Valproate-Associated Reproductive Hormone Abnormalities: Do Bipolar Men have the Same Risk as Epileptic Men?

Ebru ALDEMİR[1], Fisun AKDENİZ[2], Ahmet Barış ALTAY[3], Şehnaz ARICI[4], Mehmet UMUL[5], Hikmet Hakan AYDIN[6], Mehmet ÇELEBİSOY[7], Simavi VAHİP[8]

SUMMARY

Objective: The effects of valproate on male reproductive hormones have been studied in epileptic patients and animals, but the results are inconsistent because reproductive hormone abnormalities may be independent of the use of valproate and may be due to epilepsy itself. The aim of this study was to determine if there is an association between valproate and reproductive abnormalities in men with bipolar disorder or if the association is unique to men with epilepsy.

Materials and Method: The study included 39 male patients aged 18-50 years with a DSM-IV diagnosis of bipolar disorder (21 on lithium monotherapy and 18 on valproate monotherapy or valproate in combination with lithium therapy) and 15 male epilepsy patients on valproate monotherapy that were evaluated in terms of reproductive hormones.

Results: Duration of illness, duration of lithium and valproate therapy, daily dose and serum concentrations of lithium and valproate, duration of marriage, spouse's gravidity, the serum estradiol, luteinizing hormone, sex hormone-binding globulin, and free testosterone levels, and the free testosterone:luteinizing hormone ratio were not significantly different between the groups. Serum prolactin and follicle-stimulating hormone levels were significantly higher in the epilepsy patients than in the bipolar disorder patients on lithium monotherapy.

Conclusion: The findings show that valproate did not have a negative effect on male reproductive hormones in the bipolar patients. The elevated prolactin and follicle-stimulating hormone levels observed in the epilepsy group should be attributed to epilepsy. To the best of our knowledge this is the first study to compare reproductive hormones in bipolar disorder and epilepsy patients on valproate therapy.

Keywords: Bipolar disorder, epilepsy**,** male reproductive hormones, valproate

INTRODUCTION

Bipolar disorder (BD) is a recurrent mood disorder associated with significant disability. Due to its recurrent nature, it requires long-term treatment; however, long-term use of mood stabilizers may lead to serious side effects. Valproate (VPA) is commonly used to manage manic episodes in BD patients and for prophylactic treatment (Spina and Perugi 2004). One of the side effects of VPA treatment that has not been investigated is its negative effect on male reproductive functioning. In fact, to the best of our knowledge the impact of VPA on reproductive functions in male BD patients has not been studied, although relevant data have been published in studies on male epilepsy patients and animals (Aldemir and Akdeniz 2009).

Several studies evaluated 2two aspects of male reproductive functions: reproductive hormones and sperm parameters. Changes in serum androgen and gonadotropins (follicle-stimulating hormone, luteinizing hormone) levels were observed in male epilepsy patients following VPA treatment (Roste et al. 2005; Mikkonen et al. 2004; Rattya et al. 2001a, 2001b), and VPA was associated with abnormalities in sperm morphology and motility, as well as a decrease in the sperm count (Hayashi et al. 2005; Isojarvi et al. 2004; Roste et al. 2003). Although most such studies were cross-sectional in design,

Received: 13.07.2011 - **Accepted:** 22.12.2011

[1]MD, Trabzon Numune Training and Research Hospital, Department of Psychiatry, Trabzon; [2,8]Prof., Ege Univ. School of Medicine, Department of Psychiatry, Affective Disorders Unit, Izmir; [3]Prof., Ege Univ. School of Medicine, Department of Urology, Izmir; [4]MD, [7]Assoc. Prof., İzmir Atatürk Training and Research Hospital, Department of Neurology II, İzmir; [5]MD, Gediz Hospital, Department of Urology, Kütahya; [6]Prof., Ege Univ. School of Medicine, Department of Biochemistry, İzmir, Turkey.

Ebru Aldemir, MD: *ozturk_ebru2000@hotmail.com*

one1 study reported that the effect of VPA on male reproductive hormones appeared during the first month of treatment and that they persisted through out the course of treatment (Rattya et al. 2001b).

