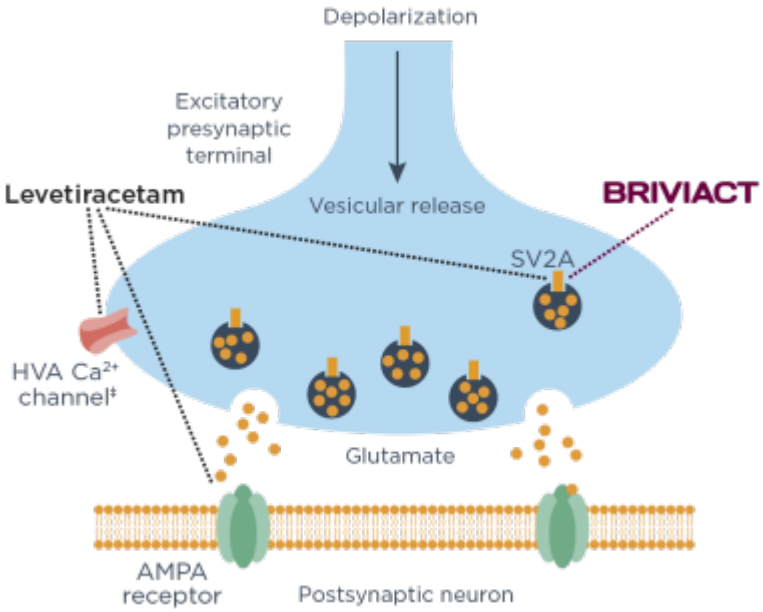
Brivaracetam



Brivaracetam (trade name Briviact), a chemical analog of levetiracetam, is a racetam derivative with anticonvulsant (antiepileptic) properties.

Brivaracetam is the 4R-propyl analogue of the anticonvulsant levetiracetam.

Indications

Brivaracetam is used to treat partial seizures with or without secondary generalisation, in combination with other antiepileptic drugs. No data are available for its effectiveness and safety in patients younger than 16 years.

Adverse effects

The most common adverse effects include sleepiness, dizziness, nausea and vomiting. More rarely, coordination problems and changes in behaviour can occur.

Interactions

Coadministration of brivaracetam with carbamazepine may increase exposure to carbamazepine-epoxide, the active metabolite of carbamazepine, and could theoretically lead to reduced tolerability. Coadministration of brivaracetam with phenytoin may increase phenytoin levels. Coadministration of other antiseizure drugs are unlikely to affect brivaracetam exposure. Brivaracetam provides no added therapeutic benefit when administered in conjunction with levetiracetam that acts on the same protein.

[[mechanism of action]]

Brivaracetam is believed to act by binding to the ubiquitous synaptic vesicle glycoprotein 2A (SV2A), like levetiracetam. but with 20-fold greater affinity.

There is some evidence that racetams including levetiracetam and brivaracetam access the luminal side of recycling synaptic vesicles during vesicular endocytosis. They may reduce excitatory neurotransmitter release and enhance synaptic depression during trains of high-frequency activity, such as is believed to occur during epileptic activity.

Pharmacokinetics

Brivaracetam exhibits linear pharmacokinetics over a wide dose range, is rapidly and completely absorbed after oral administration, has an elimination half-life of 7 to 8 hours, and has plasma protein binding of less than 20%. It is extensively metabolized (>90%), primarily via hydrolysis of the acetamide group, and secondarily through hydroxylation mediated by the liver enzyme CYP2C19. The three major metabolites (hydroxy, acid, and hydroxyacid) are pharmacologically inactive. Brivaracetam is eliminated as urinary metabolites, with over 95% of a radioactive test dose recovered in the urine within 72 hours, including only 8.6% as unchanged brivaracetam.

Pharmacogenetics

As noted above, brivaracetam is primarily metabolized by hydrolysis, via amidase enzymes, to an inactive metabolite. To a lesser extent, it is also metabolized by a minor metabolic pathway via CYP2C19-dependent hydroxylation. Individuals who have no CYP2C19 enzyme activity, “CYP2C19 poor metabolizers”, will have a greater exposure to standard doses of brivaracetam. Because they are less able to metabolize the drug to its inactive form for excretion, they may have an increased risk of adverse effects. The most common adverse effects of brivaracetam therapy include sedation, fatigue, dizziness, and nausea. The FDA-approved drug label for brivaracetam states that patients who are CYPC19 poor metabolizers, or are taking medicines that inhibit CYP2C19, may require a dose reduction.

