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Brief Communication

Treatment of refractory and super-refractory status epilepticus with brivaracetam: A cohort study from two German university hospitals

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ABSTRACT

Purpose: We aimed to ascertain the possible use of brivaracetam (BRV) as an option for treatment of status epilepticus (SE).
Methods: A review of medical records was carried out to detect BRV administration in SE patients treated in Frankfurt and Greifswald during the period February 2016 to January 2017. The primary outcome question concerned SE resolution after BRV initiation.
Results: During that period, BRV was started with eleven adult patients with SE. Five of these were female, and the median age was 64 (interquartile range [IQR] 21 years). The median SE duration before BRV initiation was 5 days (IQR 9 days); the median number of previous anticonvulsants used was 4 (IQR 5). Initial BRV doses ranged between 50 mg and 400 mg (median 100 mg), titrated to a daily dose of 100 to 400 mg (median 200 mg). There was a cessation of SE in the first 24 h of BRV in three patients (27%). While taking BRV, no serious side effects were seen.
Conclusion: Based on these cases and previous data from animal experiments, BRV may prove useful in SE treatment, and trials would be warranted to examine BRV's efficacy in treating SE and how this efficacy might be influenced by co-administration with levetiracetam.

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1. Introduction

The characteristics of refractory (RSE) and super-refractory status epilepticus (SRSE) include lack of response to initial treatment with anticonvulsants and, in the latter case, anesthetic therapy [1–4]. Refractory SE and SRSE have high fatality and morbidity rates and difficulties in treatment include first-, second- and third-line therapy failure [3–6]. There is little controlled or randomized study data on RSE and SRSE, so that the basis of therapeutic management tends to be expert opinion, clinical reports, and pathophysiological assumptions arising from experimental data [1,3–5].

Given the severity of RSE and SRSE and the unfavorable outcomes experienced by patients [3–7], new therapies are urgently needed to stop ongoing seizure activity. When new antiepileptic drugs (AEDs) are introduced, an opportunity arises for improved seizure control in some patients. The latest approved AED is brivaracetam (BRV) [8,9], a high-affinity synaptic vesicle protein 2A (SV2A) ligand. It exceeds levetiracetam (LEV)'s binding potential by between 10-fold and 30-fold [8,9]. A number of factors point to BRV's potential as an alternative second- or third-line RSE and SRSE therapy:

- Its availability as an intravenous solution;
- The speed of onset of action;
- A noticeable reduction in the cumulative duration of seizures in the rat model of self-sustained SE induced by perforant path stimulation [10,11].

We considered BRV as an option for compassionate use in RSE and SRSE, and this retrospective study's purpose was to assess usage, efficacy, and tolerability for BRV in this patient cohort.

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2. Patients and methods

We reviewed the medical records for a cohort of SE patients treated at the Frankfurt and Greifswald university hospitals between February 2016 and January 2017 (11 months) for BRV administration. The detailed evaluation of all SE patients is part of a study on SE outcomes, and this study is registered at the German Clinical Trials Register (DRKS00008718), and was approved by the local ethics committees. Patients under 18 years of age and patients with hypoxic–ischemic encephalopathy were excluded. None of our patients with hypoxic–ischemic encephalopathy was treated with BRV. The 2015 ILAE definition and classification of SE were used [12]. Super-refractory SE was defined as a SE that continues or recurs 24 or more hours after treatment initiation with anesthetic drugs, and RSE as recurrent seizure activity in spite of administration of two AEDs appropriately selected and dosed, including a benzodiazepine [1,3].

Included in the collected data were etiology, semiology, clinical diagnosis, demographics, history of seizures or SE, total length of stay (LOS) in hospital, ventilation time, modified Rankin Scale (mRS), and the Status Epilepticus Severity Score [13] at the time of admission. Four experienced, EEG-board-certified physicians interpreted the EEG data (AS, BG, FvP, FR). Follow-up of SE was done by repeated routine EEGs usually at 24-h intervals. Duration of SE before BRV initiation and number of AEDs previously used were analyzed. Additionally, the timing of BRV in relation to SE onset and cessation, and presence of adverse events, were collected.

Status epilepticus cessation upon treatment with BRV within the next 24 h and absence of further seizures were the primary outcome measures to determine if a patient had benefitted from BRV, and were regarded as successful outcomes of SE treatment where there had been no further administration of other anticonvulsants before Status epilepticus cessation. SE cessation time was defined as the time of the first EEG that showed that electroencephalographic signs of SE had ceased. Secondary measures of outcome included number of AEDs, LOS, and mRS score at discharge as well as disposition (which could be home, rehabilitation, nursing home, or death). IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

3. Results

During the period under evaluation, a total of 205 patients with SE (n = 107/205 female, 52.2%) with a mean age of 62.5 (SD 19.2; range 18–99) years were treated at the two hospitals. Brivaracetam was used to treat eleven Caucasian patients (5.4% of the cohort) with RSE (n = 8) and SRSE (n = 3) (See Table 1; patient sequence is by age and SE refractoriness). The median age was 64 (IQR 21), five patients were female (45%), and four patients (36%) had a previous epilepsy history and were already taking AEDs at the time of admission. Etiology was mainly vascular (6/11), and infectious or inflammatory causes of epilepsy or SE were not present in any patient. A generalized tonic–clonic SE (GTCSE) was present in three cases, six cases had a non-convulsive SE (NCSE) with coma as predominant symptom while one patient presented with a simple-partial and one with a complex-partial SE.

