

Effects of Valproate on Male Reproductive Functions

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Abstract

Valproate is an antiepileptic commonly used in the treatment of psychiatric and neurologic diseases. Some of the most frequently seen side effects affect the gastrointestinal, neurological, and hematological systems. Its side effects on reproductive functions have not been sufficiently studied. The use of valproate by females with bipolar disorder and epilepsy may cause menstrual cycle abnormalities, polycystic ovary syndrome, and hyperandrogenism. The effects on male reproductive functions have been researched only in epileptic patients and animals, and the results have been conflicting, because reproductive function abnormalities may be independent of the use of valproate and may be due to epilepsy itself.

In the first part of this review reproductive function abnormalities due to epilepsy will be discussed, independent of the use of valproate or any other antiepileptic. Then, the results of research on valproate's effects on male reproductive functions (hormonal levels and sperm parameters) will be presented, including the possible underlying mechanisms of these effects, the effect of the duration of valproate use, and whether or not the effects are reversible. In the second section we review the results of animal research, which could be beneficial in assessing the effects of valproate and epilepsy.

Key Words: valproate, male reproductive hormones, sperm parameters

INTRODUCTION

Valproate (VPA) is an antiepileptic drug that is used in neurology for the treatment of generalized and partial epilepsy, especially in cases in which absence, myoclonic, tonic-clonic, atonic, and mixed type seizures are seen, and for prophylaxis of childhood febrile convulsions (Johannessen and Johannessen, 2003; Wheless et al., 2007). It is also preferred in cases in which the type of epileptic seizure cannot be determined and for prophylaxis of migraine headaches (Johannessen and Johannessen, 2003; Spina and Perugi, 2004).

In psychiatry it is used for the treatment of bipolar disorder manic episodes and for prophylactic treatment (Spina and Perugi, 2004). It can also be used long-term as a supplemental agent for impulse control disorders

and schizophrenic disorder (Sadock and Sadock, 2004; Pirildar, 2005).

The most commonly encountered side effects of VPA treatment are associated with the gastrointestinal system, including nausea, vomiting, and diarrhea. Other common side effects are sedation, ataxia, dysarthria, and tremor. Side effects like hair loss, weight gain, changes in liver function tests, hyperammonemia, and benign thrombocytopenia have also been reported. One of the side effects that can be observed, but is not frequently considered, is the negative effect on reproductive functions (Bialer and Yagen, 2007).

It has been reported that in women that use VPA menstrual cycle dysregulation, polycystic ovary syndrome, and hyperandrogenism can be seen. In particu-

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lar, in those that receive VPA treatment before the age of 20 years the prevalence of polycystic ovary syndrome or hyperandrogenism is almost 80%. While impairment of reproductive functions has been observed in epileptic women that received VPA, in the past 5 years similar results have been reported in women with bipolar disorder that received VPA treatment (Isojarvi et al., 1993; 1996; 1997; Murialdo et al., 1997; 1998; Tauboll et al., 1998; Akdeniz et al., 2003; Rasgon et al., 2005).

The findings on VPA's effects on male reproductive functions come from studies on patients diagnosed with epilepsy or from animal studies. A search of MEDLINE showed that this issue was not addressed in the psychiatric literature. Data from male epilepsy studies are contradictory. Reproductive function disorders may be a result of either epilepsy itself or of the drugs used in the treatment of epilepsy, as it is in women (Herzog, 2008).

METHOD

A search for English language publications in PubMed, Medline, ProQuest, EBSCOHost, and PsycINFO databases was performed using different combinations of the keywords, bipolar disorder, epilepsy, psychiatry, valproate, male sexual dysfunction, male fertility, gonadal hormones, sperm parameters, and animal studies. Among the results, full text articles from the Ege University Online Journals and Ege University Medicine Faculty Library were included.

RESULTS

1. Reproductive Dysfunction Seen in Male Patients Diagnosed with Epilepsy

This section focuses on reproductive dysfunction due to epilepsy and drug use, the relationship between this dysfunction and the duration of drug use, whether or not this dysfunction is reversible, and the potential mechanisms underlying this dysfunction.

