Intravenous brivaracetam in status epilepticus: correlation between loading dose, plasma levels and clinical response.

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Abstract

Brivaracetam is available in intravenous formulation, and its favourable pharmacokinetic profile makes it a promising agent in the treatment of status epilepticus (SE). Its availability as an intravenous formulation and its favourable pharmacokinetic profile make it a promising agent in the treatment of status epilepticus. Our aim was to assess the correlation between BRV exposure and clinical response.

We retrospectively studied all consecutive SE patients treated with BRV in our centre from September 2016 to March 2018. Correlations between loading doses, plasma concentrations, extrapolated exposures (approach based on a population pharmacokinetics model) and the clinical response (defined as BRV being able to resolve SE without the need of further treatment), were analysed.

Among 14 patients, 7 (50%) responded to BRV. Responders received significantly greater median loading dosage per body weight (3.3mg/kg) compared to non-responders (1.5mg/kg) ($p=0.02$); no responders had loading doses below 1.9 mg/kg. There was a significant correlation of the clinical response with calculated exposure parameters, whereas measured BRV concentrations did not.

BRV doses higher than 1.9mg/kg are associated with greater probabilities of response in SE; consequently, a minimum dose of 2 mg/kg seems advisable in treatment of SE. It is unclear whether increasing further BRV loading doses would provide any additional benefit. BRV concentrations performed outside the frame of a standardised protocol merely ascertain BRV administration. This study is however limited by its small sample size.

Introduction:

Status epilepticus (SE) is a frequent neurological emergency associated with high mortality and morbidity, defined by seizure lasting more than 5 minutes or consecutive seizures without recovery of consciousness between them(Trinka et al. 2015). Its treatment involves intravenous (IV) administration of benzodiazepines, followed by IV non-sedative antiepileptic drugs (AEDs) (Beuchat et al. 2017). In the last years, new generation AEDs such as levetiracetam (LEV) and lacosamide (LCM) were increasingly used with a progressive phasing out of older AEDs, like phenytoin(Beuchat et al. 2017).

Brivaracetam (BRV) is available in both oral and intravenous formulations since 2016 and has been approved as adjunctive therapy for focal-onset seizures in adults. (Strzelczyk et al. 2016). The pharmacological action of BRV relies on its high-affinity binding with synaptic vesicle protein 2A (SV2A), that exceeds the binding potential of LEV by 10-30 fold (Gillard et al. 2011). Regulatory studies have shown that daily oral doses between 50mg and 200mg were efficacious as add-on in patients with chronic epilepsy (Biton et al. 2014, Gillard et al. 2011). Intravenous BRV was mostly studied in dose up to 200mg daily administrated as two dosing regimen (Stockis et al. 2016). Although BRV is not labelled for SE treatment, preclinical studies have been encouraging, showing efficacy in SE at dosage ranging from 0.3 to 300mg/kg. Because of its higher lipophilicity as compared to LEV, BRV rapidly crosses the brain-blood-barrier, with peak concentration in cerebral spinal fluid (CSF) reached within 10 min, in comparison to 30-60 min for LEV (Nicolas et al. 2016, Niquet et al. 2017, Strzelczyk et al. 2017). This favourable pharmacokinetic profile makes it a promising new agent in the treatment of SE, since an early treatment has been found to be associated with a greater chance of response. Like most new generation AEDs, BRV is used off label in SE. Only three retrospective case series (Kalss et al. 2018, Strzelczyk et al. 2018, Strzelczyk et al. 2017) have been published so far, that report a good tolerance of IV BRV at dosages comprised between 100-400mg. In fact, there is generally a limited experience on the use and adequate dosage of BRV in SE, as BRV dosages used as oral therapy replacement (100mg

BRV intravenous) are unlikely to represent a universally sufficient loading dosage in SE.

The aim of our study is to assess BRV dosage range that can be used in SE. Clinical response will be correlated with measured BRV concentrations and extrapolated exposure parameters calculated using a population pharmacokinetics model.

