Drug Corner

Placement of Oral Formulations of Brivaracetam in Various Patient Profiles: An Indian Perspective

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Brivaracetam (BRV), an analog of levetiracetam (LEV), lowers seizure frequency through a unique mechanism. Although BRV is approved for focal epilepsy in patients aged ≥1 month (by the US Food and Drug Administration) or ≥16 years (in India), clinical studies have suggested its potential role in other indications such as generalized seizures, secondarily generalized tonic-clonic seizures, and drug-resistant focal epilepsy, and in certain special populations. Here, we discuss the potential role of BRV in different patient populations and present expert opinions for positioning the pre-existing and newly available oral formulations of BRV to aid both clinicians and diverse patient groupswith a simple and easy dosing and titration-based treatment, including safe and effective switching from LEV to BRV.

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Globally, over 65 million people are affected by epilepsy, making it the fourth common neurological disorder[1]. India shares nearly one-sixth of the global disease burden as approximately10–12 million people live with epilepsy in the country[2]. Brivaracetam (BRV), an analog of levetiracetam (LEV), decreases the excitability in hyperexcited neurons by binding to SV2A within the presynaptic axon terminal, which prevents neurotransmitter release from synaptic vesicles[3]. Currently, BRV has been approved for monotherapy and adjunctive therapy of focal-onset seizures in patients aged ≥1 month by the United States Food and Drug Administration (USFDA) [4]and for adjunctive therapy of patients aged ≥16 years by the Drugs Controller General of India (DCGI)[5].

Brivaracetam is a third-generation Anti-Seizure Drug (ASD) whose efficacy at doses 50-200 mg/day has been demonstrated by clinical studies[9]. Additional benefits of BRV include low potential for interdrug interactions, except for carbamazepine and rifampicin[1,4], and a favorable cognitive profile,similar to LEV[4,6]. Brivaracetam is now available in the following oral formulations: film-coated oral tablets of 10,25,50, 75, and 100 mg strengths and oral syrup (10 mg/mL)[1]. Patients intolerant to LEV owing to psychiatric adverse

Editor's Comment :

- Brivaracetam is a promising therapeutic option for the treatment of epilepsy patients with a wide range of patient profiles and forms of epilepsy. Clinicians and patients will benefit from the availability of a range of oral BRV formulations and strengths.

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events and those with uncontrolled seizures due to inefficacy of LEV can be immediately switched to BRV[13,18] and can also be easily switched over to LEV[7]. The safety of switching from LEV to BRV has been clearly demonstrated in multiple studies as it has improved mental health symptoms related to LEV[8, 9-15].

A series of advisory board meetings were held across different cities in India from May 2021 to June 2021. The experts included neurophysicians, neurosurgeons, and pediatric neurologists. The objective of these meetings was to understand different patient profiles for various strengths of oral BRV formulations, switching scenarios from LEV to BRV, and positioning different strengths of oral formulations across different patient profiles. The present article summarizes the literature evidence related to oral BRV formulations and the expert opinions formed during these advisory board meetings.

Positioning Brivaracetam According to Patient Characteristics :

There is extensive literature to demonstrate the efficacy and tolerability of BRV in epilepsy patients including adults with focal epilepsy [16-18], adults with generalized epilepsy[19], pediatric population[20, 21], elderly population[22], patients in ICU[1], and patients with renal[23]and hepatic[24] impairments.

The expert opinions on BRV initiation, titration, switching, and use in different patient populations are presented in Table 1.

Table 1 — *Expert opinions on the use of BRV in different clinical scenarios and patient populations*

Expert Comments for Various Scenarios
I. BRV initiation and titration ■ BRV can be initiated at 50 mg/day and then gradually up titrated by 50 mg/week to achieve target dose of 100 mg twice daily in 3–4weeks. ■ BRV can be initiated as monotherapy in a few patients who are prone to develop behavioral adverse events. ■ Pediatric patients have high chances of somnolence; therefore, BRV should be initiated at lower doses and then up titrated. ■ Dosage break-up can be followed in patients with day-time sedative effects of BRV; 25 mg BRV as morning dose and 75 mg BRV at night. ■ BRV can be initiated at a higher dosage among patients with high seizure frequency or already using LEV. ■ BRV should not be stopped directly, but it is recommended to down-titrate it to 20 mg twice daily before withdrawal. ■ BRV 25-mg tablet is useful in down-titration/up-titration.
II. Switching from LEV to BRV: ■ A gradual switch should be preferred among patients with LEV inefficacy to prevent breakthrough seizures and behavioral breakdown. ■ LEV dosage among patients on higher doses (2–3 g/day) should be down-titrated to at least 50 mg before stopping it; BRV should be initiated during down-titration of LEV and gradually up-titrated to avoid breakthrough seizures. ■ While switching without titration (immediate switch), a conversion factor of 10:1 to 15:1 is used. If the dose of LEV is 1–1.5 g/day, then a 10:1 conversion ratio should be used. For LEV doses >1.5 g/day, a 15:1 dose conversion ratio should be used. ■ An overnight switch to BRV can be preferred in patients with LEV intolerance or in place of BRV oral tablets. ■ The BRV switch works relatively better in LEV-intolerant patients as compared to LEV-inefficacious patients.

III. BRV based on seizure type (focal/generalized/multiple seizures)

- BRV is used in both focal and generalized seizures and used as an add-on drug in refractory epilepsies.
- Clinically, BRV is not so good in myoclonic spasms and absence seizures.