1.1. Reproductive dysfunctions due to epilepsy

Epilepsy, independent of the drug used for treatment, may cause anovulation, hyperandrogenism, and a decrease in the efficacy of oral contraceptives in women, and sexual dysfunction, symptoms of androgen deficiency, testicular atrophy, and impairment in the stages of spermatogenesis (changes in sperm motility and morphology, decrease in number and viscosity) in men, as well as a decrease in fertility in both sexes (Herzog, 2002a; Yerby, 2000; Bauer et al., 2002; Isojarvi et

al., 2004). In previous studies a decrease in libido was reported in 38%-71% of male patients diagnosed with epilepsy (Herzog, 1997). Decreases in sperm count, and abnormal sperm morphology or impairment in sperm motility have been reported in almost 90% of male patients diagnosed with epilepsy (Herzog, 2008).

Epileptic seizures are known to cause deviance from normalcy in hypothalamic and pituitary hormones. The temporolimbic system is an important system involved in adult epilepsy. Input to the hypothalamo-pituitary-gonadal axis from the cerebral cortex, amygdala, and hippocampus changes during epileptic seizures. Epileptic discharges may cause stimulation or inhibition of the hypothalamus, depending on the part of the amygdala that is affected. This results in an increase or a decrease in the level of gonadotropin-releasing hormone (GnRH). In addition, the release of GABA and glutamate also affects the release of hypothalamic and pituitary hormones (Montouris and Morris, 2005).

In patients diagnosed with epilepsy it has been shown that pituitary hormones are not normal. In some male and female patients an increase in LH level and its pulsatile release was seen during generalized seizures, while a decrease was observed during seizures centered in the temporal region. Moreover, in male patients diagnosed with epilepsy, epileptiform discharges were shown to cause immediate increases in prolactin (PRL) levels (Montouris & Morris, 2005) and immediate changes in LH release (Herzog, 2002b). Quigg et al. (2002) reported that the frequency of LH release and its mean level were low, while the release amplitude was high during the interictal period, as compared to healthy controls.

Bauer et al. (2004) showed that free testosterone levels were lower in patients diagnosed with generalized epilepsy that did not use antiepileptic drugs than in healthy controls. They posited that this negatively affects reproductive functions. Nonetheless, the similarity in LH, follicle stimulating hormone (FSH), free testosterone, and inhibin B levels in the 2 study groups (patients whose seizures were controlled and those whose seizures were not controlled) showed that epilepsy may disturb testicular testosterone production in a different way than a decrease in ictal or interictal LH release. In the same study, although it was shown that the hormonal changes were not affected by the location of epileptic focus, actually it has been thought that the type of epilepsy may be in relation with the male reproductive abnormalities. Specifically, changes in LH levels over GnRH were proposed to occur in patients with temporal lobe epilepsy, due to the

TABLE 1. Studies on the effects of VPA on reproductive hormones and sperm parameters in male epilepsy patients.

	Study Design	Study Duration	Epilepsy Type	Number of Patients	Healthy Control Group	Comparison Drug	Effects on Hormonal Parameters	Effects on Sperm Parameters
Isojarvi, 1990	Cross-sectional	-	Partial and Generalized	63	+	CBZ, PHT	LH ↓, FSH ↓, E2 ↑	-
Rättyä, 2001a	Follow-up	3 months	Partial and Generalized	22	-	CBZ	FSH ↓, DHEA ↑, P ↑, LH ↓*	-
Rättyä, 2001b	Cross-sectional	-	Partial and Generalized	90	+	CBZ, OCBZ	FSH ↓, T ↓, LH ↓*	-
Mikkonen, 2004	Cross-sectional	-	Partial and Generalized	70	+	CBZ, OCBZ, LTG	A ↑	-
Røste, 2005	Cross-sectional	-	Partial and Generalized	35	+	CBZ	DHEA-S ↑, FSH ↓, LH ↓, fC/tC ↓	-
Duncan, 1999	Cross-sectional	-	Unspecified	118	+	CBZ, PHT	No effect	-
Verrotti, 2000	Cross-sectional	-	Unspecified	48	+	CBZ	No effect	-
Stephen, 2001	Cross-sectional	-	Partial and Generalized	32	+	LTG	No effect	-
Stephen, 2007	Follow-up	12 months	Partial, Generalized, and Juvenile Myoclonic	116	-	LTG	No effect	-
Chen, 1992	Cross-sectional	-	Partial and Generalized	10	+	CBZ, PHT, PB	-	Inhibition of sperm motility
Røste, 2003	Cross-sectional	-	Partial and Generalized	36	+	CBZ	-	Sperm tail abnormality ↑
Isojarvi, 2004	Cross-sectional	-	Partial and Generalized	60	+	CBZ, OCBZ	A ↑	Impairment of sperm movement, any sperm abnormality ↑, testicular volume ↓

*Statistically insignificant. fC: Free carnitine; tC: total carnitine; T: testosterone; A: androstenedione, PHT: phenytoin; PB: phenobarbital; LTG: lamotrigine; CBZ: carbamazepine; OCBZ: oxcarbazepine; DHEA(S): dehydroepiandrosterone (sulfate).

interactions of the limbic system with the hypothalamus (Quigg et al., 2002). In this group testosterone levels are lower than in non-temporal epileptic patients following temporal lobectomy, in whom testosterone levels are normal (Bauer et al., 2000) and libido and sexual functions improve (Blumer & Walker, 1967). Generally, in one third of the patients diagnosed with temporolimbic epilepsy, hypogonadism (a decrease in gonadal functions: a

decrease in serum testosterone levels and/or a decrease or abnormality in sperm production) may be seen and the frequency of hypogonadism increases with age (Herzog et al., 2004; 2005). In addition to the epileptic focus, the age of onset of epilepsy is also suggested to affect sexual functions (Herzog, 2008).

Furthermore, lateralization of epileptic discharges is also important. Sexual dysfunction is more frequently

TABLE 2. Studies on the effects of VPA on reproductive hormones and sperm parameters in animals.

	Animal type	Study duration	Control group	Effects
Cohn (1982)	Rat	3 months	-	Sperm quantity ↓, Fertility ↓
Walker (1990)	Rat, Dog	13 months	-	Spermatogenesis ↓, Testicular atrophy
Snyder (1995)	Rat	8 weeks	+	Spermatogenesis ↓, Testicular development ↓
Røste (2001)	Rat	3 months	+	Testicular atrophy

observed in men with seizures due to right temporolimbic focus than in men who experience seizures due to left temporolimbic focus (Herzog, 2008).

1.2. Reproductive Dysfunction due to VPA

Before discussing the effects of VPA on reproductive functions, the effects of other antiepileptic agents will be summarized. Agents that cause enzyme induction, such as carbamazepine (CBZ), phenytoin, and phenobarbital, stimulate the aromatase and cytochrome P450 enzymes, increasing levels of sex hormone-binding globuline (SHBG) and decreasing the level of biologically active testosterone. As a result of CBZ use, a decrease in FSH and LH levels is observed, while the estradiol (E2) level may increase. Surprisingly, a slight increase in the E2 level affects the negative feedback on gonadotropin production (Herzog, 2008). As for sperm parameters, it was reported that CBZ decreases sperm motility and increases the possibility of encountering morphologically abnormal sperm (Isojarvi et al., 2004; Roste et al., 2003).

Oxcarbazepine (OCBZ) is an antiepileptic agent structurally similar to CBZ, but its pathway in the liver is different and it does not have an induction effect on the oxidative P450 system. Although previous research has shown that changes in the endocrine system due to CBZ use decline after changing the treatment modality to OCBZ, current studies show that when administered in higher doses OCBZ may also induce the release of liver enzymes that cause an increase in SHBG and serum testosterone levels (Rattya et al., 2001a). One study reported that OCBZ may be associated with an increase in the frequency of morphologically abnormal sperm (Isojarvi et al., 2004).