Methods

Patients have been identified in the previously described prospective SE registry database (Novy et al. 2010), approved by our institutional review board, which includes all consecutive adult patients treated at our hospital for SE. SE is defined as a single seizure lasting more than 5 minutes, or consecutives seizures without complete recovery between the episodes. Episodes occurring in patients younger than 16 years old or after cardiac arrest were excluded because of excessive differences in prognosis. Resolution of SE was determined as the time of seizure cessation, as demonstrated by clinical examination and subsequently confirmed by EEG documentation, usually obtained within 24 hours.

Patients' demographics, body weight, SE duration and clinical characteristics, such as the presence of aetiologies that may be potentially fatal(Rossetti et al. 2006), were collected prospectively. The Status Epilepticus Severity Score (STESS) (Rossetti et al. 2006), a validated prognostic score, was prospectively calculated for every patient to account for the episode severity. The exact sequence and timing of administration of treatments including loading BRV doses, as well as time of plasma samples were carefully collected. Response of BRV was considered if BRV was the last AED introduced before SE resolution. From BRV administration, the observation period lasted until the end of SE for responders, or the introduction of another AED for non-responders (BRV being considered as ineffective).

Plasma concentrations of BRV were measured by the laboratory of clinical pharmacology using an adaptation of the previously published method by ultra-performance liquid chromatography-tandem mass spectrometry (Decosterd et al. 2015). The laboratory participates to an External Quality Proficiency Program for antiepileptic drugs, including BRV (LGC Standards Proficiency Testing, Lancashire, United Kingdom).

Population pharmacokinetics model was used to calculate exposure parameters.
This previously published population pharmacokinetic model (Schoemaker et al. 2016) describes BRV disposition by a one-compartment model with first order elimination and proportional residual error. According to this model, BRV apparent clearance is affected by various covariates retrieved in each patient (body weight and concomitant intake of enzyme inducers). BRV distribution volume depends only on body weight. Using this model, a Bayesian maximum-likelihood approach was applied to our experimental available samples measurements, and *a posteriori* parameters were determined for each patient and used to estimate individual BRV exposure. The pharmacokinetic analysis was performed using the NONMEM program (version 7.3), running with Pirana (2.9.3) and PSN-toolkit (4.2).

Statistical analyses were done with SPSS version 25 (IBM corp., Armonk, NY). Chi Square/Fisher test, Mann-Whitney U were used for univariate analyses, as appropriate. A binary logistic regression was used to adjust for predictors of outcome, namely the position of BRV in the treatment sequence, STESS (including age) and potentially fatal SE aetiology.

Results

We included 14 SE patients treated with BRV between September 2016 and March 2018, for whom BRV plasma levels were monitored. Among these 14 SE episodes, 7 (50%) responded to BRV. Demographics and SE characteristics in responders and non-responders are compared in Table 1. There was no meaningful difference between both groups. Responders were younger and the duration of their SE was understandably shorter. SE semiology was mostly focal (64%), four patients had convulsive SE and 1 non convulsive SE in coma (as worst seizure type). BRV was given after a median of four AEDs (range 2-7).

The first four patients received (probably empirically according to BRV label) 100 mg of BRV loading dose, which was then increased to 200 mg. All patients (except one at 300mg) had the same maintenance of 200 mg daily dose regimen. Mean loading dose was 171.4 mg and median loading dose 200 mg. Mean maintenance dose was 207.1 mg and median maintenance dose 200 mg. There was a difference between responders and non-responders in term of loading dose, with responders receiving a higher median loading weight adjusted

dose (3.3mg/kg versus 1.5mg/kg) (figure 1). No patient responded after BRV loading doses below 1.9 mg/kg. No adverse events were reported related to BRV treatment.
Plasma samples were collected after a median of 15.5 hours, (range 3-25) following the loading dose. We did not find any correlation between routinely measured BRV plasma concentrations and clinical response (p=0.3, U test). When considering levels measured after 6 h (before 6 h, n=3) or only residual concentrations (n=11), there was no significant difference (p=0.9, U test) in both groups. There was, however, a statistically significant difference in term of mean calculated BRV concentrations during observation period, (2.6 mg/L in responders, versus 1.8 mg/L; p=0.01, U test). Minimum BRV calculated concentrations, after the loading dose, were also significantly higher in responders (2.2 mg/L versus 1.2mg/L; p=0.9, U test).
When analysing the association between SE response (outcome in the analysis) and routinely measured BRV levels, BRV position in the treatment sequence, STESS score (which includes age) and presence of potentially fatal aetiology were not predictors using a sequential correction (one correction each time) in a logistic regression. This was also the case when analysing the association between SE response and loading dose.

