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Valproate Level Variation with Menstrual Cycle Phase in Bipolar Disorder

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Abstract

Objectives: The purpose of this study was to investigate the changes in serum valproate (VPA) levels and their relationship to progesterone levels during the menstrual cycles of fertile women.

Materials and methods: Female patients compliant with VPA (n=14) were included in this study. Serum VPA and progesterone levels were measured during two periods, in which progesterone levels may be the lowest (early follicular phase) and the highest (mid luteal phase).

Results: Serum VPA levels were significantly different between the two periods. Serum progesterone levels increased in 64.3% of the sample during menstruation, revealed a noticeable but not significant mean increased. There was no correlation between serum valproate and progesterone levels (r=0.209, p>0.05) in the menstrual phase.

Conclusion: This study shows that serum VPA levels varied greatly during the menstrual cycles. The results of this study also implying that VPA levels may be relationship to sex steroid levels in menstrual cycle. Particularly in cyclic premenstrual exacerbation of affective symptoms, this interaction should be considered in the evaluation of treatment may be beneficial.

Keywords: Bipolar disorder; Valproate; Menstrual cycle

Introduction

An increasing number of studies has reported potential gender differences in clinical manifestations, disease course, reactions to medications, and neurobiological background of many psychotic disorders, especially in a mood disorders [1,2]. Female with bipolar disorder (BD) frequently involve more mixed and depressive episodes throughout the course of illness, more frequent seasonal episodes, and increased rates of refractory to treatment than male [2-4]. In addition, women have been relation with higher risk of rapid cycling, cycle acceleration, and the increasing severity of onset than men, and gender differences in the ratio of rapid cycling pattern were usually reported in patients with BD-II [5,6]. Contrast with male, women also involve that people with bipolar depression have more frequent changes in body weight and appetite, oversleeping, and difficulty maintaining sleep at night [7]. Affective disorders and emotional fluctuation often occur or worsen in life experiences associated to hormone level changes: menarche, hormonal cycle, pregnancy, puerperium, and perimenopausal periods [8-10]. The symptom deteriorations that happen in some stages of the menstrual cycle may be attributed to the instability of hormone levels; gonadal steroids can modify the main activity of norepinephrine, 5-Hydroxytryptamine, and γ -aminobutyric acid.

In general, VPA is the most frequently used and is prescribed mostly to patients with weaker predictors of reaction to $Li2^{+}$, such as mixed episodes, psychotic features, and comorbidity with anxiety and substance abuse [11,12]. while, regarding VPA for women with BD of fertile age needs supply of information concerning the risks relation with exposure to VPA during pregnancy and the requirements for appropriate contraception [13]. It is recognized that the achievement of a stable state plasma level in an appropriate range is important to get a maximal pharmacological effect. In this study, we dedicated to investigate the potential variability in VPA levels in the menstrual cycle and to identify the correlation between serum VPA and progesterone levels.

Methodology

We initiated this research at Jingzhou mental health hospital, established in 1957. All participants met the following inclusion criteria: (i) young female, age of 16-35 years, who had menstrual cycles, (ii) compliant with VPA (n=14), the dose had not changed in the past fifteen days and emotional stability, VPA and other cotreatments had not change between two blood collection periods (iii) met the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) diagnosis of bipolar disorder (depression or mania episode) by two psychiatrists, no organic brain syndrome (iv) no patient had a record of use of psychoactive substances, including alcohol. The clinical and demographic data were obtained from the medical charts. Serum VPA and progesterone levels were measured between 7:00-8:00 am during two periods in the menstrual cycle (the follicular phase and the luteal phase). when the sex steroid levels might be the highest (days 20 to 22, midluteal phase) and the lowest (days

one to three, menstrual or early follicular phase. VPA and reproductive hormone levels were analyses by chemiluminescence immunoassay. The sample size was calculated using PASS software (version 15.0), both the means of paired difference and the standard deviation were set according to the results of our Pre-test. The power was set at 0.9, and the significance level was set at 0.05. This gives a sample estimate that requires 5 patients. However, selected sample size of 14 patients was selected based on the study time and cost.

