Seizure 39 (2016) 28–33

Contents lists available at ScienceDirect

Seizure

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

Levetiracetam vs. brivaracetam for adults with refractory focal seizures: A meta-analysis and indirect comparison

Zhang Lin[1], Li Shaoping[1], Li Hua, Zou Xiaoyi*

Department of Neurology, West China Hospital, Sichuan University, Chengdu, China

ARTICLE INFO

Article history:
Received 29 March 2016
Received in revised form 9 May 2016
Accepted 10 May 2016

Keywords:
Refractory focal seizures
Levetiracetam
Brivaracetam
Meta-analysis

ABSTRACT

Purpose: The study aimed to compare the efficacy and tolerability of levetiracetam (LEV) and brivaracetam (BRV) in adults with refractory focal seizures.
Method: We systematically queried Medline, Embase, and the Cochrane Library. We looked for additional studies in the references of all identified publications and ClinicalTrials.gov. The cutoff day was November 6, 2015. Randomized, double-blind, placebo-controlled trials were included. The indirect comparison for 50% responder rate, seizure-free rate, and adverse effects were conducted.
Results: Thirteen trials enrolling 1765 patients in the LEV group and 1919 patients in the BRV group were included. No statistically significant differences were found in efficacy between LEV and BRV at various dose levels. However, most risk ratios (RRs) at three dose levels and the overall RR were >1 for 50% response proportions. The majority of statistically significant differences for adverse events and withdrawal of LEV and BRV were found at high- and middle-dose levels. The indirect comparison of adverse effects (AEs) showed statistically statistical differences in dizziness.
Conclusion: Our results suggested that LEV might have a slightly higher efficacy with a lower probability of dizziness compared with BRV for patients with refractory focal seizures.

1. Introduction

Levetiracetam (LEV) shows good efficacy and tolerability when it is used to treat refractory focal seizures (RFS) [1]. Its antiepileptic effect most likely occurs as it binds to synaptic vesicle protein 2a (SV2A), which is located in presynaptic membranes and regulates the calcium-dependent exocytosis of neurotransmitters into the synaptic gap [2]. Brivaracetam (BRV) is a highly selective and reversible SV2A ligand with a 15- to 30-fold higher affinity than levetiracetam has in the rat or human brain [3]. Studies have shown that BRV might also be efficacious and well tolerated as adjunctive treatment in patients with RFS [4–10]. However, it is still unclear which one has a better efficacy or tolerability for treating patients with RFS. The efficacy and tolerability of LEV and BRV have been investigated in many randomized, double-blind, placebo-controlled trials for patients with RFS. These data provide an opportunity to compare the efficacy and tolerability of LEV and BRV in patients with RFS. The aim of this study is to compare LEV with BRV indirectly in the treatment of RFS patients.

2. Methods

We followed the recommendations of the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement [11]. The study protocol was based on the Cochrane Review Methods (www.cochrane-handbook.org).

2.1. Search strategy and selection criteria

Three electronic databases (Medline, Embase, and the Cochrane Library) were searched. We looked for additional studies in the references of all identified publications and ClinicalTrials.gov. The cutoff day was November 6, 2015. The detailed search strategy is provided in Appendix. We selected randomized, double-blind, and placebo-controlled trials, which reported the detailed adverse effects (AEs) of LEV and BRV in patients with RFS. In addition, only articles published in English with the full text available were included.

* Corresponding author at: No. 37 Guoxuexiang, Chengdu 610041, China. Tel.: +86 18980602115; fax: +86 028 85553329.
E-mail address: xiaoyizou@163.com (X. Zou).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.seizure.2016.05.004
1059-1311/

2.2. Assessment of heterogeneity and quality and data extraction

The bias and quality of publications with randomized controlled trials (RCTs) were assessed using the tool for assessing risk of bias in the Cochrane handbook 5.1.0. According to the levels of unclear risk, low risk, and high risk, the publications were considered as good quality if the result with low risk was over 50%. Two authors searched and screened the titles, abstracts, and full-text articles independently. The same two reviewers independently extracted relevant information from each eligible study using the same extraction form. For each of the included studies, the first author, study design, inclusion criteria of patients, dose of LEV or BRV, number of patients (intent-to-treat, ITT), percentage of patients using LEV, percentage of males, age, titration, treatment duration, duration of epilepsy, baseline seizure frequency (BSF), 50% responders rate, seizure-free rate, number of any AEs, and number of AEs withdrawal were recorded if they were presented. If there were divergences, they were resolved through discussion among all authors. We planned that the missing data, if there were, should be calculated according to the statistics method published in the Cochrane handbook 5.1.0; however, this was not necessary in the study. We assessed clinical heterogeneity by comparing the distribution of important patient factors between studies (age, epilepsy type, duration of epilepsy, and BSF) and trial factors (study design and type of control group). We assessed statistical heterogeneity by using the I^2 statistic. If the I^2 value were 75% or more, we made an a priori decision not to carry out meta-analysis. If $I^2 > 50\%$, the heterogeneity was unacceptable and the data were analyzed with the random-effect model. If $I^2 < 50\%$, the heterogeneity was acceptable and the data were analyzed with the fixed-effect model.

