EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2021,16 (32) 141-144
(*FORMERLY: CAPSULA EBURNEA*)

Review

EFFICACY OF BRIVARACETAM IN PEDIATRIC EPILEPSY: AN UP-TO-DATE

Antonio Gennaro Nicotera [#], Laura Turriziani [#], Giulia Spoto, Greta Amore, Maria Midiri, Gabriella Di Rosa

[#] These authors contributed equally to this work

Unit of Child Neurology and Psychiatry, Department of Human Pathology of the Adult and Developmental Age, "Gaetano Barresi" University of Messina, Messina, Italy

ARTICLE INFO

Article history:
Accepted 27 Jul 2021
Revised 22 Sep 2021
Published 31 Oct 2021

Keywords:
antiepileptic drugs, brivaracetam, epilepsy, children.

ABSTRACT

Among the newest antiepileptic drugs, brivaracetam (BRV), previously known as "ucb34714", is one of the most interesting molecules available, increasingly getting the attention of researchers. The clinical efficacy of BRV as adjunctive therapy has been extensively assessed in six randomized, controlled, phase III trials, the results of which demonstrated BRV efficacy in reducing seizures at the dosage of 20–200 mg/day. However, to date, only few data on the pediatric population are available. Here we briefly report the data available on BRV and its usage in the pediatric population suffering from epilepsy to highlight the potential benefits of this drug in this population.

1. Introduction

The incidence of epilepsy in children ranges from 41 to 187 new cases/100,000 in pediatric population per year, and the prevalence is estimated to be 4-6/1000 children under 20 years of age, regardless of the types of seizures (1, 2).

Pediatric epilepsy accounts for several types of phenotypic presentations and etiologies, making the diagnostic and therapeutic processes difficult to make; this is even truer if some peculiar factors, strictly related to the pediatric population, are taken into account, namely the consistent percentage of drug-resistant patients (9-23%) and the few clinical trials addressing this specific age-group (1).

Nowadays, many antiepileptic drugs (AEDs) are available to treat pediatric epilepsy, although none of them are devoid of side effects, particularly impacting the neuropsychiatric and behavioural domains. Therefore, since the introduction of the first AEDs, research has been continuously conducted on this topic to offer new therapeutic options with superior antiepileptic potential and higher profiles of tolerability and safety and, consequently, less risks (1).

Among the newest AEDs, brivaracetam (BRV), previously known as "ucb34714", is one of the most interesting molecules available, increasingly getting the attention of researchers.

Developed by UCB Pharma during a research plan designed to discover more potent synaptic vesicle protein 2A (SV2A) ligands than levetiracetam (LEV), BRV was formerly approved as an adjunctive treatment for the therapeutic management of focal-onset seizures, with or without secondary generalization, in adults and adolescents older than 16 years (3). The clinical efficacy of BRV as adjunctive therapy has been extensively assessed in six randomized, controlled, phase III trials, the results of which demonstrated BRV efficacy in reducing seizures at the dosage of 20–200 mg/day (4).

Currently, only few data on the pediatric population are available. Nevertheless, thanks to data extrapolation from studies on adults, BRV has also been approved for treating focal seizures in patients older than 4 years. However, it is noteworthy that extrapolating pharmacokinetics (PK) and safety data from adults to children is not directly possible, since PK and safety profiles may differ among diverse populations, requiring additional tolerability, safety, and PK studies (4).

Here, we briefly report the data available on BRV and focusing on its indications in children suffering from epilepsy, also aiming to highlight the potential benefits of this drug in the pediatric population.

* *Corresponding author*: Antonio Gennaro Nicotera, *antonionicotera@ymail.com*.
DOI: 10.3269/1970-5492.2021.16.32
 ISSN: 2279-7165 - Available on-line at www.embj.org

2. Brivaracetam pharmacodinamic

BRV, (2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl] butanamide, is a pyrrolidone derivative, binding the SV2A glycoprotein, an integral membrane protein essential for the proper functioning of the synaptic vesicles (4, 5).

Particularly, SV2A is implicated in the calcium-dependent exocytosis mechanism and it is considered the primary regulator molecule of neurotransmitter release in the synaptic space, where it acts through the binding of synaptotagmin-1 (SYT-1) (5, 6). In addition, it has been demonstrated that neurons without SV2A show lower levels of SYT-1, also supporting evidence for a role of SV2A in the regulation of SYT-1 expression (5).

Furthermore, SV2A has been hypothesized to maintain the assembly of the soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) complex, as lower levels of SNARE have been detected in SV2A-KO animals. Although the regulatory role of SV2A in normal synaptic vesicle function is commonly accepted, the precise mechanism of action of this molecule has yet to be fully cleared (5).

Recently, another potential mechanism of action of BRV has been proposed, involving a perturbance of several ionic currents, such as M-type and delayed-rectifier K+ current, hyperpolarization-activated cation current, voltage-gated Na+ current, and a large-conductance Ca++-activated K+ channel. Taking into account the involvement of several ionic channels (e.g., KCNQx, SCNx and KCNMA1), BRV could find a further indication (7).

