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Brivaracetam - A newer drug in the management of epilepsy

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Abstract

Epilepsy is one of the most common, serious neurologic diseases, affecting over 65 million people worldwide. Despite the expansion of the anti-seizure drug (ASD) repertoire, with over 16 new ASDs having become available during the past three decades, one-third of patients with epilepsy do not respond to ASD treatment.

Brivaracetam (BRV), a high-affinity synaptic vesicle protein 2A ligand, was initially approved in 2016 by the Food and Drug Administration (FDA) for adjunctive treatment of focal seizures in patients aged 16 years and older. In 2017, the FDA approved a supplemental new drug application for BRV as monotherapy for focal seizures in patients 16 years and older with epilepsy.

Keywords: Brivaracetam, Epilepsy, Synaptic vesicle, Protein 2A Ligand

Introduction

Epilepsy is one of the most common, serious neurologic diseases, affecting over 65 million people worldwide.[1] Despite the expansion of the anti-seizure drug (ASD) repertoire, with over 16 new ASDs having become available during the past three decades,[2] one-third of patients with epilepsy do not respond to ASD treatment.[3]Further, many patients suffer from adverse effects of ASDs, which is responsible for poor adherence and discontinuation of ASD therapy, contributing to increased risk of death and increased utilization of unscheduled care.

Brivaracetam (BRV), a high-affinity synaptic vesicle protein 2A ligand, was initially approved in 2016 by the Food and Drug Administration (FDA) for adjunctive treatment of focal seizures in patients aged 16 years and older. In 2017, the FDA approved a supplemental new drug application for BRV as monotherapy for focal seizures in patients 16 years and older with epilepsy. Since 2018 BRV has been approved as monotherapy and adjunctive therapy in the treatment of partial onset (focal) seizures in patients age 4 years and older.[4-10]

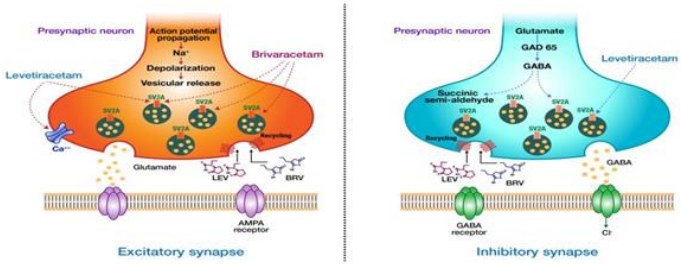
This review discusses pharmacological properties, details of efficacy, tolerability, and safety profiles of BRV.

Pharmacodynamics

SV2A is an integral transmembrane glycoprotein expressed throughout the central nervous system and plays a significant role in regulating neurotransmitter release, although the exact mechanism remains unknown.[11] It has been proposed that SV2A could act

like a transporter or modulate exocytosis of transmitter-containing SVs and modify synaptic function.[11]

BRV is postulated to exert its anticonvulsant action by binding the SV2A and modulating its effect on neurotransmitter release.[12] Although the details of how the binding to SV2A result in its anticonvulsant effect are not known, it is hypothesized that BRV binding may stabilize the conformation SV2A, enabling the protein to fulfill a protective role during seizures.[13]BRV was suggested to inhibit voltage-gated sodium channels (VGSC), however, the reported inhibition of BRV on VGSC currents is not believed to contribute to its anticonvulsant properties.[14]



Pharmacokinetics

Available doses

BRV is available for oral (film-coated tablets of 10, 25, 50, 75, and 100 mg or oral solution 10 mg/mL) and intravenous (injection or infusion, 50 mg/5 mL) use. A recent crossover study demonstrated these formulations to be bioequivalent.[15] BRV 100 mg intravenous bolus also had the same bioavailability to that of 50 and 100 mg tablets.

BRV is rapidly absorbed after oral administration with close to 100% bioavailability.[16] High-fat meals may delay absorption, and prolong peak time from 1 to 3 hrs.[17]For tablets the median time to peak (tmax) after oral intake is approximately 2 hrs., whereas oral solution shows faster absorption with a tmax of 37.8 mins.[17]

Metabolism

BRV is highly lipophilic and can rapidly enter the brain. It crosses the blood–brain barrier (BBB) by passive diffusion without involvement of transporters, and engages with SV2A within minutes.[18]BRV is weakly bound to plasma proteins (<20%) with volume of distribution of 0.6 L/kg.[19]The mean elimination half-life of BRV is around 7–8 hrs, which does not vary with dose.[17]The steady-state concentration is typically achieved after 2 days of repeated dosing.[18] BRV is extensively metabolized in the liver to three inactive metabolites.

