوية مضادة للصرع مثل الكاربامزبين يحتاجون عناية خاصة حول هذا الموضوع .

Epilepsy remains a major cause of personal and social disability despite the development of a variety of effective medication over the last 40 years.[1,2] Epilepsy by itself may affect hormone balance.[3] On the other hand, antiepileptic drugs have been well documented to affect the endocrine balance and most studies revealed endocrine abnormalities in both men and women with epilepsy especially when treated with liver-enzyme inducing anticonvulsants.[4,5] Diminished libido and hyposexuality are interesting hormonal problem in patients with epilepsy even though the underlying reason has not yet been identified.[6] Factors which may disturb hormonal function in patients with epilepsy include, psychological influence,[7] antiepileptic medication[4] and the disease itsel.[8] The aim of this study was to assess male sex hormonal levels in patients on carbamazepine monotherapy.

Subjects and Methods

This study was carried out in the Department of Pharmacology, College of Medicine, University of Mosul and Hospital of Nuclear Medicine, from Oct. 2004 to May 2005. Patients received and interviewed with the main exclusion criteria from the study as follow: epileptic patients receiving other drugs or polytherapy, female sex, duration of therapy less than 6 months, signs or symptoms of liver disease, renal disease, thyroid disease or diabetes mellites, abnormal neurological examination.

Eventually, 43 epileptic men with a mean ±SD age of 27.14±7.60 year (ranged between 15 and 45 years), were included in this study.

Apparently healthy 40 male subjects, who has no chronic disease and did not receive chronic therapy, were included in this study as a control group. Their ages ranged between 17 and 43 years (mean ±SD age of 26.68±5.54 years).

From both patients and controls, 7 ml venous blood samples were drawn nearly afternoon for the analysis of serum testosterone, prolactine, luteinizing hormone (LH), follicular stimulating hormone (FSH) and estradiol .

Serum samples were frozen at about -15°c pending analysis. The concentration of serum parameters were measured by radioimmunoassay kit obtained from Immunotech-France, all the assay were performed according to the instruction of the kits manufacturer using Gamma Counter.

The following statistical methods were used for the analysis of data: The data were represented as mean±SD. Unpaired Z-test was used to compare results for measured biochemical parameters between the study group and controls, analysis of variance (ANOVA) was used to find the effect of age on measured biochemical parameters. Unpaired student t-test was used to find the effect of dose on measured parameters. Pearson correlation coefficient was applied to find the relationship between the duration of therapy and the studied parameters. Differences between observations were considered significant at $P<0.05$.

Results

By comparing measured parameters between patients on CBZ monotherapy (n=43) and the control (n=40), there was insignificant differences in the level of testosterone, LH, FSH, prolactin and testosterone/ LH ratio. While there was a significant difference in estradiol level and testosterone/ estradiol ratio (Table 1).

The results of correlation analysis reveal no significant relationship ($p<0.05$) between the duration of therapy (which ranged between 1 and 25 year) and the serum levels of testosterone, LH, FSH, prolactin and estradiol were r=0.07; 0.15; 0.03; 0.05 and 0.05, respectively.

There was no significant variation in the measured parameters in different age group in the control and in patients on CBZ monotherapy .

No significant effect were also noted of the dose of CBZ on the studied parameters (Data not shown).

Table 1. *Comparison of measured parameters between patients on CBZ and control group*

Parameters	Mean± SD		P-value
	Control case (40)	Patients (n=43)	
Testosterone (ng/ml)	5.43±0.036	4.90±0.29	>0.05
LH (IU/L)	5.04±0.29	5.71±0.38	>0.05
FSH (IU/L)	4.68±0.50	5.70±0.55	>0.05
Prolactine (ng/ml)	3.94±0.31	5.29±0.50	>0.05
Estradiol (pg/ml)	6.14±2.15	8.25±4.23	<0.05
Testosterone/estradiol	1.06±0.74	0.76±0.48	<0.05
Testosterone /LH	1.19±0.64	0.97±0.15	>0.05

