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Real-life experience with brivaracetam in 101 patients with difficult-to-treat epilepsy—A monocenter survey

Bernhard J. Steinhoff*, Matthias Bacher, Iancu Bucurenciu, Barbara Hillenbrand, Tassanai Intravooth, Reinhold Kornmeier, Christoph Kurth, Jakob Stockinger, Anke M. Staack

Kork Epilepsy Center, Kehl-Kork, Germany

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ABSTRACT

Purpose: To assess the efficiency of brivaracetam under real-world conditions in a tertiary referral epilepsy center.
Methods: We consecutively collected patients treated at our center with brivaracetam (BRV). After a minimum observation period of six months we retrospectively analyzed the efficiency of BRV.
Results: Data of 101 patients (mean age 42 years, range 18–81 years, 54 females,) were analyzed. The median number of antiepileptic drugs (AEDs) used prior to BRV was 10 (range 2–18). The initial dose of BRV was at least 50 mg per day, the mean maintenance dose at cut-off was 168.6 mg (median 200 mg, range 50–400 mg).
Efficacy data were assessed for the last three months or at the time of the last observation carried forward if BRV had been discontinued prematurely. Responder rate was 27.8% (n = 28) with 7% seizure-free patients. Adverse events (AEs) occurred in 37 patients (37%). Most frequent AEs were dizziness (16%) and somnolence (11%). Psychiatric adverse events comprised irritability, aggression, depression and psychosis in single cases. Retention rate after six months was 51.5%. Main reason for discontinuation was a lack of efficacy.
In 43 cases LEV and BRV were switched. The switch was performed abruptly without complications. In 26 cases (60%) BRV was discontinued and re-switched to LEV within weeks, mainly due to a lack of better efficacy. After the switch from LEV to BRV we even saw an aggravation both of seizure frequency and severity in 5 cases. Retention rate in patients who had not been on LEV was 57%.
Conclusion: In our hands BRV appeared to be well tolerated and easy to handle. The retention rate was influenced by patients who were switched from LEV and re-switched because BRV was not more efficient. Switching from and re-switching to LEV was easy.

1. Introduction

Like levetiracetam (LEV), brivaracetam (BRV) is a ligand of the synaptic vesicle protein SV2A. This mechanism is thought to be the principle one [1,2].

BRV was recently approved for the adjunctive treatment of adults and adolescents ≥16 years with partial seizures with and without secondary generalization in the European Union and the United States [1]. It was introduced to the market in Germany in February of 2016.

The Kork Epilepsy Center is one the largest traditional epilepsy centers in Germany offering 122 in-patient beds and more than 6.000 out-patient appointments per year. As a consequence, many of our patients suffer from difficult-to-treat epilepsy syndromes with ongoing seizures in spite of numerous previous therapeutic strategies [3,4]. As soon as a new antiepileptic drug (AED) is marketed many of those patients who have been urgently waiting or a new treatment option will be treated with such a new AED within a relatively short period of time [3].

This report comprises patients who were treated with BRV from the time of launch in February of 2016 on. After a minimum observation time of six months, i.e., in November of 2016, we

* Corresponding author at: Epilepsiezentrum Kork, Landstraße 1, 77694 Kehl-Kork, Germany.
E-mail address: bsteinhoff@epilepsiezentrum.de (B.J. Steinhoff).

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made a cut-off and retrospectively analyzed efficacy and tolerability of BRV.

2. Patients and methods

From February of 2016 on we consecutively collected data from adult out- and inpatients of the Kork Epilepsy Center who were treated with BRV. Data comprised age, etiology, classification of epileptic seizures and syndromes, baseline AED medication and seizure frequency according to patient's diary or inpatient observation by our staff. BRV was always started according to a bid regimen with 25 mg bid, 50 mg bid or 100 mg bid, respectively. Patients on levetiracetam (LEV) were switched abruptly to BRV according to a ratio as follows: 1000 mg LEV were replaced by 50 mg BRV, 2000 mg LEV by 100 mg BRV and 3000 mg LEV by 200 mg BRV. BRV was increased, decreased or stopped according to the clinical course.

We stopped recruiting in May of 2016. Patients were consecutively followed and contacted monthly. In case of any question, adverse event, or any other clinically relevant problem, patients had the opportunity to contact us by telephone, fax or e mail at any time. In an emergency case admission to the hospital was possible.