Elimination

Elimination of unchanged BRV and its metabolites occurs via kidneys within 72 hrs, with 8.6% of administered dose eliminated unchanged.[14,15] The renal drug clearance approximates 1.68 L/h in healthy subjects.[16] Studies have demonstrated that the pharmacokinetic profile of BRV in elderly and renally impaired subjects is similar to that in healthy subjects.[19] Conversely, severe impairment of liver functions dictates reduction of BRV dose by one third, with a maximal daily dose of 150 mg.[20,21]

Dosage formulation-Oral	25,50,75,100 mg
Intravenous	50 mg/5 ml
Bioavailability	100% (may be delayed by high fat meal)
Time to peak	2 hr
Protein binding	15-20%
Elimination t1/2	7-8 hrs.
Time for steady state	2 hours
Clearance	Via kidney

Drug Interactions

Recent observational studies caution against the concomitant use of BRV and LEV due to concerns of

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severe behavioral disturbance.[22]Concomitant use of BRV and LEV could also unmask masked depression,[22]A dose-dependent and reversible inhibition of carbamazepine epoxide hydrolase (CBZ-E) by BRV could occur when it is co-administrated with CBZ,[23] however a post-hoc analysis of three regulatory randomized clinical trials (RCTs) (N01252, N01253, and N01358) did not support this association

Efficacy/clinical trials

Several double-blind RCTs have reported the safety and efficacy of various doses of oral BRV as adjunctive therapy for uncontrolled focal-onset seizures with or without secondary generalization.

The findings of Phase I study (N01297) in 16 healthy volunteers suggested that the profile of cognitive, subjective, and electrophysiologic effects of BRV is similar to LEV and placebo.[24]In a double-blind, placebo-controlled, parallel-group sequential cohort study of three successive panels of 12 healthy male subjects, BRV was well tolerated at doses of 200–800 mg daily for 2 weeks. Additionally, BRV demonstrated a favorable pharmacokinetic profile, characterized by rapid absorption, volume of distribution limited to total body water, apparent single-compartment elimination, and dose proportionality.[20] In a Phase I randomized open-label, 5-year crossover study involving 25 patients the bioequivalence of oral and intravenous formulations of BRV was established.[15]

An exploratory, Phase IIb, double-blind, randomized, parallel-group, placebo-controlled, dose-ranging study in patients 16–65 years old (N01193) found that adjunctive BRV at a daily dose of 50 mg (but not at 5 or 20 mg doses) was associated with significant reductions in focal seizure frequency per week.[25]In another Phase IIb, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study (N01114), the primary efficacy analysis did not reach statistical significance, however statistically significant differences were observed as compared with placebo on several secondary efficacy outcomes with BRV at a 50 mg daily dose.[26]

A prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose trial (N01253) reported that adjunctive BRV at a daily dose of 50 mg is associated with statistically significant reductions in seizure frequency compared with placebo.[27]In another double-blind, randomized, placebo-controlled trial (N01252), the primary efficacy analysis based on the 50 mg/day dose was not statistically significant.[28] In comparison, BRV at 100 mg/day reduced baseline-adjusted focal seizure frequency/week by 11.7% over placebo, achieving statistical significance (p=0.037). Secondary efficacy analyses, median percent reduction, and >50% responder rate also provided supportive evidence for the efficacy of BRV at 100 mg/day. The third pivotal Phase III randomized, double-blind, placebo-controlled, multicenter study (N01358) reported that adjunctive BRV at 100 and 200 mg/day was efficacious in reducing focal-onset seizures in adults without concomitant LEV use.[29]

Two Phase III, randomized, double-blind, multicenter, historical-controlled, conversion-to-monotherapy studies (N01276; N01306) were conducted to evaluate the efficacy, safety, and tolerability of conversion to BRV 50 mg/day monotherapy in adults with uncontrolled focal seizures.[30]In this study, patients aged 16–75 years, with 2–40 focal seizures per 4 weeks during an 8-week baseline, and on stable doses of 1–2 ASDs were enrolled. Patients were randomized to BRV 50 or 100 mg/day (3:1) in two equal doses without titration. The treatment period comprised 1-week BRV add-on, 8-week baseline

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ASD tapering, and 8-week BRV monotherapy periods. Primary efficacy endpoint was Kaplan–Meier estimate of the cumulative exit rate due to pre-defined exit criteria at Day 112 (50 mg/day, efficacy population). After randomization of 150 patients, both studies were terminated as interim analysis revealed the studies were unlikely to attain a positive outcome for the efficacy analysis, however BRV 50 mg/day monotherapy demonstrated an exit rate lower than historical control.

Indications: Brivaracetam is mainly indicated for the management of partial onset seizure in children >= 4 years and in adults

Dosing

Adults and Children>=16 yrs -25 to 200 mg

Children>=1month to<16 years-<11 kg- start at 0.5 to 1.25 mg/kg bd, max of 6 mg/kg/ day

11-20 kg-start at 0.5-1 mg/kg, max of 5 mg/kg/day

20-50 kg-start at 0.5-1 mg/kg, max of 4 mg/kg/day

>=50 kg-start at 25-50 mg bd /day, max of 200 mg /day

Adverse effects

The overall relative risk for treatment withdrawal due to treatment emergent adverse events (TEAEs) or any reason were 1.58 (1.04–2.40) and 1.27 (0.93–1.73), respectively. The TEAEs significantly associated with BRV were dizziness, somnolence, fatigue, and irritability. The most common psychiatric adverse events (PAEs) were irritability (3.2% of BRV-treated patients vs 1.1% of placebo-treated patients), insomnia (2.9% BRV vs 1.5% placebo), anxiety (2.0% BRV vs 1.3% placebo), and depression (2.0% BRV vs 1.1% placebo) effects [31]

Relative contraindications

No absolute contraindications other than hypersensitivity to the medication. But it should be used with caution in those having history of psychosis or suicidal thoughts, any respiratory ailment and in elderly population.

Use in special population

Pregnancy: Adequate data not available

Lactation: Adequate data not available

Geriatric age: Can be used.

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