The findings in studies on male patients diagnosed with epilepsy are inconsistent. Some researchers reported that reproductive dysfunction is a consequence of epilepsy itself, irrespective of VPA use (Herzog 2008). Epilepsy may lead to impairment in sexual functioning in males, testicular atrophy, and abnormal spermatogenesis (alterations in sperm motility and morphology, and a decrease in the sperm count and sperm viscosity) (Isojarvi et al. 2004; Herzog 2002).

In view of the changes in sexual functioning associated with VPA in male epilepsy patients, evaluation of the effect of VPA treatment in patient groups other than epilepsy—for example male patients diagnosed with BD—may help to elucidate if the hormonal disturbances observed in male epilepsy patients treated with VPA are directly related to VPA. As such, the present cross-sectional study aimed to investigate if the disturbances in reproductive hormones in male epilepsy patients that are frequently linked to VPA treatment also occur in male BD patients. The main limitation of such a cross-sectional study on male patients with BD is that psychotropic medications other than VPA that can induce reproductive hormone abnormalities are also employed; therefore, only BD patients receiving lithium treatment were included in the study and patients using additional psychotropic drugs were excluded. In this context the hypothesis was that male BD and epilepsy patients using VPA would have higher rates of reproductive hormone abnormalities than BD patients using only lithium.

MATERIALS and METHODS

Sample

Male patients diagnosed with BD, according to DSM-IV criteria, treated with lithium or VPA that were followed-up at Ege University, Psychiatry Department, Affective Disorders Outpatient Unit and male patients diagnosed with idiopathic generalized epilepsy (IGE; Commission on Classification and Terminology of the International League Against Epilepsy, 1989) treated with VPA that were followed-up at İzmir Atatürk Training and Research Hospital, II., Neurology Clinic Epilepsy Outpatient Unit were included in the study. Patients were aged 18-50 years and had been using lithium and/or VPA for ≥3 months. Patients with a history of alcohol or substance use, a history of testicular surgery or varicocele, testicular abnormality, or infertility prior to lithium or VPA treatment, a history of epileptic convulsion during the previous month, and use of any hormone drug or psychotropic drug (except for lithium and VPA) were excluded from the study.

From among the outpatient follow-up files, 50 BD patients that met the above criteria and were using lithium and/or VPA, and 21 IGE patients that were using only VPA were invited to participate in the study. Via telephone interview they were informed about the aim and the methods of the study. In all, 11 patients with BD (22%) (7 were using only lithium, 2 were using only VPA, and 2 were using both lithium and VPA) and 6 patients with IGE (28.5%) refused to participate in the study. In total, 54 male patients (21 BD patients using lithium only, 18 BD patients using VPA only or both VPA and lithium, and 15 epilepsy patients using VPA only) were enrolled in the study. The patients provided written informed consent to participate and the study protocol was approved by the Ege University, School of Medicine Ethics Committee..

Data collection

Medical, psychiatric, reproductive, and psychopharmacologic/antiepileptic treatment history data were obtained via patient interviews and patient follow-up files. Medical and psychiatric disease history (age at onset of BD/epilepsy, current psychotropic/antiepileptic treatment, and drug doses), reproductive history (age of puberty, duration of marriage, spouse's gravidity), alcohol and tobacco use, and exposure to chemicals were recorded in case file forms.

Blood samples were drawn between 08:00 and 10:00 after 12-h fasting, and were stored at –20 °C until analysis. In all, 54 blood samples were evaluated at Ege University, School of Medicine, Training and Research Laboratory using the same kit. The blood samples were analyzed for serum estradiol (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), sex hormone-binding globulin (SHBG), free testosterone (free T), free T:LH ratio (a sensitive marker of testicular dysfunction), lithium, and VPA.