Efficacy data comprised the seizure count and the assessment of seizure type on the basis of the patient's reports and diaries. All patients used seizure diaries. During their hospital stays seizures were classified and documented by the staff. The seizure frequency was evaluated for the last three months prior to the individual cut-off and compared to a retrospective baseline of three months prior to the initiation of adjunctive BRV. If patients had discontinued prematurely this observation period was shortened accordingly. Patients who discontinued BRV due to tolerability reasons within one month were counted as non-responders concerning seizure frequency. Tolerability and adverse events were updated at least monthly. Patients were asked for any adverse events they observed. In addition a list of potential adverse events like dizziness, fatigue, somnolence, ataxia, dysarthia, blurred vision, diplopia, irritability, aggression, depression and psychotic symptoms was covered during the interview. Cut-off for the data analysis presented here was in November of 2016, so that the minimum observation period was 6 months (if patients had been started with BRV in May). Adverse events were assessed at the time of the last observation both in patients who were still on BRV in November of 2016 and in patients who had discontinued the drug in the meantime. Retention was documented monthly.

3. Results

We included 101 patients. Mean age was 42 years with a range between 18 and 81 years. Fifty-four patients (53%) were female. Etiology was distributed as follows: Structural causes were apparent in 71%; the etiology was unclear in 27%. In one case each a genetic cause with a mutation in the SCN1A gene and elevated anti-GAD antibodies were evident. In all patients partial-onset seizures occurred, three of them had only generalized tonic-clonic seizures with presumably partial onset. The remaining 98 patients (97%) had partial-onset seizures with and without secondary generalization. Secondary generalized tonic-clonic seizures (GTCS) were apparent in 86 cases (85%); the seizures of the remaining 15 patients did not tend to generalize.

The median number of antiepileptic drugs (AEDs) used prior to BRV was 10 (range 2–18). When BRV was initiated, three patients were on a monotherapy with LEV and switched to an off-label monotherapy with BRV. The remaining 98 patients got BRV as adjunctive AED. Their baseline treatment consisted of one AED in 35%, of two AEDs in 46%, of three AEDs in 16%, and of 4 AEDs in 4%. In patients on baseline monotherapy the most commonly used AED was lamotrigine (LTG). The new AEDs that were introduced to Germany most recently and that are still available are lacosamide (LCM) eslicarbazepine acetate (ESL) and perampanel (PER). These belonged to the baseline medication in 18, 10 and 10%, respectively and were even used in off-label monotherapy occasionally (LCM: n = 6, ESL: n = 4, PER: n = 1). In 43% LEV and BRV were switched. The switch was performed abruptly and did not cause problems.

The initial dose of BRV was at least 50 mg per day, the mean maintenance dose at cut-off was 168.6 mg (median 200 mg, range 50–400 mg).

Considering efficacy 27.8% (n = 28) was responders with a seizure reduction by at least 50% per month over the last three months. Seven of these patients (7% of all) were completely seizure-free. All seizure-free patients were on a baseline monotherapy or on a combination of 2 AEDs. The number of previously used AEDs was lower than in the whole patient group (median = 6, range 2–8). Mean BRV dose in the seizure-free patients was 135.8 mg and thus lower than in the whole patient group. Among the 89 patients with GTCs including 3 patients with GTCS only 10 were seizure-free under BRV (11.2%).

Fourteen patients took doses beyond the recommended maximum 200 mg per day according to the labeling. In five of them, additional response was seen. However, in 2 of these 5 responders we had to decrease the dose of 250 mg and 300 mg, respectively, again due to dizziness.

Adverse events (AEs) occurred in 37 patients (37%). Most frequent AEs were dizziness (16%) and somnolence (11%). Psychiatric advents were assessed by personal examination and comprised irritability, aggression, depression and psychosis in single cases. We observed no hematological, cardiovascular or dermatological complications. In several cases carbamazepine epoxide was markedly elevated under the influence of BRV which led to dizziness which resolved after reduction of carbamazepine. In another case a severe hyponatremia of 123 μmol/l occurred with BRV and ESL only after the introduction of BRV which resolved after the discontinuation of BRV due to a lack of efficacy. Table 1 summarizes the adverse events.

Retention rate after six months was 51.5% (n = 52). The main reason for discontinuation was a lack of efficacy (30.6%) according to the patient's opinion. In no case did patients wish to discontinue BRV due to a lack of efficacy if they observed a reduction of seizure frequency of at least 50%. Adverse events were the only reason for discontinuation in 3 cases only. Two patients complained about dizziness, one of each about additional ataxia and somnolence, respectively. The third patient discontinued due to marked somnolence and irritability. In the remaining cases both lack of efficacy and tolerability issues led to the discontinuation of BRV.

In 26 cases (60%) BRV was discontinued and re-switched to LEV resulting in a retention rate of 40%, mainly since the efficacy of adjunctive BRV was not clearly superior. Tolerability was the reason for a switch in 6 patients only. Three of them benefitted because of less irritability (n = 2) or somnolence (n = 1). After the

Table 1
Adverse events.

Adverse event	%	N
Dizziness	15.8	16
Somnolence	9.9	10
Ataxia	5.0	5
Increase of seizure frequency/severity	5.0	5
Irritability	4.0	4
Depression	2.0	2
Psychosis	2.0	2
Headache	1.0	1
Nausea	1.0	1