Lamotrigine (LTG), another antiepileptic agent frequently used to treat epilepsy and compared to VPA in studies on epilepsy, was shown to have no effect on hormonal changes in several studies (Carwile et al., 1997; Mikkonen et al., 2004; Herzog et al., 2004; 2005).

The effects of new generation antiepileptics (felbamate, gabapentin, levetiracetam, pregabalin, tiagabine, topiramate, and vigabatrin) on male reproductive functions have yet to be determined.

VPA is not an enzyme-inductive antiepileptic, but it has been shown that the drug negatively affects male reproductive functions. Its effects may be explored by classifying its effects on hormones and semen parameters.

1.2.a. Hormonal Alterations Due to VPA

When male patients receiving VPA were compared to healthy controls LH and FSH levels were significantly lower in the patient group than in the control group, while E2 levels were significantly higher (Isojarvi et al., 1990). Hormone levels were assessed during the first and third month of treatment in a group of male patients that received VPA or CBZ for the first time. In the VPA group a decrease in serum FSH and an increase in progesterone (testosterone antecedent) were observed in the first month of the treatment, and in the third month of the treatment an increase in serum DHEA (testosterone antecedent) and an insignificant decrease in LH were observed. The results show that the effect of VPA on male reproductive functions began in the first month of treatment and that they were stable or progressive. These effects did not cause complaints in any of the patients. Although it was not reflected as a change in serum testosterone levels, it was suggested that an increase in serum testosterone antecedents change serum androgen levels slightly and that this change activates the negative feedback mechanism that causes a decrease in the levels of FSH and LH (Rattya et al., 2001b).

In another study conducted by the same researchers patients diagnosed with epilepsy that received VPA, CBZ, or OCBZ were compared to healthy controls, in terms of reproductive hormones. In the VPA group serum testosterone levels were high and compared to the control group, the mean FSH level was significantly lower, while

the LH level tended to be low. Nonetheless, the similarity in FSH and LH levels in the normal group and the group that had higher serum testosterone levels led the authors think that the decrease in FSH and LH was not a result of the negative feedback mechanism. While there was no significant difference between the 2 drug groups in terms of FSH and LH, only in the CBZ group was a significant increase in mean serum SHBG concentration observed (Rattya et al., 2001a). It was suggested that this increase was associated with the inductive effect on liver enzymes responsible for the production of SHBG.

In a study conducted with men diagnosed with epilepsy that received VPA or CBZ it was reported that VPA caused a significant increase in DHEA-S (testosterone antecedent) levels, and a significant decrease in FSH and LH levels. At the same time, when carnitine levels, an indicator of epididymal functioning, were assessed it was observed that the ratio of free carnitine/total carnitine was low in the VPA group (Roste et al., 2005).

By using the fermentation-based *in vitro* bioassay method, Death et al. (2005) showed that within therapeutic blood ranges, VPA blocked androgen and progesterone receptors, while it did not block estrogen receptor activity. Blockage of progesterone receptors does not have a known effect in men, whereas androgen receptor blockage may delay the onset of puberty, impair reproductive functions, and androgenic effects.

In a study conducted with male adolescents and young adults diagnosed with epilepsy in which the permanent effects of antiepileptic drugs on reproductive hormones were examined, a significant decrease in the levels of testosterone and DHEA-S were noted in the CBZ group, while similar decreases were not observed in the VPA group. There was a significant increase in SHBG levels only in the CBZ group. FSH, LH, PRL, and total testosterone levels were normal in both groups. No hormonal changes were observed in the healthy control group. The hormonal changes seen in the patients were temporary and returned to normal soon after the medication was stopped, showing that the antiepileptic drugs did not cause any permanent hormonal changes (Verrotti et al., 2000). In a study in which a group of male patients diagnosed with epilepsy in the pubertal maturity state (patients received CBZ, VPA, OCBZ, or LTG) were compared to healthy controls, serum testosterone levels were within the normal range in the entire study group, while serum androstenedione levels were high in the VPA group. An increase in SHBG level and a decrease in DHEA-S level were detected in the CBZ

group. In young male patients diagnosed with epilepsy VPA and CBZ (OCBZ and LTG had no effect) were reported to be associated with changes in serum sex hormone levels (Mikkonen et al., 2004).