History

Positive preliminary results from stage III trials were recorded in 2008, along with evidence that it is around 10 times more potent for the prevention of certain types of seizure in mouse models than its analogue levetiracetam.

On 14 January 2016, the European Commission, and on May 12, 2016, the Food and Drug Administration approved brivaracetam under the trade name Briviact. The Drug Enforcement Administration (DEA) has issued an interim final rule placing brivaracetam into schedule V of the Controlled Substances Act (CSA) effective Mar 09, 2017. As of May 2016, brivaracetam is not approved in other countries, including Australia, Canada and Switzerland.

In a review, Palleria et al., conducted an online database search using Medline, PubMed, Embase, and the Cochrane Online Library to review the available studies highlighting the clinical relevance of side effects, pharmacological interactions, safety and tolerability of the newest AEDs: Brivaracetam (BRV), Cannabidiol (CBD), Eslicarbazepine acetate (ESL), Lacosamide (LCM), and Perampanel (PER).

The principal benefit of the newest AEDs, in addition to reduced frequency and seizure severity, is the low number and severity of ADRs reported compared to more historic drugs.

Early detection of ADRs could lead to an improvement in patients' quality of life, therefore it is important to monitor ADRs and to adequately perform post marketing surveillance in the clinical practice setting [1)]

A cohort study from two German university hospitals aimed to ascertain the possible use of brivaracetam (BRV) as an option for treatment of status epilepticus (SE).

A review of medical records was carried out to detect BRV administration in SE patients treated in Frankfurt and Greifswald during the period February 2016 to January 2017. The primary outcome question concerned SE resolution after BRV initiation.

During that period, BRV was started with eleven adult patients with SE. Five of these were female, and the median age was 64 (interquartile range [IQR] 21years). The median SE duration before BRV initiation was 5days (IQR 9days); the median number of previous anticonvulsants used was 4 (IQR 5). Initial BRV doses ranged between 50mg and 400mg (median 100mg), titrated to a daily dose of 100 to 400mg (median 200mg). There was a cessation of SE in the first 24h of BRV in three patients (27%). While taking BRV, no serious side effects were seen.

Based on these cases and previous data from animal experiments, BRV may prove useful in SE treatment, and trials would be warranted to examine BRV's efficacy in treating SE and how this efficacy might be influenced by co-administration with levetiracetam [2)].

In 2016 two prospective, randomized, double blind studies investigating the novel SV2A ligand, brivaracetam, in genetically confirmed Unverricht-Lundborg patients have been performed with disappointing results. When treating PMEs, particular care should be paid to avoid drugs known to aggravate myoclonus or myoclonic seizures, such as phenytoin, carbamazepine, oxcarbazepine, lamotrigine, vigabatrin, tiagabine, gabapentin, and pregabalin. The emergency treatment of motor status, which often complicates the course of PMEs, consists of intravenous administration of benzodiazepines, valproate, or levetiracetam [3)].

A analysis provided Class I evidence that adjunctive BRV is effective in reducing partial-onset (focal) seizures (POS) frequency in adults with epilepsy and uncontrolled seizures [4)].

The effect of BRV on action myoclonus was not statistically significant. However, action myoclonus

score showed wide intrapatient variability and may not have been the optimal tool to measure severity of myoclonus in EPM1. Both studies had very high completion rates (95.3% overall), and a high percentage of patients (88.7% overall) entered long-term follow-up; both likely to be influenced by good tolerability. These studies demonstrate the feasibility of rigorous trials in progressive myoclonic epilepsy [5].

In 2015 a study confirmed significant effects of BRV as adjunctive treatment of refractory partial seizures. This study also demonstrated the good tolerability profile of adjunctive BRV for patients with epilepsy. Further large clinical and pharmacovigilance studies are needed to investigate the long-term efficacy and safety of BRV and, furthermore, to suggest an optimal BRV dosage for clinical use [6].

References

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