Measurements

Serum LH, FSH, and PRL were measured via automated chemiluminescence using an Elecsys 1010 analyzer (Roche Diagnostics, Basel, Switzerland); intra-assay CVs (coefficients of variation) were 4.2%, 5.1%, and 3.2%, respectively, and interassay CVs were 3.1%, 5.7%, and 4.2%, respectively. Serum free T, E2, and SHBG were measured using DSL reagents (Diagnostic System Laboratories, TX, USA) and the radioimmunoassay method; intra-assay CVs were 5.1%, 4.5%, and 3.0%, respectively, and interassay CVs were 4.9%, 4.1%, and 4.1%, respectively. Serum VPA was measured using an Axsym immunoassay analyzer (Abbott Diagnostics, IL, USA) and serum lithium was measured using the flame photometric method.

Statistical evaluation

Quantitative data are expressed as mean ± SD. The chi-square test was used to compare categorical data. Quantitative data with normal distribution were analyzed via one-way ANOVA, and parametric data with normal distribution were analyzed via Student's-t test and Tukey's post-hoc test. Variables without normal distribution were compared using the Mann-Whitney U test. Correlations were calculated via Pearson's correlation analysis. Statistical significance was set at $P < 0.05$.

RESULTS

Clinical characteristics

The clinical and reproductive characteristics of the patients included in the study are shown in Table 1. In the BD group mean uninterrupted duration of lithium use was 533.6 ± 448.7 weeks (range: 12-1404 weeks) in the lithium-VPA subgroup . In the BD-valproate subgroup 7 patients used VPA only and 11 patients used lithium and VPA. In the BD group mean interrupted duration of VPA use was 141.7 ± 134.7 weeks (range: 20-416 weeks) in the VPA subgroup and 227.1 ± 165.7 weeks (range: 100-536 weeks) in the lithium-VPA subgroup. Among the IGE patients using VPA, mean duration of treatment was 212.1 ± 220.0 weeks (range: 24-780 weeks). There wasn't a significant difference in duration of VPA treatment, daily dose of VPA, or mean serum VPA level between the BD-VPA subgroup and the IGE group.

Reproductive characteristics

Age of puberty was significantly lower in the BD-lithium subgroup than in the IGE group (BD-lithium subgroup vs. IGE group: F = 3.551, P = 0.036; BD-lithium subgroup vs. BD-VPA subgroup: P = NS; BD-VPA subgroup vs. IGE group: P = NS); however, there wasn't a significant difference between the three 3 groups with respect to mean duration of marriage and spouse's gravidity. There wasn't a difference in alcohol or cigarette use between the groups, and none of the patients were exposed to chemicals.

Reproductive hormones

Reproductive hormone levels in the three 2 patient groups are given in Table 2. The serum PRL level was significantly higher in the IGE group than in the BD-lithium subgroup (Tukey's post-hoc comparison, P = 0.008). In all, 3three IGE patients (20%) had FSH levels over upper levels (normal range: 1.5-12.4 mIU mL^{-1}), whereas none of the BD patients had an elevated FSH level. When comparison was made, the difference was significant between the BD-lithium subgroup and the IGE group (BD-lithium subgroup vs. IGE group: χ^2 =6.300, P=0.043; BD-lithium subgroup vs. BD-VPA subgroup: P=NS; BD-VPA subgroup vs. IGE group: P=NS). There weren't any significant differences in the other hormone parameters, including E2, LH, SHBG, free T, and the free T:LH ratio, between the IGE and BD patients.

DISCUSSION

The aim of this cross-sectional study was to determine if the disturbances in reproductive hormones that occur in epilepsy patients and are frequently linked to VPA treatment also occur in male BD patients. The present findings indicate that VPA treatment had no effect on reproductive hormones in the male BD patients.

Table 1. Patient clinical characteristics

Mean ± SD	BDP-lithium subgroup (n = 21)	BDP-VPA subgroup (n = 18)	IGE group (n = 15)	Statistical analysis
Age (years)*	42.7 ± 8.9	38.2 ± 9.3	31.1 ± 11.1	F = 6.320, P = 0.004
Age at disease onset (years)	22.1 ± 6.1	22.8 ± 9.5	18.4 ± 7.8	NS
Duration of VPA treatment (months)	_	193.9 ± 156.2	212.1 ± 220.0	NS
VPA daily dose (mg)	_	1069.4 ± 294.6	1133.3 ± 399.4	NS
Serum concentration of VPA (mg L^{-1})	_	74.1 ± 10.7	71.8 ± 20.3	NS
Age of puberty (years)**	13.9 ± 0.9	14.2 ± 0.7	14.6 ± 0.8	F = 3.551, P = 0.036
Duration of marriage (years)	n = 19 19.4 ± 7.1	n = 10 14.6 ± 10.2	n = 7 14.1 ± 9.0	NS
Spouses' gravidity	n = 19 2.3 ± 1.2	n = 10 2.3 ± 1.8	n = 7 2.2 ± 2.0	NS