All statistical analyses were handled using IBM SPSS Statistics version 21. The normal distribution of continuous data was examined by the Kolmogorov-Smirnov one-sample test. Correlations between VPA and progesterone levels were evaluated by Spearman correlation analysis. Other statistical tests are indicated in the tables. For all analyses, $p<0.05$ was considered significant. The study was authorized by the Ethics Committee of the Jingzhou mental health hospital.

Results

The patient demographics, clinical characteristics were provided in Table 1. The descriptive statistical were shown using the mean and standard deviation for quantitative variables. Serum valproate levels were significantly different between the two periods. Although serum progesterone levels increased in 64.3% of the sample, not different during the two periods (Table 2). No significantly correlation was found between VPA and progesterone levels ($r=0.21$, $p=0.29$).

Demographic and clinical features	n (total 14)
Age, in years	25.14 ± 5.22
Age at psychosis onset (years)	16.21 ± 3.21
BMI	32.5± 8.03
Education (years)	9.29 ± 2.16
Psychosis duration (years)	8.93 ± 5.24
Treatment dosage (gram)	0.67 ± 0.27
Menarche age (years)	12.79 ± 0.43

Table 1: Demographic and clinical characteristics of the patients.

Parameter	First periods (luteal phase)	Second periods (follicular phase)	p value
Valproate level (μg/mL)	41.79 ± 31.47	104.59 ± 48.28	0
Progesterone (ng/mL)	0.23 ± 0.10	1.66 ± 3.53	0.16

Table 2: Comparison of values during the two periods of the menstrual cycle.

Discussion

As far as we know, just two studies investigated whether the physiological fluctuations within reproductive hormone levels over all stages of the menstruation cycle or the usage of Combination Oral Contraceptives (COC) may alter VPA serum levels [14,15]. Female with periodic menstrual cycle and without COC indicated a decrease (8.3%) of VPA concentration in the mid-luteal stage. Menstrual stage alteration could change transcapillary fluid dynamics, with subsequent fluid redistribution between the intravascular and extravascular spaces [16]. The growth in fluid preservation and the peak of hepatic metabolism in mid-luteal cycle; it might induce lower concentrations of medication in the luteal phase.

Several studies have emphasized the significance of these variations on medication treatments [17]. As female have a decreased gastrointestinal secretion and a delayed stomach emptying than male, they subsequently have reduced absorption ratios that might affect the serum level of medications. It is probably attributed to higher progesterone level over the luteal stage [18]. Women usually have a low rate of lean and fat mass [19], so fat-soluble drugs could have a higher volume of distribution in female particularly in long-term and multi-drug management.

On the other hand, the absence of clinical researchers assessing menstrual variations of VPA concentrations in female with BD could be understood with the truth that most studies highlighted on VPA-caused side effects on menstruation cycle regularity, or focused on the relation between VPA and polycystic ovary syndrome [20]. The use of VPA in fertile women should pay attention to warning the probability of teratogenic effects related to VPA exposure during pregnancy and the essential for appropriate contraception. Thus, detailed description of the relationships between mood stabilizer and reproductive hormones is significant for proper management and reproductive health in childbirth women with bipolar disorder. Finally, the aim of this study was to explore the changes in serum valproate levels and their relationship to progesterone levels between the two special menstrual cycles of fertile women. The subjects were diagnosed bipolar disorder (depression or mania episode), the Hamilton Depression Scale (HAMD) or Bech-Rafaelsen mania rating scale (BRMS) was used to assess symptoms. Many studies are made to the symptom worsening according to the menstrual cycle stage and the levels of VPA. It is indeed a very interesting hypothesis of study, but since there is no symptom analysis on this study this conclusion cannot be drawn. A comparative analysis of the symptoms between the two periods, may lead to insufficient power of test due to the small sample size. Further clinical studies might be helpful.

Conclusion

It is indeed a very interesting hypothesis of study, but since there is no symptom analysis on this study this conclusion cannot be drawn. A comparative analysis of the symptoms between the two periods, may lead to insufficient power of test due to the small sample size. Further clinical studies might be helpful.

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Disclosure

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