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Letter

ABNORMAL SEMEN PARAMETERS IN BIPOLAR MEN TREATED WITH VALPROATE

Dear Editor,

Although valproate (VPA) is not indicated for the treatment of bipolar disorder, it is an antiepileptic drug commonly used to treat this disease and is mentioned in treatment guidelines prepared in view of present data. It was reported that VPA causes sperm parameter changes in male patients with epilepsy (Isojärvi et al. 2004; Røste et al. 2003); however, it was also reported that these changes are due to epilepsy independent of VPA use (Herzog 2008).

Based upon these data, we thought that evaluating the effect of VPA treatment on sperm parameters in a different patient population, for example in male patients diagnosed with bipolar disorder, may whelp to determine if such changes are directly related to the drug. The study sample was formed using the same sample used in our hormone study, *Valproate-Associated Reproductive Hormone Abnormalities: Do Bipolar Men Have the Same Risk as Epileptic Men?*, that was performed with the same aim (Aldemir et al. 2012).

Semen samples were collected from patients that participated in the aforementioned study and volunteered to provide semen samples following 3-5 d of sexual abstinence. Samples were obtained via masturbation in the Ege University, School of Medicine Andrology Laboratory, in a room containing a bathroom with toilet and sink, and a comfortable chair. The samples were examined in the andrology laboratory after liquefaction of the semen and were evaluated according to World Health Organization criteria (2010), in consideration of volume, count, motility, and morphology. Normal values were as follows: sperm count: $>15´10^6$ cc^{-1}; motility: >32%; morphology >4% (according to Kruger criteria).

The study included 6 bipolar patients that used lithium only (BD-lithium subgroup), 5 that used VPA or lithium plus VPA (BD-VPA subgroup), and 1 epileptic patient that used VPA

A decrease in the sperm count (oligozoospermia) was not observed in the BD-lithium subgroup, but was observed in 2 patients in the BD-VPA subgroup. A decrease in sperm motility (asthenozoospermia) was not observed in the BD-lithium subgroup, but was observed in 2 patients in the BD-VPA subgroup. Impaired sperm morphology (teratozoospermia) was noted in 3 patients in the BD-lithium subgroup and in 5 patients in the BD-VPA subgroup. There wasn't a significant difference in sperm abnormality between the BD-lithium subgroup and BD-VPA subgroup (χ^2= 2.396, P = 0.122). Asthenozoospermia was observed in the 1 epilepsy patient that provided a semen sample. There wasn't a significant difference in sperm parameters between the BD-lithium subgroup and BD-VPA subgroup. As the epilepsy group included only 1 patient, it was not included in this comparison and we did not have sufficient data to determine the effect of VPA on sperm parameters in this group. Determination of the effect of VPA on sperm parameters was made using sperm data from the bipolar disorder patients; however, the findings were compared with those reported for epilepsy patients, as the literature does not include any study on the effects of VPA on sperm parameters in bipolar patients.

Although the difference was not significant, oligozoospermia and asthenozoospermia were not observed in the BD-lithium subgroup, but was observed in 2 and 5 patients, respectively, in the BD-VPA subgroup. In addition, teratozoospermia was noted in 3 of the 6 patients in the BD-lithium subgroup and in all 5 patients in the BD-VPA subgroup, indicating that VPA treatment negatively affected sperm parameters. This finding is consistent with that reported by Isojarvi et al. (2004), who compared epilepsy patients using antiepileptic drugs and healthy controls. They reported that the probability of any type of sperm abnormality was higher in the VPA group. In another study 2 male epilepsy patients that had used VPA for >10 years and received infertility treatment for >5 years were observed to have extremely low sperm counts. VPA treatment was discontinued and the patients were given a different antiepileptic drug; at 3 and 6 months post VPA discontinuation both patients' sperm parameters improved, and at 15 months both patients' spouses were pregnant (Hayashi et al. 2005). In another case it was reported that VPA not only decreased the sperm count, but also had an adverse impact on sperm motility and morphology, and that all sperm parameters improved following the withdrawal of VPA (Yerby and McCoy 1999).

Animal studies also support such findings. It was reported that chronic VPA use in rats suppresses testicular development and spermatogenesis (Synder et al. 1995), and that short-term use (3 months) leads to impaired fertility due to a decrease in the sperm count (Cohn et al. 1982). As such, we think that although the present findings did not reach the level of statistical significance due to the limited number of cases, they may be considered indicative of the adverse effect of VPA on sperm parameters, independent of the presence of epilepsy, and may be worthy of presentation.

With kind regards.

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