*Post-hoc comparisons: BD-lithium vs. IGE group: P < 0.01, BD-lithium subgroup vs. BD-VPA subgroup: P = NS, BD-VPA subgroup vs. IGE group: P = NS

**Post-hoc comparisons: BD-lithium subgroup vs. IGE group: P < 0.05, BD-lithium subgroup vs. BD-VPA subgroup: P = NS, BD-VPA subgroup vs. IGE group: P = NS

Table 2. Reproductive hormone levels in the BPD and IGE groups

Mean ± SD	BDP-lithium subgroup (n = 21)	BDP-VPA subgroup (n = 18)	IGE group (n = 15)	Statistical analysis
Estradiol (pg mL^{-1})	27.50 ± 5.51	27.28 ± 11.88	25.50 ± 6.47	NS
LH (mIU mL^{-1})	4.57 ± 1.95	4.47 ± 1.83	6.84 ± 8.73	NS
FSH (mIU mL^{-1})	5.40 ± 2.80	4.34 ± 2.46	7.63 ± 9.77	NS
PRL (ng mL^{-1})*	5.42 ± 3.57	8.18 ± 5.17	10.42 ± 5.08	F = 5.342, P = 0.008
SHBG (nmol L^{-1})	24.76 ± 12.08	27.64 ± 18.74	27.27 ± 14.49	NS
Free T (pg mL^{-1})	14.69 ± 4.12	16.63 ± 4.59	14.62 ± 4.24	NS
Free T:LH ratio	3.86 ± 2.32	4.4 ± 2.28	3.25 ± 2.01	NS

*Post-hoc comparisons: BD-lithium subgroup vs. IGE group: P < 0.05, BD-lithium subgroup vs. BD-VPA subgroup: P = NS, BD-VPA subgroup vs. IGE group: P = NS

Reproductive characteristics in the BD patients

To the best of our knowledge pubertal characteristics in male BD patients have not been previously investigated. In the present study age of puberty in the BPD patients was significantly lower than that in the IGE patients, but was not thought to be clinically relevant, as the age of puberty in the BD patients (in the BDP-lithium and BDP-VPA subgroups) was similar to that in the Turkish general population (Darcan et al. 1999).

The relationship between VPA use and reproductive hormones

When designing a study on reproductive hormones in male BD patients the effect of psychotropic drugs, such as mood stabilizers, antidepressants, and antipsychotics, on reproductive hormones (such as hyperprolactinemia) should be taken into account. It was reported that lithium is a safe mood stabilizer (in terms of its effect on reproductive hormones) in healthy volunteers and male BD patients (Baptista et al. 1997; Kusalic and Engelsmann 1996; Ghadirian et al. 1992).

It is known that antipsychotics lead to abnormalities in reproductive hormones (Knegtering et al. 2003); in addition, antidepressants cause sexual dysfunction and fertility problems (Gregorian et al. 2002.) Given the probable effects of these drugs, patients that have recently or currently use them were not included in the present study—BDP patients that used only lithium and/or VPA were included. VPA can cause an increase in the E2 level due to hepatic enzyme inhibition (Herzog 2002), which could result in impotence in males. In the present study VPA had no effect on the E2 level in the BD or IGE groups, which is in agreement with Duncan et al. (1999), but contradicts Isojarvi et al. (1990).

Unlike in previous studies (Røste et al. 2005; Rättya et al. 2001a; Isojärvi et al. 1990), a significant decrease was not observed in mean FSH and LH levels in the present study's BD-VPA subgroup and IGE group, which may have been due to normal E2 levels, as E2 has a negative feedback effect on the hypothalamus in males. An elevated E2 level may result in a decrease in pituitary hormones (LH and FSH) via mediation of this negative feedback mechanism.

