Drug Corner

Brivaracetam Intravenous Formulation in Epilepsy Management in India : A Position Statement

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Brivaracetam (BRV), a propyl analog of levetiracetam, has been shown to be safe and effective in Indian patients with uncontrolled focal epilepsy. A series of advisory board meetings involving pediatricians, neurologists, and physicians were held across India to evaluate the role of IV BRV in India and formulate a position statement. The panelists opined that the potential role of BRV in the acute management of increased seizure activity, especially status epilepticus, should be explored in the Indian context. Further, there is a dearth of Indian studies on the use of BRV in epilepsy patients aged below 16 years. IV BRV holds great potential to be the therapy of choice in epilepsy management owing to the fast mode of action and lesser risk of adverse effects.

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Epilepsy is the most common neurological disease with about 50 million people living with epilepsy globally. About 80% of these people live in low- and middle-income countries[1], with India contributing to one-sixth of this population[2]. Approximately 70% of the individuals with epilepsy could live seizure-free following appropriate diagnosis and management[1]. The occurrence of seizures can be prevented with the use of antiseizure drugs (ASDs) that include valproate, ethosuximide, Levetiracetam (LEV), lamotrigine, oxcarbazepine[3]. Complete freedom from epilepsy, safety, tolerability, and potential risk of adverse reactions are significant limitations of the currently available ASDs[4]. Other concerns include relapse following discontinuation of medication, limited efficacy, withdrawal symptoms, interaction with other medications, economic burden[5], and implications in terms of contraception, pregnancy, and teratogenicity[6].

Brivaracetam (BRV), an analog of LEV,is available as oral (tablets and oral solution) and IV (injection or infusion) formulations[7]. It has been studied in different forms of epilepsy, and different patient populations, including the pediatric and the elderly. As compared to other ASDs, BRV has a unique and rapid mechanism of action with lower adverse effects[7]. However, evidence is scarce on the use of intravenous (IV) BRV in Indian patients, especially the pediatric population. Given the potential of any IV ASD in situations of emergency, such as acute seizures or status epilepticus, there is an unmet need to position the use of IV BRV in the Indian setting.Thus, a series of advisory board meetings involving physicians, pediatricians, and neurologists were held in some of the major cities of India to discuss the role of IV BRV and its current positioning in epilepsy management in India. Recommendations made by experts, during these meetings, related to its use have been discussed here.

Editor's Comment :

- Brivaracetam (BRV) has a unique and rapid mechanism of action. Intravenous BRV can rapidly cross the blood–brain barrier. It has excellent tolerability and lacks significant drug interactions. The role of intravenous BRV in the acute management of epilepsy should be explored in the Indian context.

Common Indications for IV ASDs :

Intravenous ASDs are commonly indicated for the management of acute repetitive seizures and status epilepticus and as temporary replacement therapy in patients who are unable to take oral medications[8, 9]. Administration through IV route ensures complete bioavailability with rapid delivery. Some of the commonly used IV formulations for seizure

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emergencies include diazepam, lorazepam (LZP), clonazepam, midazolam, LEV, valproic acid, and lacosamide[8].

BRV was approved by the US Food and Drug Administration (USFDA) initially as an adjunctive treatment for focal seizures in patients aged 16 years and older. Supplemental application as monotherapy for focal seizures for the same agegroup was approved in 2017. In 2018, the USFDA approved the use of BRV as monotherapy and adjunctive therapy for the management of partial-onset (focal) seizures among children aged 1 month and older[7, 10].

BRV IV Formulation : Clinical Evidence :

Numerous double-blind, randomized, controlled trials have evaluated the safety and efficacy of oral BRV (in different doses) administered as adjunctive therapy for the management of uncontrolled focal-onset seizures. These studies have reported that BRV was effective and well tolerated at doses of 200–800 mg/day[7].Bioequivalence of oral and IV formulations has been established in a 5-year, phase I, randomized, open-label, and cross-over study[11]. According to the USFDA recommendations, the IV formulation of BRV should be administered at the same dosage and frequency as oral formulations[10]. The Drugs Controller General of India (DCGI) has approved IV BRV as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy[12].

