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Safety and efficacy of cenobamate in patients with uncontrolled focal seizures - a review of the literature

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Abstract

Epilepsy is one of the most common diseases of the nervous system, characterized by the occurrence of recurrent and unprovoked seizures, which are an expression of abnormal brain activity associated with sudden and excessive bioelectric discharges. Partial seizures come from specific areas of the brain. They can run with motor, autonomic, sensory, and

psychological symptoms. Currently, new active substances are sought that can be used in the treatment of drug-resistant partial seizures.
The aim of the study is to evaluate the safety and efficacy of cenobamate in the treatment of patients with uncontrolled, partial seizures. Our study material consisted of publications, which were found in PubMed, Google Scholar, and Embase databases. In order to find the proper publications, the search has been conducted with the use of a combination of keywords like: “cenobamate”, “focal seizures”, “cenobamate in epilepsy”. The first step was to find proper publications from the last 10 years. The second step was to carry out an overview of the found publications.
Studies have shown that treatment with cenobamate significantly improved seizure control in adults with uncontrolled focal seizures. Long-term use of cenobamate is safe and well-tolerated by patients. Most adverse events are mild or moderate.

Key words: cenobamate; focal seizures; epilepsy; epilepsy treatment;

INTRODUCTION AND PURPOSE

Epilepsy is one of the most common diseases of the nervous system. It is characterized by the occurrence of recurrent and unprovoked convulsions, which are an expression of abnormal brain activity associated with sudden and excessive bioelectric discharges [1,2,3]. The frequency of active epilepsy is 6.4 per 1,000 people. Whereas the one-time occurrence rate of epilepsy is 7.6 per 1000 people [4]. The goal of therapy is to eliminate epileptic seizures, and this is achieved in most cases. Unfortunately, as many as 25% of patients are resistant to treatment, despite proper treatment, which includes taking appropriate doses of drugs in various combinations, sometimes multi-drug [5]. Therefore, new active substances that can be used in the treatment of drug-resistant epilepsy are constantly searched for.

Cenobamate (CNB) is a new carbamate derivative of alkyl tetrazole [6,7]. In 2019, it was approved by the US Food and Drug Administration (FDA) as an anti-epileptic drug for the treatment of uncontrolled partial seizures in adults [8,9]. This drug has a dual mechanism of action. It enhances the inactivation of voltage-gated sodium channels, showing a preference for inhibition of the persistent component of the sodium channel (INaP) [10]. Additionally, it is an allosteric positive modulator of the gamma-aminobutyric acid receptor GABAA, to which it binds at the non-benzodiazepine site [11]. INaP is one of the key factors in the generation of repetitive action potentials, therefore the blocking effects of cenobamate may have an anti-epileptic application [10]. The aim of the study is to evaluate the safety and efficacy of cenobamate in the treatment of patients with uncontrolled, partial seizures. Our study material consisted of publications, which were found in PubMed, Google Scholar, and Embase databases. In order to find the proper publications, the search has been conducted with the use of a combination of keywords like: “cenobamate”, “focal seizures”, “cenobamate in epilepsy”. The first step was to find proper publications from the last 10 years.

The second step was to carry out an overview of the found publications. Three studies have been included in the writing of this review. Two of them are multi-center, double-blind, randomized, controlled-group phase 2 trials in which the efficacy and safety of CNB were assessed. The third work is a phase 3, multicentre, open-label study designed to evaluate the long-term safety of cenobamate and its effect on the concomitant use of phenytoin and phenobarbital.

RESULTS

Efficacy and safety of cenobamate in patients with uncontrolled focal seizures

Kraus et al. in their multicenter, double-blind, randomized, placebo-controlled, dose-response study enrolled 437 adult patients with uncontrolled, focal seizures (aged 18-70 years). After an 8-week baseline assessment, patients were randomly assigned (1:1:1:1) to a placebo, cenobamate 100mg per day, 200mg per day, or 400mg per day. The study consisted of a 6-week titration phase and a 12-week maintenance phase. The primary outcomes were changes in 28-day seizure frequency from baseline in the modified intention-to-treat population and responder rates analyzed in the maintenance phase population. Safety and tolerability were compared across groups for all randomized patients.

