Intravenous brivaracetam in status epilepticus: A retrospective single-center study

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Summary
Brivaracetam (BRV) is a high-affinity synaptic vesicle glycoprotein 2A ligand that is structurally related to levetiracetam (LEV). Compared to LEV, its affinity to the ligand is >10%-30% higher. Due to its more lipophilic characteristics, it might have a quicker penetration across the blood-brain barrier and potentially also a stronger anticonvulsant effect. Thus, we aimed to explore its usefulness in the treatment of status epilepticus (SE). We retrospectively assessed treatment response and adverse events in adjunctive treatment with intravenous BRV in patients with SE from January 2016 to July 2017 at our institution. Seven patients aged median 68 years (range = 29-79) were treated with intravenous BRV. Three patients had SE with coma and four without. SE arose de novo in two patients; etiology was remote symptomatic in four patients and progressive symptomatic in one patient. The most frequent etiology was remote vascular in two patients. BRV was administered after median four antiepileptic drugs (range = 2-11). Time of treatment initiation ranged from 0.5 hours to 105 days (median = 10.5 hours). Immediate clinical and electrophysiological improvement was observed in two patients (29%). Median loading dose was 100 mg intravenously over 15 minutes (range = 50-200 mg), titrated up to a median dose of 100 mg/d (range = 100-300). Median Glasgow Outcome Scale score was 3 (range = 3-5), with an improvement in 86% of patients compared to admission. We observed no adverse events regarding cardiorespiratory function. BRV might have potential as a novel antiepileptic drug in early stages of SE. Its potential may lie its ability to cross the blood-brain barrier more quickly than LEV and its favorable safety profile. Prospective studies for the use of BRV in SE are required.

KEYWORDS
EEG, epilepsy, intensive care unit, levetiracetam
1 | INTRODUCTION

Status epilepticus (SE) is one of the most important neurological emergencies. It is associated with high morbidity and mortality. \(^1\)–\(^3\) SE is defined as the “failure of mechanisms responsible for seizure termination or the initiation of mechanisms that lead to abnormally prolonged seizures (t1), which might have long-term consequences (t2), including neuronal death, neuronal injury and alteration of neuronal networks depending on seizure type and duration.” \(^4\) The pathophysiological correlate of seizure perpetuation might be the imbalance between the inhibitory transmitter γ-aminobutyric acid (GABA) and the excitatory transmitter glutamate. In the early stages of SE, GABAergic drugs, such as benzodiazepines, are most effective in seizure termination. With ongoing seizure activity, GABA\(_\text{A}\) receptors in the postsynaptic membrane are internalized and GABAergic drugs become less efficacious. In contrast, N-methyl-D-aspartate receptor receptors are increasingly expressed at the postsynaptic membrane, resulting in seizure perpetuation by offering more glutamate binding sites. \(^5\)

Brivaracetam (BRV) is a high-affinity synaptic vesicle glycoprotein 2A ligand that is structurally related to levetiracetam (LEV). Compared to LEV, its affinity to the ligand is >10%–30% higher. \(^6\) BRV has linear and predictable pharmacokinetics. It is rapidly and almost completely absorbed after oral intake, with peak serum concentrations after 0.5–2 hours. The volume of distribution is 0.5 L/kg, and <20% of the drug is protein bound; \(t_1/2\) is about 9 hours. The elimination of BRV is dependent on CYP2C8 and to a lesser degree on CYP3A4 and CYP2C19. Strong inducers increase the hydroxylation and decrease the serum concentrations by up to 50%. In patients with liver disease, the clearance may be reduced by 25%–35% and \(t_1/2\) is prolonged up to 17 hours. \(^7\)–\(^9\) In patients with renal dysfunction, the dose has to be reduced accordingly, due to the renal elimination of BRV. \(^10\) Steady state is reached after 2 days. In healthy men, BRV \(C_{\text{max}}\) serum levels reached 3.5 \(\mu\)g/mL, 7.7 \(\mu\)g/mL, and 13.3 \(\mu\)g/mL under a treatment regime of BRV 200 mg/d, 400 mg/d, and 800 mg/d, respectively, after 14 days of intake. Mean BRV levels in healthy men were between 2.02 and 2.06 \(\mu\)g/mL under treatment with BRV 200 mg/d and between 1.06 and 1.15 \(\mu\)g/mL under BRV 100 mg/d. The good water solubility allows also for an intravenous (IV) formulation. \(^11\) Due to its more lipophilic characteristics, BRV penetrated the blood-brain barrier in in vitro models more rapidly than LEV, which might translate into higher efficacy in emergency situations. \(^12\) Therefore, the inhibition of transmitter release and the fast penetration through the blood-brain barrier reveal new treatment possibilities in early stages of SE.

