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Safety and efficacy of perampanel in children and adults with various epilepsy syndromes: A single-center postmarketing study

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ABSTRACT

Introduction: Perampanel is an AMPA receptor antagonist recently approved for the treatment of partial and generalized epilepsies with tonic–clonic seizures as an add-on therapy.
Methods: This single-center postmarketing study retrospectively evaluated the efficacy of perampanel in patients with partial onset and other seizure types, with a special emphasis on its efficacy, safety, and tolerability.
Results: Review of medical records revealed that adequate data were available on 101 patients taking perampanel. Fifty-seven patients were female. Sixteen patients were of pediatric age range. The average dose of perampanel was 6.5 mg, and average treatment duration was 8.2 months. After treatment, median seizure frequency reduction was 50% overall, 50% in children, and 33% in adults; 44% in primary generalized, 38% in secondarily generalized, and 33% in partial seizures. Responder rate (50% seizure frequency reduction) was 51% overall, 63% in children, and 49% in adults; 60% in partial seizures, 43% in secondarily generalized tonic–clonic seizures, 53% in primary generalized tonic–clonic seizures, and 56% in other seizure types. Seizure freedom was attained in 6% of cases. Most common adverse events were sleepiness/fatigue (35%), behavioral problems (30%), and dizziness (22%). Adverse events were correlated with dosage. Average dose was 7.3 mg in patients with adverse events vs. 5.5 mg in those without adverse events. Patients who developed fatigue, cognitive decline, headaches, and weight gain were more likely to discontinue perampanel than those patients who experienced coordination issues and behavioral problems.
Conclusions: These findings suggest that perampanel is safe, well-tolerated, and effective in treatment of various types of adult and pediatric epilepsy syndromes. Fatigue, cognitive decline, headache and weight gain were the main causes of perampanel discontinuation.

1. Introduction

Perampanel is a noncompetitive AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist approved to treat partial and generalized epilepsies with tonic–clonic seizures as an add-on therapy [1,2]. The AMPA receptors act as postsynaptic fast excitatory neurotransmission mediators and are involved in generation and spread of epileptic impulses. In animal models, perampanel demonstrated a broad-spectrum antiseizure activity [3].

Phase 3 clinical trials showed that perampanel was highly effective in the treatment of refractory partial onset seizures [4–7]. The United States Food and Drug Administration also approved perampanel as an adjunctive therapy in patients with epilepsy 12 years or older to treat partial onset and primary generalized tonic–clonic seizures [8]. The Drug Enforcement Administration has designated perampanel as a Schedule III controlled substance because of the occurrence of euphoric mood, as well as its potential for drug abuse in some adults who likened perampanel to ketamine, especially at high doses, prompting FDA to include a black box warning for possible neuropsychiatric side effects [9]. The minimum effective dose of perampanel is 4 mg once daily; with higher doses of 8 mg and 12 mg daily providing greater therapeutic benefits but with increased adverse events. Dizziness and somnolence/sedation/fatigue are the most frequently reported dose-related adverse events [10,11]. We performed a postmarketing open-label retrospective analysis of perampanel to assess its efficacy in patients with various epilepsy syndromes, with an emphasis on its safety and tolerability.

2. Methods

We enrolled 101 adults and children with treatment-resistant epilepsy treated in this IRB-approved retrospective study. Patient

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Table 1
Patient baseline characteristics (n = 101).

Variables	Values
Median age	32 years (IQR: 23–48 years)
0–12 years	8%
12–18 years	8%
18–65 years	80%
>65 years	4%
Female	57%
Median age of seizure onset	14 years
Etiology	
Genetic	12.2%
Specific genetic/epilepsy syndrome	3%
Genetic/chromosomal	5.2%
Other	4%
Structural/metabolic	36.7%
Traumatic brain injury	10%
Infection	1%
Neoplasm	5%
Neurocutaneous	4%
HIE	11%
Other	5.7%
Unknown	51%
Seizure types	
Focal	25%
Secondarily generalized	35%
Primary generalized	32%
Other (absence, myoclonic, spasms, etc.)	9%
Concomitant antiepileptic medications	
Clobazam	29.7%
Levetiracetam	29.7%
Lamotrigine	20.8%
Valproate	14.9%
Felbamate	14%
Carbazepine/oxcarbazepine	13%
Lacosamide	11.9%
Topiramate	7.9%
Eslicarbazepine	7.9%
Zonisamide	5%
VNS	15%
Surgery	13%

HIE: Hypoxic Ischemic Encephalopathy; VNS: Vagus Nerve Stimulation.

