

## **Effects of sodium valproate monotherapy on reproductive hormonal levels in adult male epileptic patients**

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### **Abstract**

**Aims:** to assess the effects of valproate (VPA) on serum levels of testosterone, prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol ( E2) in adult male epileptic patients in comparison to healthy controls. **Methods:** This study was conducted from Oct. 2005 to Aug. 2006. Patients were received from specialist neurology Clinic. Out of 62 patients interviewed only 46 fulfilled the criteria of selection . Apparently healthy 50 subjects were also included in this study as a control group. Blood samples were taken from both patients and controls and assay of testosterone, prolactin ,FSH, LH and E2 were done using radioimmunoassay (RIA) technique. Body mass index (BMI) was calculated using special equation. **Results:** There was a significantly higher testosterone levels in epileptic male patients on VPA therapy in comparison to healthy controls, with insignificant effect on the levels of prolactin, FSH, LH and E2. The duration of therapy and the dosage of VPA had no effect on the serum levels of the above measured parameters. **Conclusion:** VPA monotherapy might be associated with significant increase in serum testosterone level with insignificant effects on serum prolactin, FSH, LH and E2 in adult male epileptic patients and the duration of therapy and daily dose have no influence on such effect.

**Key words:** adult male epileptic, valproate monotherapy, serum reproductive hormone levels.

## الملخص

**الاهداف.** لتقييم تأثيرات الفالبروات على مستوى البرولاكتين، التستوستيرون، الاستراديول، الهرمون المنبه للجريب وهرمون ملوتن في مصل الدم في مرضى الصرع من البالغين الذكور بالمقارنة مع مجموعة الضبط. **المرضى وطرق العمل.** أجريت هذه الدراسة للفترة من تشرين الاول ل 2005 الى اب 2006. تم استقبال المرضى من عيادة امراض عصبية متخصصة. من بين 62 مريضا تمت مقابلتهم فقط 46 استوفوا الشروط الخاصة بالاختيار. ايضا ادخل لهذه الدراسة 50 من الاشخاص الاصحاء كمجموعة ضبط. سحبت عينات من الدم من مجموعتي المرضى والضبط وتم قياس مستوى البرولاكتين، التستوستيرون، الاستراديول، الهرمون المنبه للجريب وهرمون ملوتن في مصل الدم بطريقة مقياسه مناعية شعائيه. تم حساب معمل الكتله الجسديه باستخدام معادله خاصه.

**النتائج.** كانت هنالك زياده معنويه في مستوى التستوستيرون عند مرضى الصرع من البالغين الذكور المثبتين على عقار الفالبروات بالمقارنة مع مجموعة الضبط، مع عدم وجود تأثير معنوي على مستوى البرولاكتين، الهرمون المنبه للجريب، هرمون ملوتن والاستراديول. كما لم يكن هنالك تأثير معنوي لفترة العلاج والجرعه الدوائيه على مستوى الهرمونات الذكوره اعلاه.

**الاستنتاج.** العلاج الاحادي بعقار الفالبروات قد يتسبب في زياده معنويه في مستوى التستوستيرون في مصل الدم مع عدم وجود تأثير يذكر على مستوى مستوى البرولاكتين، الاستراديول، الهرمون المنبه للجريب وهرمون ملوتن عند مرضى الصرع من البالغين الذكور اخذين بنظر الاعتبار عدم تأثير فتره ال علاج والجرعه على المفردات المذكوره اعلاه.

**مفتاح الكلمات:** مرضى الصرع البالغين الذكور، الفالبروات كعلاج احادي، مستوى الهرمونات التوالديه.

## Introduction

It is well known that epilepsy, antiepileptic drugs (AEDs) and the reproductive system have complex interactions(1). Antiepileptic drugs treatment is associated with multiple short and long-term side effects(2). Reproductive endocrine disorders and sexual dysfunction have frequently attributed to epilepsy itself, but AEDs also have various effects on endocrine function(3). Valproate (VPA) is an antiepileptic drug that is used in

neurology for the treatment of generalized and partial epilepsy (4) and in different conditions in psychiatry (5). It has been reported that the use of VPA in women is associated with menstrual cycle dysregulation, polycystic ovary syndrome and hyperandrogenism(6,7). The aim of this study was to assess the effects of VPA in adult epileptic male patients, on serum levels of testosterone, prolactin, FSH, LH and E2 in comparison to healthy controls.

### **Patients and methods:**

This study was conducted in the Dept. of Pharmacology- College of Medicine – University of Mosul from October 2005 to August 2006. Approval to conduct this study were obtained from the committee of Higher Education in the College of Medicine and the ethical committee of Ninawah Health Directorate. Patients were received from private neurological clinic, interviewed and out of 62 patients only 46 were selected according to certain criteria, as being adult, male patient with epilepsy, on sodium valproate (VPA) monotherapy for at least 1 year, on no other drug therapy, and with no other disease state other than epilepsy (hepatic, renal, cardiovascular, endocrinal or neurological). Their mean age  $\pm$ SD  $29.33 \pm 6.44$  years (ranged between 20 and 42 years). They were on VPA in a mean daily dose of  $565.217 \pm 159.40$ mg with a mean  $\pm$ SD body mass index (BMI)  $26.10 \pm 2.30$ . Apparently healthy 50 male individuals, with no chronic disease and did not receive any treatment during the last 2 weeks were also included as a control group. Their mean  $\pm$  SD age  $28.98 \pm 6.50$  years (ranged between 20 and 40

years) with a mean  $\pm$  SD BMI  $24.20 \pm 2.10$ .

From both patients and controls, 10 ml blood samples were taken and assay of serum testosterone, prolactin, FSH, LH and E2 were done using RIA technique, for (serum testosterone and estradiol), LH, prolactin, FSH was measured by immunoradiometric method (IRMA).

BMI were calculated using the following equation, BMI= Weight (kg)/ Height (m<sup>2</sup>) (8).

### **Statistical analysis**

Standard statistical methods were used to determine the mean and standard deviation (SD). Unpaired student Z- test was used to compare the results of measured parameters between controls and patients. Analysis of variance (ANOVA) was used to find the effect of dose on measured parameters. Pearson correlation coefficient to find the relationship between the duration of therapy and measured parameters. Difference between observations were considered significant at  $P \leq 0.05$  (9).

### **Results:**

Comparison between patients and controls with regard measured

parameters, revealed significantly increased serum testosterone level in comparison to controls with insignificant differences in prolactin, FSH, LH and E2 (Table 1).

Table 2 shows insignificant effect of the dosage of VPA at the levels of 400 mg, 600 mg and 800 mg on the serum levels of testosterone, prolactin, FSH, LH and E2 in adult male epileptic patients.

Table 3 shows insignificant effect of the duration of VPA therapy ( ranging from 1 to over 30 years) on the serum levels of testosterone ( $r= 0.13$ ), prolactin ( $r=0.14$ ), FSH ( $r=0.08$ ), LH ( $r=0.16$ ) and E2 ( $r=0.25$ ) in adult male epileptic patients.

## **Discussion**

This study revealed a significantly higher serum total testosterone levels in adult male epileptic patients on VPA monotherapy, with insignificant differences in the serum levels prolactin, FSH, LH, and E2 in comparison to healthy controls.

Epilepsy per se can not be ruled out ,since it can be associated with sexual dysfunction, symptoms of androgen deficiency, testicular atrophy and impairment of stages in spermatogenesis<sup>(10,11)</sup>

In agreement with the present work results, the study conducted by Rattya et al.,<sup>(12)</sup>. They reported that epileptic male patients treated with VPA, developed an increased serum androgen concentration which could be attributed to peripheral effect of VPA on androgen synthesis or metabolism (since VPA is a known enzyme inhibitor)<sup>(13)</sup>. This explanation given might be supported by our findings that the testosterone /LH ratio ( which is a sensitive measure of testicular function)<sup>(14)</sup> was not different from that of the healthy controls.

Also in line with our findings, the study conducted by Mikkonen et al.,<sup>(15)</sup>. They concluded that VPA therapy in boys and young men with epilepsy, associated with high androgen levels and attributed these findings to the effects of VPA on steroid synthesis.

