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Research Article

Perampanel Monotherapy- A Novel Treatment for Seizures: A Systematic Review

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Abstract

Perampanel (PER) has gained a current approval for monotherapy of treating focal-onset seizures with or without secondarily generalized seizures, and as an adjuvant therapy with concomitant antiepileptic drug (AED) for primary generalized seizures in patients aged older than 4 years. The recent studies on its monotherapy have become a breakthrough by recognizing its vast potential in clinical practices. This systematic review is aimed to correlate all the studies on monotherapy to validate the efficacy and safety profile of the drug.

Keywords: Perampanel; Monotherapy; Real-world study; Antiepileptic drug; Retention rate

Introduction

The newer generation of AEDs offer a powerful range of therapeutics with a lower risk profile for adverse drug events and controlled drug interaction compared to the older generation of anti-epileptics [1]. PER is a novel antiepileptic, which acts by selectively blocking α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor. PER ceases the agitation state of Glutamate and disrupts the epileptiform activity at postsynaptic excitatory synapses by imbibing to AMPA receptors [2]. PER has gained a current approval for monotherapy of treating focal-onset seizures with or without secondarily generalized seizures, and as an adjuvant therapy with concomitant AEDs for primary generalized seizures in patients aged older than 12 years [3].

Mechanism of action

PER has a neoteric phenomenon of selective, non-competitive antagonism for Glutamate at the postsynaptic potential (PSP) of inotropic AMPA receptors. PER drug development with its unique antagonism for AMPA receptors has a broad therapeutic index in epileptic patients. This can lead to reduced overstimulation and contributes to neuro-modulatory effects such as seizure reduction rate and freedom. AMPA receptor condemns the over-stimulation of glutamate at excitatory postsynaptic potential (EPSP). An open, active state and Closed-inactive state of AMPA receptors allow the sodium and calcium ions to influx among the neurons, safeguarding them from various neuropathological states [4] and preventing neuronal death [5,6].

Pharmacokinetics

PER is completely absorbed from the gastrointestinal tract and peak plasma concentration is attained within 0.5-2.5 hrs. It`s highly protein bound to albumin and α1-acid glycoprotein (95%-96%), but it has shown good penetrability of the blood-brain barrier. It`s extensively metabolized (>90%) in the liver and has a half-life (t½)

of 105 hours. However, the t½ can be halved, when co-administered along with strong CYP3A4 inducing drugs such as carbamazepine (CBZ), oxcarbazepine (OCZ), and phenytoin (PH). Steady-state concentration is attained within 2-3 weeks [7]. These measures may differ in the pediatric population compared to those of adults, associated with low clearance and slow metabolic rate [8].

1. Dosage and Titration strategy: The recommended initial dose is 2 mg/day OD at Bedtime. If the patient was administered CBZ, SV (sodium Valproate), PH (enzyme-inducing AED's) concomitantly, the recommended initial dose is 4 mg/day at bedtime [7], titrate the dose by 2 mg daily at weekly intervals. Depending upon individual clinical response and tolerability, the dose may be increased or decreased by 2 mg at a time [8]. Optimal maintenance dose is 4 mg/day to 6 mg/day [9].

2. Adverse Drug Reactions (ADR): Early and frequent follow-up after initiation of PER is critical to identify and manage adverse drug events before patients discontinue the drug. Several studies suggested associations between ADR's and rapid titrations of PER [7]. Dizziness, Somnolence, Headache, Irritability, Fatigue, Nausea, Vertigo, Back pain. Gait Instability are common ADR`s reported. Most previous clinical studies titrated PER rapidly with 2 mg increments every 1-2 weeks. Slow titrations of PER may reduce adverse events including psychiatric symptoms [4].

Pregnancy and Lactation: Perampanel has been classified as a Category C drug, which can produce teratogenicity by causing harm to the foetus [7]. In a recent study, Alicino et al have found the use of PER during pregnancy in 4 patients with a good outcome. PER was well tolerated and appeared safe for the foetuses, and did not result in major malformations or adverse events at birth in all their patients. Larger studies can help to assess the safety of their use in pregnancy [10].

Methods

This systematic review was done by utilizing the databases PubMed, as the source of information with keywords "Perampanel Monotherapy". Some of the prominent studies are included in the review.

Results and Discussion

PER monotherapy is progressively gaining acceptance for a broad spectrum of seizure types. Early selection of an effective AED for initial monotherapy or adjunctive therapy is critical for realizing the best possible therapeutic outcomes [11]. PER monotherapy is efficacious with more than > 60% seizure freedom rate in patients who were administered and maintained on 4 mg/day. After conducting a valid literature review, nine published papers on PER monotherapy were found. Several authors conducted authentic research on the safety and efficacy of monotherapy of PER in focal onset seizures with evidence of Multi-centre, Real-world studies, open-label & extension studies, FREEDOM studies, and Post hoc analysis.

Open-label, Phase-III trail, FREEDOM studies:

Yamamoto et al. [12] conducted a single-arm, open-label, Phase-III studies in (n=91) patients in the treatment phase with focal-onset seizures along with partial bilateral tonic-clonic seizures or epilepsies aged ≥ 12 years of age began with a dose of 4 mg/day with 32-week treatment phase of 6-week titration period and 26-weeks maintenance period in the vigilance of tolerability issues, in which 89 patients into 4-mg treatment phase and treated. Out of which, 46 patients have fulfilled the treatment phase with 22 discontinued and 21 patients promoting to 8-mg treatment phase by tolerable efficacy as the last evaluated dose. The study reported adverse reactions higher in patients of 8 mg/day treatment phase comparative to 4 mg. A seizure freedom rate of 63.0% and 74.0% was achieved in 4 mg/day and 4 mg or 8 mg/day phase, reinforcing the PER monotherapy in newly diagnosed focal-onset seizures with or without having partial bilateral tonic-clonic seizures in patients over 12 years.