Discussion

This study shows a correlation between BRV exposure (loading dose as well as calculated exposure) and clinical response, despite its small size. Increasing the loading above the IV licensed dose (50 to 100mg; marketed for replacement of oral therapy) was associated with a greater likelihood of response; no patient receiving less than 1.9mg/kg responded to BRV. These findings were confirmed by calculated exposure parameters. Absolute maintenance doses were identical in both groups; higher calculated exposure in responders seems to relate to a relative lower body weight in responders (smaller distribution volume and clearance). Similarly, to the loading dose, maintenance dosage may need to be adapted according to the patient weight.

The use of greater than licensed loading doses in SE is not unique to BRV; other newer generation AEDs (like lacosamide) used off-label for SE were shown to be more efficacious with loading doses higher than used in chronic epilepsy (Legros et al. 2014). We increased

loading doses over the course of the study period, similarly to other observations (Strzelczyk et al. 2018, Strzelczyk et al. 2017), without experiencing adverse events, demonstrating a benefit when prescribing >1.9mg/kg. It is nevertheless not clear if increasing loading doses further would lead to additional benefit, as we do not have sufficient data to explore the response associated with higher dosages. Previous studies on newer generation AEDs in SE suggested a ceiling effect in terms of response. Regarding lacosamide, a loading dose greater than 5mg/kg (Santamarina et al. 2018) was useful whereas no benefits were found when increasing higher than 9mg/kg (Perrenoud et al. 2017). These data suggest that there may not be a benefit of increasing indiscriminately loading dose in SE even if the treatment is well tolerated.

Plasma drug concentrations are often measured empirically in SE, after the loading dose. We did not find a correlation between BRV level and the weight adjusted loading dose, this even when excluding samples that were taken during the plasma peak. This is not that surprising given the short plasmatic half-life of the medication (7h, similar to levetiracetam) (Perrenoud et al. 2018). Our findings confirm that routine plasma samples taken without a standardised protocol (timing in relation to the last administration) are not useful to assess the patient's exposure and can only be used to confirm that medication was actually administered. Moreover, there is currently no validated reference interval of BRV. Pharmacokinetic modelling is needed to interpret plasma concentrations further if no standardised sampling protocol is used.

This study has limitations. Above all, the sample size is small, which did not allow fully adjusting for potential confounders such as age, cause and severity of SE as well as the position of BRV in the treatment sequence. The correction for these potential confounders is merely exploratory and precludes drawing further conclusions. BRV exposure was calculated using the only published pharmacokinetics population (Schoemaker et al. 2016): this model does not integrate liver function, potentially underestimating exposure (this case applied to one of our subjects). Our definition of SE response (last AED) can seem simplistic, because it does not consider possible synergistic effect or the natural evolution of SE, but it represents a pragmatic approach in clinical practice. Our responder rate was also higher than in a previous study (27%) (Strzelczyk et al. 2017), but this difference is probably

explained by the difference in terms of population (outside ICU for our patients) and by the fact that the medication was used earlier in our series.

In conclusion, BRV loading doses higher than 1.9 mg/kg (correlated with calculated exposure) seems to be associated with a better response rate in patients with SE. Based on this finding, it seems advisable to use at least 2mg/kg as loading in adults with SE. Plasma concentrations not performed in a standardised protocol are difficult to interpret to quantify the patient exposure and require a pharmacokinetic modelling to reflect on treatment exposure. The sample size of the study is however small and precludes firm conclusions that would require a prospective.

Figure 1 legend: Weight adjusted load doses distribution in responders and non-responders.

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