On the one hand, there is only sparse data on the use of BRV in SE. A multicenter case series on the use of BRV in SE included 11 patients from two German hospitals and documented a treatment response in 27%. \(^13\)–\(^14\) On the other hand, postmarketing studies suggest a simple usage and favorable retention rates of the drug. \(^13\)–\(^15\)

Here, we report a single case series on the use of IV BRV in SE to evaluate safety and efficacy of the adjunctive treatment with IV BRV in SE.

2 | MATERIALS AND METHODS

We analyzed all patients who received IV BRV as an add-on treatment in early, established, refractory, and superrefractory SE and who were referred to the neurological emergency room, the neurological intensive care unit (NICU), or the neurological normal ward in Salzburg, Austria from January 2016 to July 2017. We collected data on the underlying etiology, SE type, and duration of SE. We analyzed duration of hospitalization and NICU treatment, number and sequence of administered antiepileptic drugs (AEDs) before initiation of BRV, treatment response to BRV within 1 hour and >24 hours, outcome of SE, and adverse effects after add-on treatment with BRV.

The diagnosis of SE was made clinically by the physician in the emergency setting and by using electroclinical criteria for nonconvulsive SE (NCSE) proposed by the Salzburg consensus criteria on SE. \(^16\) We classified SE subtypes according to the proposal of the International League Against Epilepsy taskforce on SE. \(^4\) We distinguished between SE type A with prominent motor symptoms (including tonic–clonic SE, myoclonic SE, focal motoric SE, tonic SE, and hyperkinetic SE) and type B without prominent motor symptoms (NCSE with or without coma). \(^4\)

Etiology was classified as symptomatic when a cause was identified and as cryptogenic in the case of unknown cause. Symptomatic SE was further subclassified into acute symptomatic, remote symptomatic, or progressive symptomatic SE.
Mortality risk was calculated by the Status Epilepticus Severity Score\textsuperscript{17} (cutoff level for unfavorable outcome $= 3$ points) and the Epidemiology-Based Mortality Score in Status Epilepticus\textsuperscript{18} (cutoff level for unfavorable outcome $= 64$ points).

Treatment followed the international consensus approach.\textsuperscript{19} In stage I, benzodiazepines were administrated. In stage II, intravenous AEDs were administrated (e.g., LEV, valproate, phenytoin, lacosamide, or BRV). In case of ongoing seizure activity with impaired consciousness, stage III treatment was initiated with propofol and midazolam. Super-refractory SE was defined as persistent seizure activity for $>24$ hours. At this stage, treatment options like magnesium (Mg$^{2+}$), other AEDs, and ketamine were administered in comatose patients according to the physician in charge.

Blood samples including hemogram, C-reactive protein, basic metabolic panel including electrolytes, blood urea, nitrogen, creatinine, glucose, liver enzymes, and levels of administered AEDs were taken regularly. For those patients referred to the NICU, these samples were taken daily and blood gas analysis was performed at least twice a day.

### 2.1 Statistics

Descriptive statistics were calculated using Office Excel 2016 (Microsoft, Redmond, WA, USA). We analyzed median, range, and percentages due to the lopsided distribution. Due to the small sample size, statistical analyses between responders and nonresponders were not performed.

### 2.2 Standard protocol approvals, registrations, and patient consent

This study is a retrospective documentation of individual treatment decisions without research approach in an emergency setting. Individual treatment decisions are by Austrian law the responsibility of the operating physician. Due to the retrospective character of this study, it did not require ethics committee approval according to the Austrian Law on Research.

### 3 RESULTS

Seven patients (six women) received IV BRV between January 2016 and July 2017. Median age was 68 years (range $= 29$-79). Three patients had SE with coma, and four patients had SE without coma. On the bidirectional axis, four patients had SE type A with prominent motor symptoms and three patients had SE type B without prominent motor symptoms (NCSE). Among the patients with prominent motor symptoms, one patient suffered from tonic-clonic status epilepticus, one from myoclonic SE with coma, and two from epilepsia partialis continua. Among the three patients with NCSE, only one was in coma. The other two patients had aphasic status and aura continua, one each.

Two patients fulfilled the criteria of established SE, one had refractory SE, and three had super-refractory SE. SE was going on for $>1$ week in all super-refractory SE patients (median $= 15$ days, range $= 9$-168).

SE occurred de novo in one patient due to hypoxic brain injury. Five patients had a remote symptomatic and one a progressive symptomatic cause. The most frequent etiology was remote vascular (in two patients). The other five patients suffered from hypoxia, mitochondrial disease, lissencephaly, hypomelanosis of Ito, and brain abscess. For further details on patients’ demographics see Table 1.

BRV was administered in median after four (range $= 2$-11) AEDs. Time of treatment initiation ranged from 0.5 hours to 105 days (median $= 10.5$ hours). Median loading dose was 100 mg (range $= 50$-200 mg/d) IV over 15 minutes, titrated up to a median daily dose of 100 mg/d (range $= 100$-300).

Immediate clinical improvement was documented in two patients (29%), and early electrophysiological cessation of SE on surface electroencephalography (EEG) was observed in three patients (43%). In two of them, BRV administration and cessation of SE was documented during the EEG investigation. However, one of these three patients relapsed within 24 hours and was considered a nonresponder therefore.

In one BRV responder, SE was resolved before the EEG. In the other BRV responders, cessation of SE in EEG was documented after median 25 hours (range $= 0.5$-48). One showed periodic lateralized discharges with superposed evolution pattern (lateralized periodic discharges) over the right parietal region (Figure S1). The third showed generalized rhythmic delta activity, and the fourth displayed evolution pattern over the right frontal region.

The four BRV responders had early stage SE (two established SE) when BRV was loaded. Two of them had BRV in their premedication and therefore received BRV as stage II treatment to address the question of possible withdrawal seizures. Patient 3 had LEV in her premedication. However, it had been reduced by 250 mg (from 1500 to 1250 mg) 1 week before. One of the BRV responders had aura continua. This patient failed three AEDs, among them LEV with daily relapses after initial response. BRV treatment was initiated in this patient 15 minutes prior to valproate within 1 hour after his latest SE relapse (Data S2 and S3: clinical course BRV responders and BRV nonresponders).

Outcome after SE was severe disability in five patients. One of the BRV responders had no impairment; the other three responders regained their previous level of disability,
which was severe. Glasgow Outcome Scale overall was median 3 (range = 3–5), with an improvement in 83% of patients compared to admission. No case of death was documented.

Status Epilepticus Severity Score was true negative in three patients and Epidemiology-Based Mortality Score in Status Epilepticus score in four, yielding a negative predictive value 100% each. Positive predictive value was 0 each. Three of the patients were referred to the NICU (median duration = 18 days, range = 12–41). All of them were BRV nonresponders. No patient was catecholamine dependent on referral or after BRV administration. Mean hospitalization was 17 days (range = 0–187). Hospitalization in BRV responders was median 10 days (range = 0–17), compared to median 87 days (range = 30–187) in BRV nonresponders.

No adverse events in respect to cardiorespiratory function were documented related to BRV administration. One patient had hair loss and autoaggression later in the course. Levels of coadministered AEDs were taken regularly, without documented changes after add-on treatment with BRV. For dosing of BRV and outcomes see Table 2.

4 | DISCUSSION

Literature on the use of IV BRV in human SE is sparse. In this case series, BRV responders were treated earlier in the course of SE as opposed to BRV nonresponders. They responded to treatment within the first 2 hours after administration. One of the patients with initial EEG response to BRV relapsed within 24 hours and was considered therefore a nonresponder. In all of the BRV responders, we were able to document clinical and electrophysiological cessation of SE. In one patient, BRV was administered during EEG and clinical and EEG improvement was documented at the time. The other three responders showed fast clinical response to BRV. EEG response was documented at the latest within 48 hours, because during night shift and weekends the EEG technician is on call. Therefore, emergency EEGs are only performed if there is clinical evidence of ongoing seizure activity.

We documented a synergistic effect of valproate and BRV in one LEV nonresponder. None of our patients had either LEV or BRV withdrawal seizures. BRV Responder 3, whose BRV dose was reduced by 250 mg 1 week before, is cared for by her mother at home. A mistake in AED intake is highly unlikely. We did not consider this dose reduction causal for her SE, as she had remitting SE in her history. The rapid treatment response might be due to the rapid penetration of BRV across the blood-brain barrier. Furthermore, the effect of synaptic vesicle glycoprotein 2A modulation on GABAergic neurotransmitter release might suggest a high effectiveness of BRV in early stages of SE.

Due to the fast treatment response and the lack of cardiorespiratory adverse effects, the referral to the intensive care unit was not needed in all of the BRV responders. Early successful treatment with BRV did not only lead to shorter hospitalization but also to regaining the premorbid functional status as documented by Glasgow Outcome Scale.

5 | CONCLUSION

BRV might have potential as emergency treatment in the early SE stages. In this small series, BRV had a favorable
safety profile and a rapid onset of action. Prospective studies for the use of BRV in early SE are required.

**DISCLOSURE OF CONFLICTS OF INTEREST**

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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