IV. BRV in pediatric patients

- Based on USFDA approval, BRV can be used in children and adolescents with drug-resistant epilepsy under dire situations.
- Oral syrup is the most preferred choice for children <7 years.
- Accurate dose titration is essential for syrup.
- Oral syrup is the only option for children on a feeding tube or those who cannot swallow.
- A 10mg oral BRV tablet can be used to counter syrup palatability.
- BRV is good for focal seizures, generalized tonic-clonic seizures, and multiple seizures.
- Availability of sugar-free BRV formulation could be beneficial in children on a ketogenic diet (children with autism and attention-deficit/hyperactivity disorder).

V. BRV in elderly population

- The influence of polypharmacy (due to comorbidities) and renal/hepatic impairments should be considered among the elderly while deciding the dosage of ASD. A minimum dose of ASD is preferred for this patient population.
- Availability of an easy dosing schedule of BRV for elderly patients will ensure better compliance.
- Availability of small-sized BRV tablets will help overcome swallowing difficulties.
- BRV is a good option since no dosage adjustments are not necessary for BRV owing to minimal drug-drug interactions.
- BRV is initiated at 50 mg twice daily, and if required, it is uptitrated to 100 mg twice daily.
- BRV is very useful for acute seizures in elderly patients, such as hypoglycemia-induced seizures.
- Use of oral syrup is also common in elderly patients, especially in patients on nasogastric tube.

VI. BRV in patients admitted to the ICU

- The oral syrup of BRV is useful for patients on Ryle's tube in the ICU setting.
- If intravenous BRV formulation is not available, the oral solution can be used.

VII. BRV in neurosurgery, post-trauma, and brain tumor-related patients

- BRV is mostly for prophylactic use in post-trauma or tumor cases.
- In patients not tolerating LEV, BRV is used as a switching drug.
- In post-trauma surgery patients, BRV showed good efficacy with minimal side-effects.
- Sufficient data exists showing efficacy of BRV in tumor epilepsies.

VIII. BRV in hepatic and renal impairment

- In patients (adult patients $\geq$16 years and pediatric patients weighing $\geq$ 50 kg) with hepatic impairment, 25 mg twice daily is the recommended dose with 75 mg twice daily as the maximum dose.
- Owing to its hepatic involvement, BRV should be avoided in tuberculosis patients. Furthermore, drug–drug interactions may reduce the efficacy of both AKT and BRV in these patients.
- Dose adjustments are not required for patients with impaired renal function. It is however, not recommended in end-stage renal disease undergoing dialysis.

**According to DCGI regulations BRV is approved as an adjunctive therapy for partial-onset seizure patients aged $\geq$16 years. The opinions expressed here are that of the experts and referral to country wise regulations is suggested before usage.*

ASD: Antiseizure drug; BRV: Brivaracetam; FDA: The Food and Drug Administration; ICU: Intensive care unit; LEV: Levetiracetam; AKT: a combination of four antituberculosis drugs, namely rifampicin, isoniazid, pyrazinamide, and ethambutol.

Positioning Different Strengths of Brivaracetam in the Indian Setting :

BRV at doses 50, 100, and 200 mg/day have been found to be effective and well-tolerated in Indian patients (aged 16–80 years) with uncontrolled focal epilepsy[25] and at dose of 2 mg/kg/day in children with refractory epilepsy[26]. Table 2 summarizes the expert opinions on positioning the newly available strengths (10-mg, 25-mg, and 75-mg) of the oral formulations of BRV.

Conclusion

BRV is a promising therapeutic option for the treatment of epilepsy across the diverse spectrum of patient populations as well as epilepsy types.

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Table 2 — *Expert opinions on positioning the newly available strengths of BRV oral formulations**

Expert Comments on Positioning Different Strengths and Oral Formulations of BRV
I. Oral solution vs. 10-mg tablets ■ Scoring the 50-mg tablet is difficult in children; so syrup or 10-mg tablet will be very useful. ■ Syrup and not 10-mg tablet may be preferred in kids requiring lower dosage.
II. Clinical scenario for oral solution ■ Most useful in children with global developmental delay or encephalopathy. ■ Elderly patients (especially those with difficulty swallowing tablets) and comatose patients. ■ Children aged 5–8 years who can swallow the tablet, but are more compliant with syrup. ■ Switching from IV BRV to oral preparation (syrup) among hospitalized patients.
III. Clinical scenario for 10-mg and 25-mg tablets ■ When oral solution is not available. ■ When children have palatability issues with oral solutions. ■ Children on a keto diet, who cannot be given sugar-containing oral solutions. ■ Presently, there are only 50-, 75-, and 100-mg tablet options available, which could be effectively used in the adult population. However, usage of these tablets may be troublesome in pediatric or adolescent patients requiring lower dosages; scoring the tablet may not ensure adequate dosage. ■ Lower-strength preparation is promising in pediatric patients as the initial dose is 0.5–1 mg/kg. With 10- and 25-mg tablet and syrup availability, there will be flexibility of dose option and the dose titration is easy, especially with the syrup.
IV. Clinical scenario for 25-mg and 75-mg tablets ■ Patients on 50 mg twice daily dosage with complaints of drowsiness or sedation can be asked to take 25- mg during the day, whereas 75 mg tablet can be used in the night. ■ 25-mg and 75-mg doses can also be used in patients with renal or hepatic impairment. ■ For obese patients, the dose can be increased from 50 mg twice daily to 75 mg twice.
**According to DCGI regulations BRV is approved for adjunctive therapy of partial-onset seizures in patients aged >16 years. The opinions expressed here are that of the experts and referral to country wise regulations is suggested before usage.*
BRV: Brivaracetam; IV: intravenous

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