characteristics are reported in Table 1. Patients were recruited at a large tertiary care academic medical center. Entry criteria included the following: (i) 0–65 years of age, (ii) seizures refractory to at least two AEDs and on adjunctive treatment with perampanel, and (iii) a minimum of three-month follow-up on the final dose of perampanel. Patients who started perampanel after July 1st 2015 and those who had incomplete data were excluded from the study. Family and personal histories were recorded, and neurological examinations were performed on all patients. Lab evaluations were carried out as deemed necessary. Electroencephalograms (EEGs) were recorded during wakefulness, spontaneous sleep, and arousal. Long-term video-EEG was performed when considered useful in classifying the type of epilepsy. All patients underwent imaging studies with brain magnetic resonance imaging (MRI). Seizure types and epilepsy syndromes were classified in accordance with the International League Against Epilepsy (ILAE 2009) classification of epileptic seizures and epileptic syndromes [12]. Information regarding demographics, etiology, seizure onset and type, epilepsy syndrome, comorbidities, clinical exam, other medications, seizure frequency, medication dosage, efficacy, adverse events, surgery, and VNS were obtained from the medical records. Data on seizure frequency and types were also obtained either from telephonic encounters or from diaries that were maintained by patients or families. The Wilcoxon signed-rank test and rank-sum test were used for the statistical analysis of between-group differences of continuous variables, and Chi-square test and Fisher's exact test for categorical variables. Spearman correlation analyses were conducted to assess correlation between variables. SPSS version 21.00 and SAS v. 12 were used for descriptive and statistical analyses.

3. Results

Table 1 summarizes patients' demographics. Data from 163 patients treated with perampanel were identified. Thirty patients who started the drug after July 1st 2015 were excluded for lack of follow-up data, and 32 patients were excluded for incomplete or missing data. Among the 101 patients who met inclusion criteria, 57% were female. Median age at diagnosis of epilepsy was 32 years (range: 1 year–66 years). There were 16 (16%) pediatric patients (i.e., <18 years of age). The average age of pediatric patients was 10.9 years (median: 12.5 years), and seven children were age 12 years or younger.

Fifty-one percent of the patients had no known etiology. Of the rest, 36.7% had structural abnormalities [traumatic brain injury (10%), infections (1%), neoplasms (5%), hypoxic–ischemic encephalopathy (11%), and other undefined (5.7%)], and 12.2% had a genetic etiology. The most common seizure types were focal (25%), primary generalized tonic–clonic (32%), secondarily generalized tonic–clonic (35%), and other types (such as absences, myoclonic seizures, infantile spasms) (9%). Other concomitant AEDs used in combination with perampanel included various combinations of clobazam, levetiracetam, lamotrigine, valproate, felbamate, carbamazepine, lacosamide, topiramate, eslicarbazepine, and zonisamide.

3.1. Efficacy

A summary of the perampanel efficacy profile is described in Table 2. The average perampanel treatment duration was 8.15 ± 6.2 months (median: 6.5 months). The average perampanel dose was 6.5 ± 3.1 mg (median: 6 mg).

Perampanel treatment led to a significant reduction in seizure frequency. A seizure frequency (as obtained either from their history, telephonic encounters, or seizure diaries) reduction of at least 50% (responder rate) was achieved by 51% (52/101) of patients (Fig. 1). Of these, six percent (6/101) of the patients were seizure-free on perampanel therapy at follow-up (>6 months); all of them were adults. After treatment, the median seizure frequency in all patients was reduced by 50% (Wilcoxon signed-rank test $p < 0.0001$) (Fig. 2). The median seizure frequency reduction was 50% in children (Wilcoxon signed-rank test $p = 0.002$) and 33% in adults (Wilcoxon signed-rank test $p < 0.0001$) (Fig. 2). The median seizure frequency reduction was 33% in partial seizures (Wilcoxon signed-rank test $p < 0.0001$), 44% in primarily generalized seizures (Wilcoxon signed-rank test $p = 0.0008$), and 33% in secondarily generalized seizures (Wilcoxon signed-rank test $p = 0.0002$) (Fig. 2).

There was a positive association between dose and efficacy. The average dose of perampanel in patients who experienced any seizure reduction was 6.9 ± 1.9 mg (median: 6 mg), as compared with 5.1 ± 2.0 mg (median: 6.0 mg) in patients in whom seizure frequency did not decrease (Wilcoxon rank-sum test $p = 0.0007$). Similarly, the average dose of perampanel in patients who achieved at least a 50% reduction in seizure frequency was 7.4 ± 2.5 mg (median: 7 mg), as compared with 5.3 ± 2.0 mg (median: 6 mg) in patients who did not achieve 50% reduction in seizure frequency (Wilcoxon rank-sum test $p < 0.0001$).

A 50% or greater seizure reduction was achieved in 63% (10/16) of pediatric patients versus 49% (42/85) of adults (Chi-square $p = 0.34$) (Fig. 1). In addition, among children 12 years of age or younger, all eight had a 50% or greater reduction in seizures.

Perampanel efficacy did not differ across seizure types. A 50% or greater reduction in seizure frequency was observed in 60% (15/25) of patients with focal seizures, 43% (15/35) with secondarily generalized seizures, 53% (17/32) with primary generalized seizures, and 56% (5/9) with other seizure types (Fisher's exact test $p = 0.61$) (Fig. 1).