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The adverse event profile of brivaracetam: A meta-analysis of randomized controlled trials

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ABSTRACT

Purpose: To comprehensively evaluate the adverse events (AEs) significantly associated with brivaracetam (BRV) treatment in a large selection of randomized control trials.
Methods: We conducted an online database search using Pubmed, Embase, Cochrane Online Library, and Clinicaltrial.gov for all available randomized control trials (RCTs) that investigated the therapeutic effects of brivaracetam. Serious AEs (SAEs), withdrawal, and treatment-emergent adverse effects were then assessed for their association with brivaracetam. Finally, a meta-analysis was performed using Review Manager 5.3 software.
Results: Eight RCTs with a total of 2505 patients were included in our study, 1178 of which were randomized with respect to brivaracetam (BRV). Serious AEs, overall withdrawal, AE-related withdrawal and psychiatric adverse events (PAEs) were not significantly associated with BRV treatment. BRV was also not significantly associated with a heightened risk of AE-related withdrawal and PAEs with increasing doses. Of the 17 AEs included in our meta-analysis, three AEs (dizziness, fatigue, and back pain) were found to be significantly associated with BRV treatment. But we did not find that the risk of them was obviously increasing with the increasing doses.
Conclusion: This meta-analysis showed that BRV treatment was reasonably tolerated by patients and rarely caused serious AEs. Further clinical studies will be needed to more concretely determine the safety and tolerability profile of BRV.

1. Introduction

Epilepsy is typically characterized by recurrent and unprovoked seizures [1]. According to the WHO, approximately 50 million people throughout the world have epilepsy [2]. Despite the recent introduction of some new antiepileptic drugs (AEDs), many patients remain inadequately treated. This insufficient treatment may be due to lack of access to appropriate treatment, noncompliance, adverse effects, lack of efficacy of treatment and so on. To this end, up to 30% patients ultimately develop refractory epilepsy [3]. Therefore, there is a great therapeutic need to explore new AEDs that have both improved efficacy and a better tolerability profile.

Brivaracetam {(2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl] butanamide} is a novel AED that is currently being investigated for the treatment of epilepsy. Two Phase IIb studies (NCT00175929 and NCT00175825) and four Phase III studies (NCT00490035, NCT00504881, NCT00464269 and NCT0216358) have shown that BRV may be efficacious and well-tolerated as an adjunctive treatment in patients with refractory epilepsy. BRV displays an approximately 10-fold higher affinity than levetiracetam (LEV) for binding to synaptic vesicle protein 2A [4]. BRV also inhibits voltage-dependent sodium currents [5] and reverses the inhibitory effects of negative modulators on gamma-amino-butyric-acid (GABA) and glycine induced currents [6]. However, inhibition ofexcitatory neurotransmission may result in dysfunction in some areas of the central nervous system associated with cognitive and/or motor function impairment [7]. Considering the potential adverse events of BRV, it is necessary to first exhaustively examine the current clinical studies literature and identify adverse events (AEs) that are significantly associated with brivaracetam treatment.

2. Methods

According to PRISMA principles, the search strategy, selection of study, data extraction and data analysis were pre-designed but were not registered on any website [8].

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2.1. Data sources and search

We searched online databases including Pubmed, Embase, and Cochrane Online Library with no language limitations. The words we used in this search included: brivaracetam, UCB34714 and butanamide. We also searched Clinical trial.gov (https://www.clinicaltrial.gov/) for unpublished trials. Two reviewers independently reviewed the titles and abstracts from the search results for any article that was potentially relevant studies. Published trials without articles were also evaluated based on the summary of information online.

2.2. Selection of studies

The two reviewers independently assessed the eligibility of potentially relevant studies according to the predefined inclusion and exclusion criteria. Disagreements were resolved by consensus between investigators.

Inclusion criteria:

1. Study design: randomized, double-blind, placebo-controlled trials; subject contents $\geq$50.
2. Population: adults aged 16–80 years; the included subjects diagnosed with different neurological disorders.
3. Intervention: brivaracetam was used at different dosages; no restriction was imposed on the route of administration.
4. Outcomes: all data must come from full journal publications or summary of clinical trial reports; at least one of the following data must be provided by the included studies: serious AEs, withdrawal, and/or treatment-emergent adverse effects.

