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Evaluate the effects of antiepileptic drugs on reproductive endocrine system in newly diagnosed female epileptic patients receiving either Valproate or Lamotrigine monotherapy: A prospective study

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ABSTRACT

Objective: To investigate the development of reproductive endocrine changes in Indian women with epilepsy initiating on either Valproate (VPA) or Lamotrigine (LTG) monotherapy.

Methods: Reproductive hormonal profiles, hirsutism, ovarian morphology by ultrasonography and menstrual cycle data in newly diagnosed women with epilepsy taking VPA (n = 34) or LTG (n = 32) monotherapy were compared. None of the women were receiving hormonal contraception. Patients gave details of seizure type and frequency, medical and drug history. Body weight and fasting insulin, glucose, testosterone, dihyroepiandrosterone sulfate (DHEAS), androstenedione, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH) were measured. Body mass index, free androgen index and homeostasis model assessment of insulin resistance (HOMA-IR) were calculated. Longitudinal evaluations were done at 6th month and at 12th month. After 12th month some VPA-treated women were replaced with LTG and further followed-up twice in next six months.

Results: The mean testosterone level was significant increased in VPA-treated women at 6th month ($p = 0.03$), then at 12th month ($p = 0.01$). More women in the valproate group than the lamotrigine group developed hirsutism ($p = 0.06$), menstrual disturbances ($p = 0.02$) and PCOS ($p = 0.001$). Before valproate therapy, 32% of the patients were obese, this percentage rose to 47% after treatment ($p = 0.03$). A significant positive correlation was existed between obesity (BMI > 25) and the development of menstrual disturbances ($p = 0.006$), serum testosterone levels ($p = 0.02$) and PCOS ($p = 0.03$). Insulin resistance (HOMA-IR > 2.5) was significant correlated with menstrual disturbances ($p = 0.03$) and serum testosterone levels ($p = 0.02$). Substitution of VPA with LTG results in significant reduction in mean testosterone levels ($p = 0.005$) and means body weight at 6th month ($p = 0.01$).

Conclusion: Long-term valproate therapy in Indian women with epilepsy was associated with development of menstrual disturbances, alterations in reproductive hormonal function and increased the risk to developed PCOS.

1. Introduction

Epilepsy is the most common, chronic serious neurological disorder and affects 5–10 out of every 1000 people in India. It is estimated that there are more than 10 million peoples with epilepsy in India. The prevalence among Indian males (5.1 per 1000) was much higher than Indian females (2.2 per 1000) (Santhosh et al., 2014). Therapeutic drugs successfully control seizures in about 70% of patients. However, medication is long-term requirement and side effects are common; these include effects on the reproductive endocrine system of females (Harden, 2005; Isojarvi, 2008). One of the most widely prescribed antiepileptic drugs is valproic acid (VPA), with anti-convulsant and mood stabilizing properties (Reynolds and Sisk, 2007). VPA is also used in the treatment of bipolar disorders, migraines and neuropathic pain (Sidhu and Sadhotra, 2016). Over the past 20 years it has emerged that there is an increased incidence of polycystic ovarian syndrome (PCOS)-like symptoms in epileptic women taking VPA suggesting that the drug can perturb ovarian function and androgen synthesis, possible as a result of multiple effects on the hypothalamic-pituitary-ovarian axis (Bilo and Meo, 2008; Verrotti et al., 2011). PCOS is a very common reproductive endocrine disorder affecting 6–8% of women of reproductive age (Franks et al., 2006); but high prevalence of 12–26% is reported in

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women with epilepsy (Rasgon, 2004). This disorder is characterized by polycystic ovarian morphology, hyperandrogenism, galactorrhea, hirsutism, menstrual abnormalities and infertility (Morrell et al., 2008); in addition it is also associated with an increased risk for type 2 diabetes, obesity, insulin resistance, and dyslipidemia, features of the so-called metabolic syndrome (Solomon, 1999; Pasquali et al., 2006). The pathogenic mechanisms underlying the association between VPA and these endocrine disorders have not been fully elucidated. Some researchers claim that epilepsy itself play a pathogenic role (Verrotti et al., 2009; Atif et al., 2016); whereas others propose that the endocrine disorders may be at least partly attributed to the use of antiepileptic drugs (AEDs), particularly sodium valproate (Bilo and Meo, 2008; Atif et al., 2016). The association between VPA treatment and PCOS-like symptoms was first reported by Isojarvi et al., 1993 who found that almost 50% of women treated for epilepsy with VPA had menstrual irregularities compared with 19% of women taking carbamazepine. Same author group have published a number of articles examining the effects of AEDs on the reproductive endocrine system in women with epilepsy. These articles have had tremendous impact on the prescribing of AEDs in women with both epilepsy and bipolar disorders. However, it is important to note their limitations. Most of these studies took place in a Finnish or Scandinavian population, and these findings may not extrapolate to multicultural populations or those with varying racial background and lifestyles. Secondly, these were retrospective studies and their findings should not be confused with those from prospective randomized controlled trials.