The median reduction in seizure frequency was 24.0% for the placebo group compared with –35.5% for the 100 mg dose group, –55.0% for the 200 mg dose group, and –55.0% for the 400 mg dose group. Adverse events occurred in 70% in the placebo group, 65% in the 100 mg group, 76% in the 200 mg group, and 90%) in the 400 mg group. The percentage of patients who had at least one treatment-emergent adverse event (TEAEs) was 70% in the placebo group, 65% in the 100 mg cenobamate group, 76% in the 200 mg group, and 90% in the 400 mg group. The most common (>10%) were somnolence, dizziness, headache, fatigue, and diplopia. There was one serious case of drug reaction with eosinophilia and systemic symptoms (DRESS). No clinically meaningful results were observed in changes from baseline in hematology, clinical chemistry, laboratory values, ECG studies, vital signs, or physical or neurological examinations [12].

In a multicenter, double-blind, randomized, placebo-controlled study, Chung et al. enrolled 222 adults from 18 to 65 years of age, with uncontrolled, focal seizures. They were randomly assigned (1:1) to the placebo or cenobamate group after an 8-week baseline period. The treatment period consisted of a 6-week titration phase and a 6-week maintenance phase. The primary outcome were changes (from baseline) in 28-day seizure frequency during the double-blind treatment phase.

Compared to placebo, CNB got a greater median percent seizure reduction - 55.6 % vs 21.5%. 28.3% of cenobamate-treated and 8.8% of placebo-treated patients were seizure-free, during the maintenance phase. TEAEs were reported in 76.1 % of patients treated with cenobamate and in 63.3% of patients treated with placebo. The most common TEAEs (>10%) were somnolence, dizziness, headache, nausea, and fatigue. One drug hypersensitivity reaction of moderate-intensity was reported. No other serious dermatologic TEAEs, including cases of drug reaction with eosinophilia and systemic symptoms or Stevens-Johnson

syndrome. There were no clinically meaningful changes in laboratory values, physical and neurologic examinations, vital signs, or ECGs [13].

Sperling et al. enrolled 1347 patients 18-70 years with uncontrolled, focal seizures taking stable doses of one to three antiseizure medications (ASM). Patients started taking CNB 12,5 mg per day. The dose of CNB increased at 2-week intervals to 25, 50, 100, and 200 mg per day. Then biweekly 50 mg/d increases to 400 mg/d were allowed. During the titration phase, phenytoin/phenobarbital doses could be decreased by 25-33%.

Somnolence (28.1%), dizziness (23.6%), and fatigue (16.6%) were the most common TEAEs. 108 patients had serious TEAEs: seizure (14), epilepsy (5), pneumonia, fall, and dizziness (4 each). No cases of DRESS. suggesting that initiating cenobamate at a low dose and slowing the titration rate may lower the risk of DRESS. 43.4 % of patients in the phenytoin group and 29.7% of patients in the phenobarbital group decreased their doses. Mean levels of phenytoin and phenobarbital in plasma were comparable to baseline [14].

Quality of life and outcome during up to eight years of treatment of focal-onset seizures with cenobamate