Serum free T may influence pituitary hormone levels via a negative feedback mechanism and an increase in serum free T may cause a decrease in serum LH and FSH levels (Rättya et al. 2001a). In the present study significant change was not observed in mean serum free T levels in the BDP-VPA subgroup or the IGE group, which is congruent with Duncan et al. (1999) and Stephen et al. (2001, 2007). Normal serum free T levels may be the reason why there was no drop in LH and FSH levels. In addition, there wasn't a correlation between VPA use and the free T:LH ratio—a sensitive indicator of testicular dysfunction, as reported by Bauer et al. (2004).

In the present study mean serum SHBG was not affected by VPA use, which is agreement with earlier studies (Mikkonen et al. 2004; Rättya et al. 2001a; Verroti et al. 2000). VPA does not induce liver enzymes responsible for SHBG production and no abnormality in SHBG levels is expected with its use.

It was reported that pituitary hormones in epilepsy patients are not normal (Aldemir and Akdeniz 2009); the significantly elevated FSH levels observed in the present study's IGE group are thought to be consistent with this finding. Moreover, the significantly higher standard deviation in the mean serum LH and FSH levels observed in the IGE group may indicate that these hormone levels were abnormal values in the IGE group, even if the differences between those in the BD groups were not significant.

In the present study there wasn't a significant difference in the mean serum PRL levels between the BD-VPA subgroup and the IGE group while (they were significantly higher in the IGE group than in the BD-lithium subgroup. However), whereas, Verroti et al. (2000) reported normal PRL levels in male epilepsy patients using VPA. According to Montouris and Morris (2005), elevated PRL levels were observed in epilepsy patients observed during interictal periods, regardless

of treatment. In the present study the lack of a significant increase in PRL levels in BP patients using VPA suggests that the increase was related to epilepsy itself, not VPA.

Strengths and limitations of the study

To the best of our knowledge the present study is the first to investigate the relationship between diagnosis in male population (BPD vs. epilepsy), VPA use, and their probable effects on reproductive hormone abnormalities. It was observed that VPA did not cause abnormalities in reproductive hormones. Although the present study's small population could be considered a limitation, it is similar to that of other published studies (Roste et al. 2005; Mikkonen et al. 2004; Rättya et al. 2001a; Stephen et al. 2001; Verroti et al. 2000).

Another limitation of this study is its cross-sectional design. As the effect of VPA on reproductive hormones was evaluated during a particular time period, it's difficult to establish a definitive causal relationship. Due to these limitations, in order to clarify the effect of disease and the effect of VPA independent of disease, follow-up studies with larger patient populations are required.

Conclusion

The present findings indicate that VPA did not cause reproductive hormone abnormalities in the male patients; however, the IGE patients had a greater propensity to such hormonal changes, regardless of VPA treatment. Despite its limitations, the present study demonstrates that VPA may be considered a safe mood stabilizer in male patients with regard to endocrine functions.

Acknowledgements

This study was supported by the Ege University Scientific Research Projects Unit and the Turkish Psychiatry Association. We offer our thanks to Oya Özken and Özlem Bulut for their help drawing blood samples, and to Dr. Zeynep Kurt for data collection.

REFERENCES

Aldemir E, Akdeniz F (2009) Valproatın erkek üreme işlevleri üzerine etkisi. Turk Psikiyatri Derg; 20: 376-84.

American Psychiatry Association (1994) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), 4th Edition. American Psychiatric Association, Washington, DC.

Baptista T, Alastre T, Contreras Q et al. (1997) Effects of lithium carbonate on reproductive hormones in healty men: Relationship with body weight regulation-A pilot study. Prog Neuropsychopharmacol Biol Psychiatry; 21: 937-50.

Bauer J, Blumenthal S, Reuber M et al. (2004) Epilepsy syndrome, focus location, and treatment choice affect testicular function in men with epilepsy. Neurology, 62: 243–6

Commission on Classification and Terminology of the International League Against Epilepsy (1989) Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 30, 389–99.