Previously named ucb34714, BRV has been developed by UCB Pharma during a research plan designed to discover more potent SV2A ligands than levetiracetam (LEV) (3). In particular, BRV has been demonstrated to have a 10 to 30 times higher affinity and selectivity than LEV (3, 8).

3. Brivaracetam pharmacokinetic

Both LEV and BRV share a favourable PK profile since they undergo a rapid and almost complete absorption, resulting respectively in 95% and 100% bioavailability (9).

The time of peak concentration (Tmax) and the mean elimination half-life occur respectively at 0.5-1 and 8-9 hours (9-11). BID administration is suggested in the light of this latter datum (11). Plasma steady state is usually reached within 2 days after BRV initiation (10).

The percentage of protein bound drug to proteins is about 20%, with similar BRV distribution volume and total volume of body water (11). Moreover, food ingestion does not appear to interfere with drug absorption (11).

BRV presents simultaneous pharmacologic peak activity and peak plasma levels, thanks to its high lipogenicity that allows a fast and an unrestricted access to the Central Nervous System (CNS) across the blood-brain barrier (9,12). In addition, it appears that BRV has a higher passive diffusion permeability in comparison to LEV, without evidence of transporter-mediated extrusion from the brain (9).

BRV is primarily metabolized by an amidase (causing hydrolysis of the acetamide group to the carboxylic acid metabolite) and secondly by cytochrome P450 (CYP)2C9 (that hydroxylates the compound forming a hydroxyl-acid metabolite). In addition, CYP2C19 plays a role in an alternative minor metabolic pathway, causing the β-oxidation of the propyl side chain, resulting in a hydroxic acid metabolite. The three main metabolites resulting from the pathways above mentioned (namely the carboxylic, hydroxyl, and hydroxic acids) are inactive (9; 10). BRV is almost completely (>95%) eliminated in the urine in in the form of inactive metabolites for the 91.4% and 8.6 % of unchanged drug in less than 3 days (9).

Age, sex, race and creatinine clearance do not appear to interfere with the pharmacokinetics of BRV (10).

Regarding the interaction with other AEDs, published data suggest that, although enzyme-inducing AEDs (i.e. carbamazepine and phenobarbital) increase BRV clearance, their effect is not clinically relevant, thus not requiring dose adjustments.

Interestingly, when co-administered with valproate (VPA), BRV levels increase by 11%; although, concerning BRV metabolism, VPA appears to inhibit only the CYP2C9 (minorly involved in BRV deactivation), hence, not fully justifying BRV augmented plasma levels (which, anyhow, do not require any further dosage modifications) (2). In a large cohort of patients participating in BRV clinical trials, it has been demonstrated that BRV did not alter the steady-state plasma concentration of several AEDs (i.e., LEV, CBZ, lacosamide, LTG, 10-hydroxy-oxcarbazepine, phenobarbital, pregabalin, phenytoin, topiramate, valproate, and zonisamide) (10). Interestingly, cannabidiol has been recently reported to increase BRV levels by 95–280%, probably due to the cannabidiol-induced inhibition of CYP2C19 (13).

Schoemaker et al. (2), conducted a 2nd phase study involving a pediatric population (NCT00422422; N01263) and demonstrated that the majority of children affected by epilepsy treated with BRV (2.0 mg/kg bid under 8 years and 1.6 mg/kg bid with a maximum of 100 mg bid for patients ⩾8 years) in add-on to 1 to 3 AEDs, reached a similar exposure to adults (2)

It has also been suggested that an age-independent dosing regimen of 2.0 mg/kg bid with a maximum of 100 mg bid would result in profiles comparable to those attained with the weight and age-dependent trial dosing regimen (2).

Furthermore, due to the similarities of LEV and BRV, an immediate switch from LEV to BRV at a ratio from 10:1 to 20:1 is possible (as well as the reverse) (10).