Other human studies suggest that VPA does not negatively affect male reproductive functions, but these studies are relatively small in number. In a study in which male patients that received antiepileptic treatment and patients that did not were compared to healthy controls it was shown that VPA did not affect SHBG, free testosterone, total testosterone, DHEA-S, or E2 levels (Duncan et al., 1999). This might have been because the epilepsy patients included in the study may have had shorter duration of illness and less severe illness than patients included in other studies.

When male patients diagnosed with epilepsy that received VPA or LTG for at least 2 years were assessed, there was no difference between the 2 groups regarding SHBG, DHEA, testosterone, androstenedione, LH/FSH ratio, or free androgen index (Stephen et al., 2001). Yet, there were only 17 patients in the VPA group and 15 in the LTG group, which could be considered a limitation of the study.

In a randomized, open-ended 1-year follow-up study conducted with newly diagnosed male epileptic patients that assessment of the effects of VPA and LTG on reproductive hormones, no significant differences were reported between the 2 groups at the beginning or the end of the treatment in terms of SHBG, androstenedione, testosterone, and free androgen index (Stephen et al., 2007). Different studies have shown that LTG use does not cause any hormonal abnormality; however, as for VPA, this result may be associated with short follow-up periods.

1.2.b. Differences in Semen Parameters

In a study that compared patients that used antiepileptic drugs (VPA, CBZ, phenytoin, phenobarbital) for a long time with normal controls, in terms of the effects of these drugs on sperm motility, it was observed that all the drugs significantly inhibited sperm motility, both *in vitro* and *in vivo* (Chen et al., 1992).

When epileptic patients receiving VPA or CBZ were compared to healthy controls, regarding semen parameters, no difference was observed between the 2 treatment groups; however, in the patient groups there was a significant decrease in fast-motile forward number and a significant increase in sperm-head abnormality compared to the controls. In the VPA group there was a sig-

nificant increase in sperm tail abnormality compared to the controls. When the treatment groups and controls were compared regarding testicular measures, no significant differences were observed (Roste et al., 2003).

In another study in which epileptic patients receiving antiepileptic treatment were compared to healthy controls, it was reported that the possibility of increased impairment in sperm movement and any sperm abnormality was higher in the VPA group (Isojarvi et al., 2004).

Two male cases that received VPA for the treatment of epilepsy for more than 10 years that were also undergoing infertility treatment had low sperm counts and sperm motility. When VPA was stopped and a different antiepileptic drug was administered, their sperm parameters significantly improved in the third and sixth months of the new treatment, and it was reported that their wives got pregnant 15 months after the new treatment had begun (Hayashi et al., 2005). In another case it was suggested that, along with a decrease in sperm count and motility, VPA also negatively affected sperm vitality and morphology, and that all the parameters improved after VPA treatment ended (Yerby & McCoy, 1999).

The effects of VPA on reproductive hormones and sperm parameters in male patients diagnosed with epilepsy are summarized in Table 1.

1.3. Duration of VPA Use and its Relationship to Reproductive Dysfunction

Research regarding this issue has been mainly cross-sectional in design; therefore, no definitive conclusions can be drawn concerning the duration of VPA use and its relationship to reproductive dysfunction. Nonetheless, one study reported that the effects of VPA on male reproductive functions emerged during the first months of treatment and that these effects were permanent and stable as long as the medication was taken (Rattya et al., 2001b).

1.4. The Effect of Terminating VPA Treatment on Reproductive Dysfunctions

Numerous studies and case reports have shown that changes in hormones and sperm parameters due to VPA use are reversible after the medication is stopped, and that VPA does not cause any permanent hormonal change (Yerby & McCoy, 1999; Verrotti et al., 2000; Hayashi et al., 2005).