2.3. Statistical analysis

All statistical analyses were performed using Review Manager 5.3 (Cochrane Collaboration) and indirect treatment comparison (ITC) software (www.cadth.ca). The Mantel–Haenszel test, RR, and 95% confidence interval (CI) were used to compare discontinuous variables. We analyzed the data concerning the intention-to-treat populations. Outcome measures were 50% responder rate (the percentage of patients with a ≥50% reduction in focal-onset seizure frequency from baseline), seizure-free rate (the percentage of patients completing the treatment period without experiencing seizures of any type), AEs, and adverse withdrawal effects. Because of the higher affinity of BRV to SV2A ligand and the dose of LEV and BRV, we performed the comparison in high- (3000 mg LEV vs. 200 and 150 mg BRV), middle- (2000 mg LEV vs. 100 mg BRV), and low- (1000 and 500 mg LEV vs. 50, 25, 20, and 5 mg BRV) level doses, which represent about 15–30-fold dose difference. We summed and integrated all frequencies of LEV/BRV-treated and placebo-treated 50% responder rate, seizure-free rate, AEs, and adverse withdrawal effects. Using these data, we first compared the 50% responder rates, seizure-free rates, AEs, and adverse withdrawal effects of LEV/BRV against placebo in patients with RFS. Then, because no studies compared LEV with BRV, we were unable to use weighted methods to find RRs. Instead, we performed an ITC for LEV against BRV in patients with RFS using ITC software. A common reference-based indirect comparison meta-analysis is a method of synthesizing data from different interventions. For example, if we try to compare A with B indirectly, direct evidence is provided by studies that compare A with C and B with C, respectively. However, indirect evidence is provided when studies that compare A with C and B with C are analyzed jointly. The Bucher approach was applied for indirect comparisons [12]. The indirect comparison of BRV and LEV was adjusted by the results of their direct comparisons with placebo. All results were presented as statistically significant when $P < 0.05$.

3. Results

We identified 13 trials that met our criteria, including 8 studies [1,13–19] in LEV and 5 trials [4–8] in BRV comparing with placebo. A flow diagram of the identification is shown in Fig. 1. The features of the included studies are presented in Tables 1 and 2. In total, 8 studies in LEV and 5 studies in BRV included 1765 patients (Table 1) and 1919 patients, respectively (Table 2). Tables 1 and 2 also show items of clinical heterogeneity assessment, including age, epilepsy type, study design, type of control group, duration of epilepsy, and BSF. For each study, the mean values reported for the entire study group were extracted except for the BSF, which was reported by median values in most studies. The baseline characteristics were well balanced in either arms of each RCT included. In addition, we found that some I^2 values were 50% or more but not more than 75% for the statistical heterogeneity of efficacy, AEs, and withdrawal. All of the enrolled RCTs were of high quality because the result with low risk was over 50% (Table 4).

3.1. Efficacy

The RRs of efficacy in LEV-treated vs. placebo patients are depicted in Table 4. Statistically significant differences in 50% responder rate and seizure-free rate were found in all dose levels except 500 mg/d.

The RRs of efficacy in BRV-treated vs. placebo patients are depicted in Table 3. Statistically significant differences in 50% responder rate and seizure-free rate were found in all dose levels except 5 mg/d.

The aggregated data of efficacy including 50% responder rate and seizure-free rate are listed in Table 5. The indirect comparison between LEV-treated vs. BRV-treated RFS patients shows that there were no statistical differences at all dose levels. However, most RRs at three dose levels were >1 for 50% response proportions (smallest P value 0.08).

3.2. Adverse events

The RRs of AEs in LEV-treated vs. placebo patients are depicted in Table 4. Adverse withdrawal events of LEV at the middle-dose level (2000 mg) and somnolence in the low- and middle-dose levels (1000–2000 mg) exhibited statistically significant differences.

The RRs of AEs in BRV-treated vs. placebo patients are depicted in Table 3. Adverse withdrawal events of BRV at the middle-dose level (100 mg), at least one treatment-emergent adverse event at the middle-dose level (100 mg), dizziness at the high-dose level (150–200 mg), somnolence at middle- and high-dose levels (100–200 mg), and asthenia a low- and middle-dose levels (20–100 mg) exhibited statistically significant differences.

The indirect comparison between LEV-treated and BRV-treated RFS patients showed that only two AEs, including headache (RR 0.41, 95%CI 0.12–1.37, $P = 0.02$) and dizziness (RR 0.38, 95%CI 0.18–0.83, $P = 0.03$), exhibited statistically significant differences at the high-dose level, which is possibly because BRV had a higher incidence of headache and dizziness (Table 5). We also found that the overall RRs of headache was 0.67 (95%CI 0.40, 1.12; $P = 0.04$). Nevertheless, the RRs of headache included the null value of 1, which might indicate no statistically significant difference regarding headache. There were no statistically significant differences in other AEs at the middle- and low-dose levels.