<0.05 = significant >0.05 = not significant

Discussion

Reports of decreased libido or impotence were frequent among patients given primidone 22%, phenobarbital 16%, CBZ 13% and phenytoin 11%.[9] The relationship between anticonvulsants and fertility hormones has long been known; however, the actual role of antiepileptic drugs in the development of hormonal dysfunction remains a controversial issue. Several studies were performed about the effects of CBZ on sex hormones but the results were fairly different. The mechanism of such an effect is still not settled, it could be both a direct effect[10] or a centrally mediated effect.[11]

The result of this study, with regard testosterone level revealed a slight reduction. This is in agreement with Murialdo et al.[12] and Penovich[3] who found no significant change either in total or free testosterone serum levels in adult male patients with epilepsy when compared with either untreated patients or normal controls. Conversely Barragry et al.[13] and Duncan et al.[14] reported that the mean values of total testosterone serum levels were statistically higher, whereas free testosterone levels were lower than their matched controls.

A normal volunteers study suggested that antiepileptic drugs Per se may have effect on reproductive hormones, Connell et al.[15] gave CBZ to subjects without epilepsy and found arise in sex hormone-binding globulin (SHBG), along with a fall in total testosterone, free testosterone, dihydrotestosterone, after 7 days of starting medication. CBZ and phenytoin have been shown to directly after the function of hypothalamic–pituitary axis.[11,16]

This study also revealed a slight increase in plasma FSH, LH, with a light reduction in testosterone/LH ratio. Stoffel-Wagner,[17] reported that LH and FSH serum concentration in male patients with epilepsy were significantly higher than those in the control, with a statistically lower testosterone/LH ratio in such patients. They suggested that an impaired leydig cell function (as evident by testosterone /LH ratio) might underlie these observations. Despite an increased release of LH from the pituitary gland, the impaired leydig cells are not able further to increase their testosterone synthesis causing a decreased testosterone /LH ratio.

Kuhn-Velten[10] study the possibility of direct inhibition of testicular endocrine function by CBZ, phenytoin or valproic acid , using rat leydig cell model in vitro, in order to find whether such an effect could contribute to the reduction of plasma testosterone level. Only values for CBZ were in the clinically therapeutic range and CBZ acted primarily at a target between cAMP formation and cholesterol conversion to androgen, in contrast phenytoin acted by competitive interaction at cytochrome P450, which converts progesterone to androgen, valproate had by far the lowest potential to generate adverse effects in this endocrine system. Also these authors noted that rats receiving CBZ for 2 years at dosage level of 25, 75 and 250 mg/kg/d had a dose related testicular atrophy.

With regard serum estradiol level, this study revealed a significant increase in its level. This is in accordance with studies conduced by Friedman and Hezog,[18] Verrotti et al.[19] and El-Khayat et al.[20] who reported a significant elevation in estradiol level in epileptic patients on CBZ compared with the untreated patients or healthy control. The lowered testosterone/estradiol levels in the patient group in this study goes with the findings of Murialdo et al.,[12] Penovich,[3] and Harden.[22] This support the suggestion that some antiepileptic drugs lower the biologically active testosterone not only by inducing sex hormone binding globulin synthesis or increase testosterone catabolism but also by inducing aromatase, which convert free testosterone to estradiol. Similar findings regarding phenytoin have been reported by Heroz et al.[23]

With regard serum prolactin level, the present study revealed insignificant elevation of basal prolactin level. This is in agreement with Murialdo et al.[24] and Stoffel-Wagner et al.[17] The experimental and clinical evidence suggest that there is an interaction between CBZ and the dopaminergic system, which locally could account for the movement disorder, and the functional and structural similarity to phenothiazines suggests that CBZ may be an antagonist to dopamine.[25,26]

Elphick et al.[27] concluded that CBZ alter brain serotonin and dopamine function in humans and such an effect could be involved in affective disorder. Similarity such an action could have an influence on male sex hormone.[28] On the other hand the increased estrogen level may also contributes to increasing prolactin level.[29] Other antiepileptics like phenytoin are even reported to cause gynaecomastia[(30)].

In conclusion: CBZ is associated with significant changes in estradiol level with insignificant changes in other male sex hormonal levels. Age of patients, duration of therapy and daily doses of CBZ have no influence on changes in male sex hormonal levels. So an attention should be

paid to sex –hormonal levels in epileptic patients on CBZ therapy.

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