The availability of IV formulation, rapid entry across the blood–brain barrier, excellent tolerability, and lack of significant drug interactions suggest the potential beneficial role of BRV in status epilepticus[13]. Studies that have evaluated the safety and efficacy of BRV in status epilepticus have been enumerated in Table 1.

A systematic review that evaluated the clinical efficacy and tolerability of IV BRV in the treatment of status epilepticus reported BRV to be a safe option among patients with status epilepticus[18]. Nevertheless, long-term studies involving a larger cohort are necessary to further establish the role of BRV in the management of status epilepticus.A recent phase II randomized trial comparing the safety and efficacy of IV BRV vs. LZP for the acute treatment of increased seizure activity showed that after 12 hours of treatment with BRV, more patients became seizure-free as compared to LZP[19].The potential beneficial role of BRV in the acute management of increased seizure activity noted in this trial,however, needs further exploration.

Expert Opinion on Positioning IV BRV in Indian Scenario :

The opinions of experts on IV BRV in epilepsy management are summarized in Box 1.

Table 1 — *Studies evaluating the safety, efficacy, and tolerability of IV BRV*[14-17]

Authors, year	Study design	Patient population	Dosage	Study outcomes
Klein *et al*., 2016[17]	Phase III, multicenter, randomized, four-arm, parallel-group study	Patients aged 16–70 years with focal or generalized epilepsy uncontrolled by 1–2 antiepileptic drugs	7-day baseline period, 7-day double-blind run-in period (oral BRV 200 mg/day or placebo twice daily), and 4.5-day open-label evaluation period (IV BRV 200 mg/day twice daily; 2-minute bolus or 15-minute infusion, total nine doses)	IV BRV was well tolerated in general; tolerability when administered as a bolus or infusion similar to that of oral BRV tablets.
Strzelczyk *et al*., 2017[14]	Retrospective cohort study	Patients with refractory or super-refractory SE; n=11	Median loading dose: 100 mg (range: 50–400 mg), titrated up to a median dose of 200 mg/day (range: 100–400 mg)	Cessation of SE was noted within the first 24 hours in 27% of patients. No serious adverse effects were noted.
Kalss *et al*., 2018[15]	Retrospective, single-center study	Patients with SE; n=7	Median loading dose: 100 mg over 15 minutes (range: 50–200 mg)	Immediate clinical and electrophysiological improvement was noted in 29% of patients; improvement in median Glasgow outcome scale score in 86% of patients. No adverse outcomes in terms of cardiorespiratory function.
Aicua-Rapun *et al*., 2019[19]	Retrospective, single-center study	Patients with SE; n=14	Different dosages	50% of patients responded to BRV. The probability of response was higher with BRV doses >1.9 mg/kg.

BRV: Brivaracetam; IV: Intravenous; SE: Status epilepticus.

Box 1. *Expert Opinion on IV BRV's Place in Epilepsy Management in the Indian Setting*

- IV ASDs are used during brain surgery after head injury, before posterior fossa surgery in shunt and extraventricular drain, in SE, acute repetitive seizures, and in epilepsy patients unable to take oral medications.
- IV BRV seems useful in status epilepticus, acute repetitive seizures and situations where oral ASDs cannot be administered.
- IV formulations frequently used in India include valproate, phenytoin, fosphenytoin, lacosamide, and LEV. Among these, LEV is preferred and commonly used owing to its efficacy and lesser risk of adverse effects.
- IV BRV has the potential to become the drug of choice since it has lesser adverse effects compared to LEV. However, the cost can be a concern.
- Speed of action is important in the treatment of acute seizures and status epilepticus; this aspect depends on the lipid solubility of the drug being administered. BRV has a faster mode of action, especially the IV formulation.
- Switching from other IV formulations to IV BRV will require time as patients' confidence and data from various patient profiles and comorbidities must be assessed further.

ASDs: antiseizure drugs; LEV:levetiracetam; BRV: brivaracetam; IV: intravenous; SE: status epilepticus

Conclusion :

The injectable formulation of BRV is available in India. IV BRV is likely to become an important addition in the parenteral ASD repertoire. However, its potential role in the acute management of increased seizure activity and the treatment of status epilepticus need further investigation, with promising results confirmed in larger trials.

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