1.5. Possible Mechanisms of the Effects of Epilepsy and VPA on Reproductive Dysfunction

As stated above, reproductive dysfunction is seen in

male patients that have epileptic seizures originating in the temporolimbic region. Epileptic discharges that develop in the structures of the medial temporal lobe affect the release of pituitary hormones over hypothalamus that is being connected to. As a result, changes emerge in gonadal and reproductive functions (Herzog, 2008).

The underlying mechanisms of the effects of VPA on reproductive functions have yet to be determined. One suggested mechanism is an increase in E2 via its hepatic enzyme inhibition. In males E2 has a negative feedback effect on the hypothalamus. Changes in pituitary hormonal levels may occur according to this effect (Herzog, 2002a).

Another potential mechanism regarding the effect of VPA is an increase in testosterone antecedents following VPA use. This increase decreases the release of pituitary hormones via the negative feedback mechanism. Decreased release of pituitary hormones may manifest as reproductive dysfunction (Rattya et al., 2001b; Roste et al., 2005). It is also suggested that GABAergic neurotransmission may affect gonadotropin release (Isojarvi, 2008).

VPA may also have an effect on pubertal development. Serum androstenedione levels are high during all pubertal stages in patients that use VPA (Mikkonen et al., 2004).

The mechanisms of the drug's effects on sperm have not yet been determined. It was observed that the drug affects sperm motility directly in *in vitro* studies (Isojarvi, 2008). Possible explanations for this are a direct effect on spermatogenesis and an indirect effect on hormonal changes.

2. Reproductive Dysfunction in Animals Given VPA

Human studies are affected by numerous factors; dysfunction may result from the illness itself, from the side effects of the medication, or from psychosocial problems (decrease in self-confidence, social withdrawal, life events). Animal studies may provide a way to explore the illness and the effects of drugs independently of each other.

It was shown that in male rats with amygdala-based epilepsy, serum testosterone, E2, and prolactin levels were higher than in rats without generated seizures, and that their epididymes and pituitary glands weighed more, while their prostatic glands weighed less (Edwards et al., 1999).

Animal studies have shown that antiepileptics decrease semen quality. It was reported that drug administration for 4 weeks was sufficient for exploring the effects on reproduction. In animals VPA studies the results are generally negative..

After chronic VPA administration, decreases in spermatogenesis and testicular atrophy were observed in rats and dogs; however, these results were attributed to higher doses of the drug being administered to rats and dogs than to humans (Walker et al., 1990). Again, it was shown that chronic use of VPA in rats delayed pubertal maturity by blocking testicular development and spermatogenesis (Synder et al., 1995). When rats that received low-dose VPA, those that received high-dose VPA, and rats that did not receive VPA were compared, it was observed the high-dose VPA group had a significant decrease in testicular weight and testicular weight/animal weight ratio, as compared to the other 2 groups and that 75% of these rats developed testicular atrophy ranging from mild to severe. The dose with which testicular atrophy developed was reported to be equivalent to the expected human therapeutic dose range or lower (Roste et al. 2001).

In another study, VPA or CBZ was administered to rats for 3 months and the sperm count decreased in both groups; however, fertility decreased only in the VPA group (Cohn et al., 1982).

Studies on the effects of VPA on reproductive hormones and sperm parameters in animals are summarized in Table 2.

CONCLUSION

VPA, which is commonly used for psychiatric treatment, has a negative impact on reproductive hormones and sperm parameters, both in animals and humans diagnosed with epilepsy. However as the studies were conducted by the same investigators, therefore the results may have a bias. Additionally, it has been reported that epilepsy itself may cause reproductive dysfunction; therefore, reproductive dysfunction observed in patients should not be entirely attributed to VPA. As such, exploration of VPA's effects on male reproductive functions in non-epileptic samples may resolve the conflict concerning whether these dysfunctions occur due to VPA or to epilepsy itself.

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