	Patient enrolled	Median Age in y.o.* (range)	Drop out	BRV* average dose	Epilepsy type	Responder*	Seizure freedom	Seizure increased	Total AE*	Serious AE*	AE*	Follow-up in m.*	Conclusions
Gowda et al. 2021 *RT* study*	38	5.9	//	2mg/kg	West Syndrome Lennox Gestaut Syndrome Dravet Syndrome Tuberous sclerosis	36% (14/38)	10%	5.2%	//	Unknown	Drowsiness mood swings	12	BRV has 15- to 30-fold high affinity for synaptic vesicle 2A than LEV*. BRV adjunctive treatment is well tolerated, safe, and effective in children
Liu et al. 2019 *Short-RCT**	100	6.3 (0-16)	10	Increased each week: Patients aged ≥ 8 years: 0.8, 1.6, and 3.2 mg/kg Patients aged < 8 years: 1.0, 2.0, and 4.0 mg/kg (twice daily)	Focal seizures (45%) Generalized seizures (50%) Mixed (5%)	21.3% in the overall sample Focal seizures: 20% for patients under 4 years (n=15) and 36.4% for those aged 4 to 16 years (n=22)	//	//	66 (66%)	2 (6%)	Most commonly (≥ 5%): convulsion irritability, pyrexia, somnolence, decreased appetite	3	Concerning the short-term, adjunctive BRV treatment is well tolerated and effective. Plasma concentrations of BRV and metabolites increased with increasing dose
McGuire et al. 2020 *RT study*	20	12.5 (4-20)	5	3.9 mg/kg	Focal seizures (55%) Generalized seizures (30%) Mixed (15%)	63% (7/11) in Focal seizures No responders in generalized seizures 1/3 responders in mixes seizures	//	//	6 (30%)	0	Minimal side effects (30%), drowsiness (10%), tingling of the extremities (5%), behavioral concerns (15%) No patient discontinued the BRV because of side effects. Discontinued BRV because of lack of efficacy (25%)	8.2	BRV is an effective therapy for refractory focal epilepsy in children older than 4 years of age
Nissenkorn et al. 2019 *RT study*	31	13.8 (6.9-20)	Unknown	3.8 mg/kg ± 1.8	Focal seizures (65%) Epileptic Syndromes (35%)	60% (12/20) in Focal seizures 45.2% in total cohort	//	40% in Focal seizures	3 (9.6%)	1 (3%)	Mild somnolence (6.4%), psychosis (3.2%), nausea (3.2%)	6.7	8 patients had better response to seizures compared to levetiracetam. BRV is an effective add-on treatment in focal, as well as in generalized seizures in

													children, with negligible side effects, including children who failed previously on LEV
Patel et al. 2020 *Meta-analysis*	149	1m*-16	//	0.8-4 mg/kg	Focal seizures (100%)	//	//	//	140 (94%)	30 (20%)	Most commonly (≤20%): pharyngitis (22.1%), convulsion (21.5%), pyrexia (20.1%), somnolence (6.0%), naso-pharyngitis (24.8%)		BRV was generally well tolerated in children aged 4 to <16 years with focal seizures
Schubert et al. 2018 *RT study*	34	12.2 (3-17)	1	2 mg/kg, twice daily	Focal seizures (100%)	47% (16/34)	35% at 6 m. 21% at 12 m.	1/34	4 (12%) at 6 m. 9 (26%) at 12 m.	0	Irritability, Hyperactivity, aggression, somnolence, appetite decrease	3	Use of BRV in children and adolescents seems to be safe and well-tolerated.
Vita-Reni et al. 2020 *RT study*	46	11 (6-13)	26	2.8 mg/kg	Focal seizures (43%) Generalized seizures (52%) Mixed (5%)	54% (13/24) in Focal seizures 30% (6/20) in Generalized seizures	30%	//	20 (43%)	3 (15%)	Drowsiness (17.3%), irritability (17.3%), hyperactivity, somnolence, dizziness, gastro-intestinal symptoms, skin rash	12	BRV is effective in very diverse childhood epilepsies, including some that present with primarily generalized seizures

*y.o: years old; BRV: brivaracetam; LEV: levetiracetam; RCT: randomized clinical trial; RT: retrospective; m.: month; AE: adverse effect

Table 1. List of the retrospective studies and short randomized controlled trials investigating brivaracetam in treating epilepsy.

3. Discussion

Retrospective studies and short randomized controlled trials about BRV have been summarized in table 1 (1, 14-19). In these seven studies, the cohort of patients involved ranges from a minimum of 20 subjects to a maximum of 149, aged from 0 to 20 years old. Only two studies considered subjects with focal seizures, while the others included generalized seizures and epileptic syndromes. Positive responses have been reported with patients affected by Lennox Gastaut Syndrome, Dravet Syndrome, juvenile myoclonic and myoclonic-atonic epilepsy.

The percentage of responders (patients presenting reduction of seizure frequency $\geqslant$ 50%) was variable and appeared to be higher in subjects with focal epilepsy. Among the responders, 10% to 35% achieved seizure freedom, though attention must be paid to the follow-up period. Three studies reported a worsening of seizures in terms of frequency, from 2% to 19% cases.

The analysis of the literature data has demonstrated the safety, well-tolerance and efficacy of BRV in pediatric patients, especially in children aged 4 to 16 years with focal seizures. Adequate response rates were also achieved in patients with encephalopathic epilepsies. Several minor side effects have been reported, such as drowsiness, irritability, pyrexia, which rarely led to discontinuation of therapy (20). Psycho-behavioural adverse events appear less critical than with LEV, so that a switch to BRV can be considered in patients who experience adverse events following therapy with LEV (19). In addition, differently to LEV, the administration of BRV has not been associated with appearance of status gelasticus or gelasticus seizures (21).

In conclusion, although only in a limited sample, efficacy, and tolerability of BRV are showing promising data in pediatric children; following the footsteps of LEV, BRV may be used more frequently in children. Moreover, the good efficacy, PK properties, and high tolerability of BRV, suggest that it may be a suitable anticonvulsant even in status epilepticus, as already hypothesized by other authors (10).

However, further scientific studies need to confirm these promising data, in particular, to verify the efficacy and safety of this drug in children younger than four years old.

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