Exclusion criteria:

1. Study design: design of trial is not double-blind, placebo-controlled or non-RCTs; subject contents $<$50.
2. Population: studies in which subjects already took brivaracetam before the baseline period were excluded.
3. Outcome: the integrity of data was not ensured or over 15% of the included patients were lost in the follow up period.

2.3. Data extraction and evaluation of evidence

The two reviewers independently extracted relevant information from each eligible study using a data extraction form, which included the first author, study design, inclusion criteria of patients, dose of BRV, number of patients (intent-to-treat, ITT), percentage of patients using BRV, percentage of males, age, duration of epilepsy, titration, percent of baseline 1–2 concomitant AEDs, the kind of concomitant AEDs, seizure-free rate, number of any AEs and seizure types. The bias of included studies was assessed using the guideline for assessing risk of bias in the Cochrane handbook 5.1.0 [9]. The quality score for each study was evaluated according to Jadad score [10], which included the domains of randomization, allocation concealment, blinding, and an explanation of withdrawal or loss to follow-up. The studies were considered as high quality if the score $\geq$4 and low quality if the score $<$4. Any discrepancies were resolved by consensus between investigators.

2.4. Outcome measure

Serious AEs, study withdrawals due to AEs and treatment-emergent adverse effects were investigated for measuring the adverse event profile of BRV. AEs were categorized as serious (SAEs) if they were life-threatening, resulted in death, a persistent or significant disability, a congenital birth defect, or needed in-patient hospitalization.

2.5. Data analyses

Revman 5.3 software was applied to perform meta-analysis for data processing [11]. For dichotomous variables, we calculated the risk ratios (RR) and 95% confidence intervals (95% CI) to demonstrate pooled effects using the Mantel–Haenszel method. For continuous variables, we used a reversed variance method and calculated the mean difference [12]. Fixed-effect models weight the studies by the amount of available information whereas the random-effects model accounts for between-study heterogeneity in the weighting of each study. Heterogeneity between studies was assessed using the I-squared statistic (I^2). I^2 values of 25% indicate low heterogeneity, values of 50% suggest moderate heterogeneity, and values of 75% suggest high levels of heterogeneity [13]. Intent-to-treat population was applied for all included studies where anyone who qualified for the baseline period was considered to be involved. Sensitivity test was performed by switching statistical values and removing low-quality studies or study of high heterogeneity compared to others.

3. Results

3.1. Study selection

Clinical trials databases were searched for RCTs that used BRV treatment and had been published up to March 2016. This search yielded 92 papers in Pubmed, 264 in EMBASE, 66 in MEDLINE, and 28 in clinicaltrial.gov. From our initial screening, we excluded non-randomized, placebo-controlled trials as well as studies performed on healthy volunteers. After exclusion criteria were applied, seven papers were identified, reporting on eight RCTs (two RCTs were reported in one study [20]). A flowchart detailing the study selection process is shown in Fig. 1.

3.2. Characters of included studies

The seven selected studies included a total of 2505 patients, 1787 of whom were randomized to a brivaracetam treatment group and 718 to placebo. Of the eight RCTs, five featured brivaracetam that had been administered to drug-resistant partial-onset seizures [14,15,17–19], one where brivaracetam had been administered for uncontrolled focal and generalized epilepsies [16], and two [20] that had administered brivaracetam for treatment of Unverricht–Lundborg disease (EPM1). In all studies, drug was administered twice a day. In all but one of the studies [20], data were obtained from fixed-dose trials. The remaining study [20] featured a flexible-dose trial. Patients from the selected studies were from a wide age range, with either drug-resistant partial epilepsy [14–19] or generalized epilepsy [16]. But in one study, eligible patients had genetically ascertained EPM1 [20]. Brivaracetam was used as an add-on antiepileptic drugs in all studies. Patients included in four of the eight studies [14,16,20] underwent an up-titration period of increasing brivaracetam doses until the final dose was reached. All other included studies did not have this up-titration period [15,17–19]. Study duration ranged from between 7 and 16 weeks. Study and patient characteristics of the included studies are shown in Table 1.

3.3. Risk of bias

According to the Cochrane Handbook of Systematic Review, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment,