Epilepsy & Behavior 85 (2018) 120–128

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Effects of valproate on reproductive endocrine function in male patients with epilepsy: A systematic review and meta-analysis

Shanshan Zhao [a,1], Xiaoyin Wang [a,1], Yu Wang [a], Junjie Xu [b], Gang Zhu [c], Chuansheng Zhao [a], Weiyu Teng [a,*]

[a] Department of Neurology, The First Hospital of China Medical University, Shenyang, China
[b] Laboratory of AIDS Immunology of Health Ministry, The First Hospital of China Medical University, Shenyang, China
[c] Department of Psychiatry, The First Hospital of China Medical University, Shenyang, China

ARTICLE INFO

Article history:
Received 17 March 2018
Revised 8 April 2018
Accepted 29 April 2018
Available online xxxx

Keywords:
Valproate
Reproductive endocrine function
Patients with epilepsy
Meta-analysis

ABSTRACT

Background: Valproate (VPA) is a broad spectrum antiepileptic drug (AED) that is generally used as a first line agent for most idiopathic and symptomatic generalized epilepsies. Many studies have indicated that AEDs cause reproductive endocrine disorders in males, but the exact etiology underpinning these dysfunctions is not clear. This meta-analysis and systematic review was intended to evaluate the effect of VPA on reproductive endocrine function in male patients with epilepsy.

Methods: A literature search was performed using electronic databases up to December 2017 for eligible studies. The differences in the levels of the reproductive factors, luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone binding globulin (SHBG), testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione (ADION) in the male patients with epilepsy treated with VPA (treatment group) were compared with the those of the healthy controls (control group) by the use of the Standardized mean difference (SMD) with 95% confidence intervals (CIs).

Results: Six publications with a total of 316 subjects were identified. The result revealed that the levels of FSH (SMD = −1.33, 95% CI: −2.60 to −0.07, P = 0.039) and testosterone (SMD = −0.45, 95% CI: −0.87 to −0.03, P = 0.038) of the treatment group were decreased significantly compared with the healthy controls. There was an increase in the levels of SHBG (SMD = 0.41, 95% CI: −0.21 to 1.03, P = 0.197), DHEAS (SMD = 0.20, 95% CI: −0.06 to 0.45, P = 0.126) and ADION (SMD = 0.73, 95% CI: −0.10 to 1.57, P = 0.086), and a decrease in that of LH(SMD = −0.71, 95% CI: -1.49 to 0.07, P = 0.075) in the male patients with epilepsy treated with VPA, but the differences did not reach statistical significance (P > 0.05).

Conclusions: This meta-analysis indicates that VPA may lead to a significant decrease in the levels of FSH and testosterone and alter the concentrations of LH, DHEAS, SHBG, and ADION to some extent, which might contribute to the reproductive endocrine dysfunction in male patients with epilepsy. It is important for clinical neurologists to be cautious when prescribing VPA to reproductive-aged male patients with epilepsy.

1. Introduction

Epilepsy is one of the most common serious chronic central nervous system neurological disorders, yet our understanding of its detailed pathophysiology and treatment rationale is still somewhat incomplete. The first-line treatment for epilepsy is antiepileptic drug (AED) therapy, and nearly 60%–70% of patients with epilepsy will achieve seizure control with medication. Valproate (VPA) is a broad-spectrum antiepileptic drug, which is effective against many types of seizures. It is known to be especially effective in treating primary generalized seizures, tonic–clonic seizures, myoclonic seizures, and absence seizures [1–4]. Valproate exerts some side effects, such as gastrointestinal and liver dysfunction, weight gain, trembling, sedation, and abnormal blood parameters [5]. It is known that women with epilepsy receiving VPA treatment have an increased risk of experiencing anovulatory cycles, menstrual disorders, polycystic ovary syndrome (PCOS), and hyperandrogenism since the drug interferes with both central and peripheral hormones [6–10], whereas there remains an on-going controversy about the effect of VPA on the reproductive endocrine function of male patients with epilepsy. It has been reported that VPA may interfere with many reproductive factors, which might contribute to the sexual and reproductive dysfunction in male patients with epilepsy [2,5,10–14]. There is also evidence that VPA is associated with reduced sperm motility and increased frequency of morphologically abnormal sperm, as well as a small testicular size in epileptic men [2,5]. However,

* Corresponding author.
E-mail address: tengweiyucmu@126.com (W. Teng).
[1] These authors contribute equally to this work.

https://doi.org/10.1016/j.yebeh.2018.04.029
1525-5050/

in the literatures, the effects of VPA on the reproductive factors in male patients with epilepsy seem to be inconsistent due to differences in study design, demographics, drug combinations, and follow-up duration, as well as the limited number of patients that have been evaluated. The association between the changes in the levels of these reproductive factors and the reproductive endocrine dysfunction in male patients with epilepsy is far from clear [15–17]. Thus, we conducted this systematic review and meta-analysis to clarify the effect of VPA treatment on the reproductive endocrine function in male patients with epilepsy.

2. Methods

A systematic review and meta-analysis was conducted according to the guidelines previously published for a meta-analysis of observational studies in epidemiology (MOOSE). Ethics committee approval was not necessary for this study.

2.1. Search strategy

We comprehensively and systematically searched the electronic databases of PubMed, the Cochrane Library, Medline, Web of Science, and Chinese Wanfang Data, CNKI database, Chinese Biomedical Database, and Chinese VIP database up to December 2017 with the methods of quick search and advanced search. The following combinations of variables were used: ('Valproate' or 'valproic acid' or 'antiepileptic drug' or 'anticonvulsant drug') and ('epilepsy' or 'epileptic' or 'seizure') and ('male') and ('reproduction' or 'reproductive endocrine function' or 'reproductive factors' or 'procreation' or 'proliferation' or 'fertility') not ('rat' or 'mice'). The languages were restricted to English and Chinese. In addition, the reference lists of each article obtained were manually screened to identify any additional potentially relevant citations. We also undertook a manual check of conference papers and reports in the university library about the changes of reproductive endocrine function occurring in male patients with epilepsy after administration of VPA, but failed to identify any relevant articles.

2.2. Study selection

Articles were considered eligible if they met the following criteria: (1) It was an observational study. (2) The diagnosis was made by a clinical neurologist. (3) The age of the participants was in the range of 18 to 65 years old. (4) Treatment for male patients with epilepsy was VPA monotherapy. (5) The treatment duration of VPA was at least 3 months. (6) The control groups of each study were healthy people. (7) There was complete data of the levels of reproductive factors in the article. Nonoriginal articles, articles with insufficient data or irrelevant outcome, and review articles were excluded. Two authors independently evaluated the retrieved studies according to the selection criteria and manually reviewed the reference lists of retrieved articles to identify additional relevant studies. Discrepancies were resolved by discussion until consensus was reached.

2.3. Data extraction

Data extracted from eligible studies included the first author, research region, publication year of the articles; average age, total number of the subjects; and the mean value of the level of different reproductive factors [luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone binding globulin (SHBG), testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione (ADION)] to evaluate the effect of VPA monotherapy on male reproductive endocrine function.

2.4. Quality assessment

The quality of each article was evaluated by the 9-star Newcastle-Ottawa Quality Assessment Scale (NOS). The NOS applies a "star system" to judge the quality of article according to three broad perspectives: the selection of the study group, the comparability of the groups, and the ascertainment of the outcome of interest for cohort studies. Those publications awarded scores over 6 stars were regarded as high-quality studies. The quality assessments of the included studies were conducted independently by two investigators in order to ensure the accuracy, authenticity, and credibility of the meta-analysis. If there was any disagreement, the consensus or a third reviewer was asked to reevaluate the original study.

2.5. Statistical methods

The independent *t*-test was used to compare the differences of the age between the treatment group and the control group and the differences of epilepsy type among included studies. The statistical software Stata 12 (Stata Corp., College Station, TX, USA) was used in the statistical analyses. Standardized mean difference (SMD) with the corresponding 95% confidence interval (CI) was used to estimate the differences in the levels of the reproductive factors between the treatment group and the control group. The heterogeneity across the results was quantified by P value for the Q test and the I^2 statistic. A value of $P > 0.05$ and $I^2 < 50\%$ indicated the absence of significant heterogeneity and then the pooled SMD was estimated using the fixed effect model (the Mantel–Haenszel method). Conversely, if the heterogeneity was significant, the random effect model (the DerSimonian and Laird method) was used. The significance of overall SMD was determined by the Z test. Sensitivity analyses were conducted to assess heterogeneity in the eligible studies as well as for estimating the influence of individual datasets on the combined effect and evaluating the stability and credibility of this meta-analysis. Publication bias was examined by Egger's regression test; when $P < 0.05$, this was considered to represent a statistically significant publication bias.

3. Results

A total of 1516 studies were identified by the literature search. After removal of duplicates, 1067 studies related to the reproductive endocrine function of male patients with epilepsy were identified in the literature search. Then, 1040 of these were excluded based on inspection of the title and abstract, leaving 27 possible articles. Finally, 6 studies met our inclusion criteria, and these were included in this meta-analysis (Fig. 1).

3.1. Characteristics of included studies

The 6 studies selected for meta-analysis were all prospective studies and published between 1999 and 2013. A total of 316 subjects were analyzed i.e., 129 male patients with epilepsy and 187 healthy male controls. The baseline characteristics of the 6 eligible articles are shown in Table 1. No significant difference was detected between the age of the patients and their controls ($P > 0.05$). The therapeutic dosages of each patient in the 6 articles were all within the range recognized as effective therapeutic concentrations. The types of epilepsy were either generalized or complex partial seizure, and the *t*-test revealed that there were no significant differences between the epilepsy types in the eligible studies ($P > 0.05$). Two of the included studies had been carried out in Asia [14,18]; the other four studies were performed in Europe. The durations of the VPA treatments lasted from 3 months to more than 2 years. The values are presented as mean ± standard deviation. Any other types of value such as median (range or interquartile range) were converted to this form [19].