Elizebath R. et al. described their experience optimizing cenobamate treatment for 49 patients treated at one center for up to eight years. They assessed the influence of treatment response on measurements of quality of life (QOLIE). Forty-nine patients were evaluated from three cenobamate regulatory trials: two open-label extensions of randomized placebo-controlled studies and one open-label safety study at the Johns Hopkins Hospital (JHU). Patients had focal-onset seizures despite treatment with one to three ASMs and were 18 years of age and older. Patients kept seizure diaries for the duration of the study and had tri-monthly evaluations. Seizure responder rates were determined, and patients with long-term seizure freedom (≥six months seizure-free) were identified. Cenobamate doses were adjusted within the range of 100-400 mg/day. Johns Hopkins Hospital patients who were continuing treatment when the studies ended (n = 37) were administered the QOLIE-31 survey and a separate survey to assess changes in independence and epilepsy-linked disability at the end of the study at JHU. Thirty-seven of 49 (76%) patients continued treatment for three to eight years (median 5.6 years). In their final three months of treatment, 45% of patients achieved ≥75% seizure reduction, 29% had ≥90% reduction, and 16% were seizure-free (responder rates computed with n = 49). Posttraumatic etiologies did not reduce treatment responses. Increased dosage of cenobamate across the 150-400 mg/day range was significantly associated with higher responder rates ($p < 0.001$). High seizure responses-particularly ≥90% reduction-correlated with high QOLIE scores [15].

Mass balance, metabolism, and excretion of cenobamate after a single oral administration

The study conducted by Vernillet L. was designed to assess the mass balance and the metabolic profiling of cenobamate in humans. Absorption, metabolism, and excretion of cenobamate were investigated in healthy male subjects after a single oral dose of 400 mg of cenobamate containing 50 μCi of [14C]-cenobamate as a capsule formulation.

Cenobamate was rapidly (median time to maximum plasma concentration of 1.25 h) and extensively (≥ 88% of dose) absorbed. The mean cenobamate plasma concentration-time profile revealed a multiphasic elimination profile whereas the mean plasma/blood concentration-time curve for total radioactivity did not appear to be multiphasic, suggesting that elimination mechanisms for cenobamate and its metabolites may be different. Blood/plasma ratios observed for the area under the concentration-time curve (AUC) and peak concentration (both ~ 0.60) suggest a limited penetration of cenobamate and metabolites into red blood cells (RBCs). Eight cenobamate metabolites were identified across plasma, urine, and feces. Cenobamate was the main plasma radioactive component and M1 was the only metabolite detected in plasma (> 98% and < 2% total radioactivity AUC, respectively). All detected metabolites were found in urine, with M1 as the major radioactive component (mean cumulative recovery 37.7% of dose); unchanged cenobamate accounted for 6%. Metabolites comprised ~ 88% of the dose recovered in urine, indicating extensive metabolism by the kidneys, and/or metabolites formed in the liver were rapidly eliminated from the bloodstream. However, cenobamate metabolites appear to be formed slowly. Minor amounts of cenobamate (0.48%) and five metabolites (≤ 1.75% each; M1, M3, M6, M7, M11) were recovered in feces [16].

CONCLUSIONS

1. Adjunctive treatment with CNB improves seizure control in a dose-related fashion.
2. Most treatment-emergent adverse events were mild or moderate in severity.
3. Cenobamate was generally well tolerated in the long term.
4. No cases of DRESS suggest that initiating cenobamate at a low dose and slowing the titration rate may lower the risk of DRESS.
5. Reductions of phenytoin and phenobarbital dose, during cenobamate titration, maintained stable plasma levels.
6. Patients with drug-resistant focal-onset epilepsy had stable treatment responses during up to eight years of cenobamate treatment, they tolerated high doses of cenobamate. High responders appeared to benefit with high QOLIE scores.
7. Cenobamate is the major circulating component in plasma after oral administration and has limited penetration into RBCs; it is primarily eliminated in urine as metabolites.

Abbreviations:
CNB - cenobamate
FDA - Food and Drug Administration
INaP - persistent component of sodium channel
TEAEs - treatment-emergent adverse events
DRESS - drug reaction with eosinophilia and systemic symptoms
ASM - antiseizure medications
QOLIE - quality of life
JHU - Johns Hopkins Hospital

AUC - concentration-time curve
RBCs - red blood cells

Author contributions
All the authors made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work; and were involved in drafting the work and revising it critically for important intellectual content; and gave final approval for the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethical conduct of research
No ethical approval was required for this research.

Data sharing statement
Any additional datasets that are not provided as part of the manuscript or as supplementary materials are available from the corresponding author on reasonable request.

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