Brivaracetam was used in RSE (Table 1, #1–8) in eight patients. From SE onset to first BRV administration, latency was between the first 24 h and 16 days, and between one and six different AEDs had been given before BRV. Use of anesthesia was not considered in some of these patients with a prolonged RSE due to underlying severe disease or denial by patients or relatives. Six cases involved a direct LEV to BRV switch without overlap, i.e., BRV was administered 12 h after the last administration of LEV. In two patients (#3, #5) BRV was given within 1 h of LEV administration. Brivaracetam was rated successful in terminating RSE in three cases (#5, #6, #8).

Brivaracetam was used in SRSE (i.e., after benzodiazepines, multiple AEDs, and at least one episode of general anesthesia for at least 24 h with an EEG-proven burst-suppression pattern had all failed) in three patients (Table 1, #9–11). From SE onset to first BRV administration, latency was between 6 and 29 days, and seven to eight different AEDs or anesthetic agents had been given before administration of BRV. All three cases involved a direct LEV to BRV switch. BRV was not rated as successful in terminating SRSE in any of these cases.

Initial BRV dosage varied from 50 to 400 mg (median 100 mg, mean 150 mg) titrated up within one day to maximum daily doses of 100 to 400 mg (median 200 mg, mean 264 mg). In most cases, initial dosage and maintenance dosage exceeded the recommended daily dose for treating epilepsy. The recommended dose of BRV is between 50 and 200 mg per day in two doses, beginning at 25 mg twice daily [8,9].

Status epilepticus ceased in three patients (3/11; overall success rate 27%) within 24 h after the initial BRV administration. In case #5, activity attenuation and subsequent resolution was observed directly on EEG after BRV administration. In two cases (#6, #8), BRV was the last anticonvulsant to be added, and no SE was observed on EEG within 24 h. The final disposition was discharge to home in four patients, to a rehabilitation facility in two patients, into palliative care in four patients, and one patient deceased in hospital.

Respiratory and urinary tract infections that required treatment with antibiotics caused complications in intensive care treatment. Transient liver enzymes and creatinine elevation were also seen. No serious side effects, however, were observed during BRV treatment.

4. Discussion

Eleven adult patients were treated for RSE or SRSE with BRV. Three experienced SE resolution within 24 h of beginning BRV administration. While this is a small patient cohort, this study suggests that BRV can be well tolerated as a therapeutic approach in the treatment of RSE and SRSE patients.

Refractory SE and SRSE resist benzodiazepines and anticonvulsants, and general anesthesia is also resisted by the latter. After the onset of SE, there is rapid development of pharmacoresistance to benzodiazepines due to benzodiazepine-sensitive synaptic $GABA_A$ (γ-aminobutyric acid) receptors becoming internalized during SE [14]. In an animal model of severe cholinergic SE designed to study polytherapy with the aim of reversing effects of loss of synaptic $GABA_A$ receptors caused by seizures, there was greater effectiveness in terminating SE and preventing further seizures for the combination of diazepam with ketamine and BRV; the combination was also less toxic than benzodiazepine monotherapy [11,15]. Based on our study and that experimental animal data, BRV may be considered an option for SE treatment. Brivaracetam was administered in most cases on compassionate grounds after failure of multiple approved drugs for SE treatment or of such other drugs as ketamine, lacosamide, perampanel, or topiramate [16–18]. That this late treatment after other therapies had failed might explain the low success rate of 27%. Brivaracetam under-dosing seems unlikely as initial doses were at least 50 mg and reached the maximum daily dose of 200 mg in all but one patient, while five patients were treated with 300 to 400 mg/day.

Limitations of this study include its retrospective and non-controlled nature and the adjunctive treatment with a number of AEDs including LEV [19]. The specific order of administered AEDs and their duration were protocolled in detail, but there was no systematic recording of serum levels. The use of real-world data means that the possibility that clinical improvement and seizure freedom stemmed from other interventions cannot be excluded.

In most cases, the switch from LEV to BRV came when the next equivalent dose was due, which was usually 12 h after the last administration of LEV. However, in two cases (#3, #5), BRV administration was within 60 min after LEV infusion. Evidence is limited on how LEV and BRV co-administration might influence each drug's efficacy [20]. Randomized controlled studies of adjunctive BRV treatment in focal epilepsy (N01252, N01253 and N01254) have shown BRV to have less

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