Darcan S, Coker M, Mavi E (1999) Endokrin Hastalıklar. Çocuk Sağlığı ve Hastalıkları Kitabı, 1st Edition, A Cura (Ed), E.Ç.V. Yayınları No:6, Ege Üniversitesi Basımevi, p. 399.

Duncan S, Blacklaw J, Beastall GH et al. (1999) Antiepileptic drug therapy and sexual function in men with epilepsy. Epilepsia, 40: 197–204.

Ghadirian AM, Annable L, Belanger MC (1992) Lithium, benzodiazepines, and sexual function in bipolar patients. Am J Psychiatry, 149:801-5.

Gregorian RS, Golden KA, Bahce A et al. (2002) Antidepressant-induced sexual dysfunction. Ann Pharmacother, 36(10):1577-89.

Hayashi T, Yoshida S, Yoshinaga A et al. (2005) Improvement of oligoasthenozoospermia in epileptic patients on switching anti-epilepsy medication from sodium valproate to phenytoin. Scand J Urol Nephrol,

39: 431-2.

Herzog AG (2002) Altered reproductive endocrine regulation in men with epilepsy: Implications for reproductive function and seizures. Ann Neurol, 51:539-42.

Herzog AG (2008) Disorders of reproductionin patients with epilepsy: Primary neurological mechanisms. Seizure, 17: 101-10.

Isojärvi JIT, Löfgren E, Juntunen KST et al. (2004) Effect of epilepsy and antiepileptic drugs on male reproductive health. Neurology, 62:247–53.

Isojärvi JIT, Pakarinen AJ, Ylipalosaari PJ et al. (1990) Serum hormones in male epileptic patients receiving anticonvulsant medication. Arch Neurol, 47: 670–6.

Knegtering H, van der Moolen AE, Castelein S et al. (2003) What are the effects of antipsychotics on sexual dysfunctions and endocrine functioning? Psychoneuroendocrinology, 28(Suppl 2):109-23.

Kusalic M, Engelsmann F (1996) Effect of lithium maintenance treatment on hypothalamic pituitary gonadal axis in bipolar men. J Psychiatry Neurosci, 21: 181-6.

Mikkonen K, Tapanainen P, Pakarinen AJ et al. (2004) Serum androgen levels and testicular structure during pubertal maturation in male subjects with epilepsy. Epilepsia, 45: 769-76.

Montouris G, Morris GL (2005) Reproductive and sexual dysfunction in men with epilepsy. Epilepsy Behav, 7(Suppl.2): 7-14.

Rättya J, Turkka J, Pakarinen AJ et al. (2001a) Reprodutive effects of valproate, carbamazepine and oxcarbazepine in men with epilepsy. Neurology, 56: 31-6.

Rättya J, Pakarinen AJ, Knip M et al. (2001b) Early hormonal changes during valproate or carbamazepine treatment. A 3-month study. Neurology, 57: 440-4.

Røste LS, Taubøll E, Haugen TB et al. (2003) Alterations in semen parameters in men with epilepsy treated with valproate or carbamazepine monotherapy. Eur J Neurol, 10: 501–6.

Røste LS, Taubøll E, Mørkrid L et al. (2005) Antiepileptic drugs alter reproductive endocrine hormones in men with epilepsy. Eur J Neurol, 12: 118–24.

Spina E, Perugi G (2004) Antiepileptic drugs: Indications other than epilepsy. Epileptic Disord, 6: 57-75.

Stephen LJ, Kwan P, Shapiro D et al. (2001) Hormone profiles in young adults with epilepsy treated with sodium valproate or lamotrigine monotherapy. Epilepsia, 42:1002-6.

Stephen LJ, Sills GJ, Leach JP et al. (2007) Sodium valproate versus lamotrigine: A randomised comparison of efficacy, tolerability and effects on circulating androgenic hormones in newly diagnosed epilepsy. Epilepsy Res, 75: 122-9.

Verrotti A, Basciani F, Morresi S et al. (2000) Serum sex hormone levels in young male patients with epilepsy receiving carbamazepine and valproic acid and after their withdrawal. Eur J Pediatr, 159:871-2.