VPA, a widely used AED, has broad-spectrum activity against both generalized and partial epilepsies. It is now considered as gold standard AED for the treatment of idiopathic generalized epilepsies or those for whom classification is not possible. This was confirmed in the SANAD (Standard Against New Anti-epileptic Drug) trial which compared the effectiveness of valproate, lamotrigine (LTG) and topiramate in those with generalized or unclassified epilepsy (Marson et al., 2007). VPA does not have enzyme-inducing properties and therefore it does not reduce the effectiveness of oral contraceptives. VPA is discouraged as first-line therapy in females of reproductive age owing to the risk of teratogenicity (Harden et al., 2009). This issue is important for it use in young women, because the possible risk of increased obesity and PCOS-like symptoms for VPA could overweigh its benefit and justify the selection of an alternative AED.

The aim of this present study was to investigate the changes in reproductive endocrine parameters in Indian women with epilepsy receiving either VPA or LTG monotherapy. Secondary outcome was to explore the relationship of obesity, insulin resistance with PCOS-like symptoms among VPA-treated patients.

2. Materials and methods

2.1. Subjects (Sidhu et al., 2017), (same study groups)

The present study was conducted at the department of Neurology, M.S. Ramaiah Memorial hospital, Bangalore, India, with the approval of local Ethics committee. Informed consent was obtained from all the subjects. All subjects gave consent to use non-hormonal contraception throughout the study and for at least 3 weeks after the last dose of study drug. The type of epilepsy was classified according to the recommendations of the International League Against Epilepsy (ILAE) (Revised classification of seizures, 2017).

2.1.1. Subjects in the patients groups

The study was conducted in 66 newly diagnosed or untreated female epileptic patients. In untreated epileptic patients up to 2 weeks of treatment with any AED other than VPA or LTG is allowed prior to enrollment in the study. During the first two weeks, if a patient entered the study on an antiepileptic drug other than VPA or LTG, it should be tapered off within two weeks after the initiation of treatment with study drug. After this time period, only benzodiazepines may be used acutely (up to 24 h) for management of breakthrough seizures. Patients between the ages of 12 and 40 years, at least 2years post menarche were recruited into the study from October 2004 to May 2006. Brain magnetic resonance imaging (MRI) could not done on all the patients. Few patients had done it before screening and while other underwent MRI during screening. Thyroid function tests were interpreted as normal.

All patients reported a history of regular menstrual cycles (defined as cycle length ≥ 25 days and ≤ 35 days with a variation in cycle length of ≤4 days from one cycle to the next) with at least two-regular menstrual cycles immediately before the screening visit. Urine pregnancy test was done on all patients at the time of screening. Any positive result was not eligible for study. We strictly instructed all the patients to avoid pregnancy throughout the duration of study. Patients should notify the physician if they become pregnant during the study. Those who were followed up for fewer than 3 months or who discontinued drug treatment within 3 months of initiation, were excluded. Other exclusion criteria were breast feeding, total testosterone > 150 ng/dl, abnormal thyroid function tests, body mass index (BMI) > 30 kg/m^2, any history suggestive of clinically significant impairment of renal/hepatic dysfunction, any CNS disease (apart from epilepsy), hysterectomy, oophorectomy. Any patient had problems with excessive body hair, acne or lactation was screened thoroughly. Other screening assessments included seizure frequency, physical and neurological examinations and medical history.

2.2. Study protocol

It was an open label randomized comparative prospective study. Patients were randomly allotted into two groups, with 34 patients in VPA group and 32 patients in LTG group. All patients in both groups should received respective drugs as monotherapy for at least one year. All patients were followed for one year from time of inclusion.

2.2.1. Dosage and dosing

All patients in LTG group were initiated with LTG 25 mg once a day for 1st two weeks then 50 mg once a day for another 2 weeks followed by maintenance dose 200 mg twice a day. On the basis of clinical response the dose of LTG was titrated according to the dosing schedule to a maximum of 550 mg/day (50 mg/week). If a decision was made to discontinue LTG therapy, a step-wise reduction of dose over at least 3 weeks was recommended. For all patients randomized to VPA group were received VPA in a dose of 750 mg/day (250 mg three times a day) for the first week and escalating to 1000 mg/day in next week. Target maintenance dose for VPA was 1000–2000 mg/day.

2.2.2. Initial screening examinations

The patients with epilepsy who met the inclusion criteria mentioned above were clinically and physically examined by two neurologists, and interviewed by the first author. Anthropometric data such as weight, height were measured. All the patients were evaluated at inclusion, at the end of 6th week, at the end of 3rd month, sixth month, ninth month and 12th month. During each visit all the patients underwent complete neurological examination, review of medical history, adverse events or reactions, compliance, concomitant medications were checked. Diaries were reviewed together with menstrual cycle information and total number of seizures, by type, since the last visit.

2.2.3. Collection of anthropometric and clinical data

Age, BMI, complete menstrual history, seizure type, duration of illness, age at onset, dose of drug utilized, response to antiepileptic therapy, and family history were recorded clearly in a designed form. The height was measured to the nearest 0.1 cm with the wall- mounted statiometer. The weight was measured to the nearest 0.1 kg on electronic scale. Body mass index [BMI was calculated by using quetelet's index [weight (kg)/height (m^2)]. Patients with BMI 18.0-22.9 kg/m^2