With regard prolactin level and in agreement with our results, the study of Stoffel-Wagner et al.,<sup>(16)</sup> and EL. Khayat et al.,<sup>(17)</sup>, both these studies reported no significant differences in the serum prolactin levels between epileptic patients on VPA and the controls.

With regard effects of duration of therapy on measured parameters, our study revealed insignificant effects of both the dosage and duration of VPA

therapy on serum reproductive hormonal levels. This is in agreement with the only study around the subject conducted by Rattya et al <sup>(12)</sup>. They reported that VPA effects emerged during the first month of therapy and that these effects were permanent and stable as long as the medication was taken.

In conclusion: VPA monotherapy might cause an elevated serum total testosterone levels with insignificant effects on prolactin, FSH, LH and E2 levels in male adult epileptic patients in comparison to healthy controls, although the effect of epilepsy per se on the results can not be ruled out.

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**Table 1.** Comparison between adult male epileptic patients on VPA therapy and controls with regard reproductive hormonal levels

Parameters	Mean ± SD		
	Control ( No. 50)	Patients (No. 46)	P- value
Testosterone (ng/ml)	6.10 ± 1.27	6.64 ± 1.77	< 0.05
Prolactin (ng/ml)	5.86 ± 2.13	5.88 ± 2.11	NS
FSH (IU/L)	6.57 ± 1.59	6.29 ± 1.58	NS
LH (IU/L)	6.94 ± 1.62	6.58 ± 1.42	NS
E2 (Pg/ml)	6.10 ± 3.00	6.07 ± 3.04	NS
Testosterone /E2	1.22 ± 0.61	1.26 ± 0.53	NS
Testosterone/ LH	0.94 ± 0.35	1.10 ± 0.61	NS

NS= non- significant difference, < 0.05 = Significant

**Table 2:** Effect of dosage of VPA on serum level of reproductive hormones in adult male epileptic patients.

Parameters	Dosage of VPA			P-value
	Mean ± SD			
	400 mg (n=19)	600mg(n=16)	800mg(n=11)	
Testosterone (ng/ml)	6.23 ± 2.16	6.67 ± 1.32	7.29 ± 1.54	NS
Prolactin (ng/ml)	6.4 ± 2.17	5.71 ± 2.41	5.25 ± 1.40	NS
FSH (IU/L)	6.13 ± 1.75	6.41 ± 1.29	6.95 ± 1.87	NS
LH (IU/L)	6.57 ± 1.59	6.58 ± 1.42	6.84 ± 1.39	NS
E2 (Pg/ml)	6.31 ± 2.89	6.52 ± 3.89	5.01 ± 1.53	NS
Testosterone /E2	1.14 ± 0.55	1.22 ± 0.52	1.54 ± 0.46	NS
Testosterone/ LH	1.12 ± 0.90	1.07 ± 0.27	1.10 ± 0.28	NS

NS= non- significant difference

**Table 3 :** Effect of duration of VPA therapy on serum levels of reproductive hormones in male epileptic patients.

Parameters	Duration in years (mean± SD)				P-value
	1-10 y. (n=10)	11-20(n=15)	21-30(n=15)	> 30 (n=6 )	
Testosterone (ng/ml)	6.27 ± 1.5	6.82 ± 1.67	6.46 ± 2.06	7.24 ± 1.92	NS
Prolactin (ng/ml)	6.13 ± 2.69	6.22 ± 2.58	5.71± 1.01	5.08 ± 2.08	NS
FSH (IU /L)	5.81 ± 1.13	6.52 ± 1.90	6.45 ± 1.74	6.14 ± 0.89	NS
LH (IU/L)	6.21 ± 1.98	6.41 ± 1.75	6.88 ± 1.28	6.86 ± 1.62	NS
E2 (Pg/ml)	7.55 ± 3.19	6.49 ± 4.08	4.89 ± 1.36	5.50 ± 1.96	NS
Testosterone /E2	0.95 ± 0.42	1.23 ± 0.48	1.40 ± 0.51	1.52 ±0.73	NS
Testosterone/ LH	1.03± 0.28	1.25 ± 0.93	1 ± 0.45	1.08 ± 0.27	NS

NS= non- significant difference