Husni et al. [13] performed a post hoc analysis study of 342 PER monotherapy patients with focal onset seizures along with untreated recurrent epilepsy with an effective dose beyond initial titration to achieve seizure freedom. It is a single-arm, open-label, Phase-III study in patients with focal-onset seizures aged over 12 years, 4 mg/day with 30-week treatment phase of 4-week titration period and 26-weeks maintenance period. In the modified intent-to-treat Analysis set (n=73), the safety profile has been intervened and responders (n=46) for 4mg/day had been achieved at an early stage (n=37) and later stage (n=9). Seizure freedom has been achieved in 80.4%. Out of 27 Non-responders, those who developed seizures in titration period, 9 patients gained seizure freedom in their maintenance period. PER monotherapy may accelerate seizure freedom in patients with untreated focal-onset seizures beyond the initial titration dose of continued treatment. The study ensured to make appropriate clinical decisions precisely based on clinical response to PER monotherapy.

Patrick et al [14] reported cases of epileptic patients included in open-label extension portions of a set of 9 phase II and III adjunctive treatment studies. In the study population of open-label extension studies (n=2245), a small portion of 7 patients developed drug-resistant focal seizures. Those patients who were converted onto PER monotherapy seemed well tolerated but experienced treatment-emergent adverse events by five patients and exhibited safety profile (≥91 days) consistent with the available clinical literature in the adjunctive setting. A restricted range of data propagates the prominence of PER monotherapy, but a need for an ample amount of evident-based research studies is necessary for validating the treatment potentiality in a large population.

Multicentre, retrospective observational study:

Delgado et al. [15] conducted a multicentre, retrospective, observational study of 98 patients with focal seizures and generalized tonic-clonic seizures aged over 12 years of age. Patients in this study at 3-month baseline period are grouped into Primary monotherapy and conversion monotherapy upon 3-, 6- and 12-months follow-up period for the intervention of safety, tolerability, and efficacy assessments of PER. At low doses (4 mg/day) of PER, the patients improved their seizure frequency and proven to be effective. At the 6-month and 12-month period, the response rate has been 52.8% and 70.1% and seizure freedom with a range of 56.1% and 41.5% had reported accordingly with a low rate of adverse drug

reactions with mild intensity in 16% of the study population. PER monotherapy signifies efficacy, tolerability, and safety profile in the clinical setting at relatively low doses (4 mg/day) in two groups of primary and conversion monotherapy in patients with focal onset and generalized tonic-clonic seizures.

Nagel et al. [16] conducted a retrospective, non-interventional, multicentre study on patients that received PER as both monotherapy and adjunctive therapy. Out of 1225 patients, 69 of them in a safety set, received primary monotherapy (n=9) and secondary monotherapy (n=51). Patients in a Full Analysis set (n=40), 22 of them attained seizure freedom for 3 months. This study demonstrated an insight of monotherapy and specified efficacy is achieved in disregard of concomitant AEDs administered.

R Toledano et al. [17] reviewed current evidence on treatment with PER monotherapy after conversion from adjuvant therapy by compilation of two retrospective multicentric studies. The retention rates taken at 3 months is 90% at 3 and 70% at 6 & 12 months. The responder rate was more than 75%. Seizure freedom rates exceed at 3 and 6 months are 50 % and 37% at 12 months.

Real-world studies

Chinvarun et al [18] conducted a real-world retrospective study for the assessment of safety and efficacy of PER monotherapy in patients (n=41) aged over 15 years with new focal onset seizures, with or without partial bilateral tonic-clonic seizures. Monotherapy of PER imbibed the most effective ability inducing retention rate at an observational point at 3 months is 88%, at 6 months is 73%, at 12 months is 61%. Around 14 % of the study population had discontinued the therapy. Seizure freedom rates at the Observational point of 3-months is 78%, at 6-months is 80 % and at 1-months is 76% respectively. Treatment-emergent adverse events had reported among the subjects (n=16) of 41% in elderly patients. The intensity of adverse drug reactions can be minimized with slow titration of doses at longer drug interval periods, which can be the hallmark for optimum therapeutic effect gaining seizure freedom by supporting patient adherence.

Alsaadi et al. [19] conducted an interim pooled analysis, a real-world study on patients with focal onset seizures or generalized onset seizures or both focal and generalized onset seizures from 18 clinical practice studies/workgroups. At a period, point of 3, 6, and 12 months of PER treatment retention rates, seizure freedom rate, and responder rate (≥50%) were evaluated. Safety, efficacy, and tolerability were assessed by ruling adverse events (AEs). At baseline period, a total of 111 patients treated with PER monotherapy were identified with focal seizures (54.7%) and generalized onset seizures (42.2%), and focal and generalized (3.1%). The most effective ability-producing retention rate at an observational point was 94.4% at 3 months, 88.9% at 6 months, and 55.6% at 12 months with PER monotherapy. The frequencies of seizure independence at the commencement of focal and generalized seizures are 20.0% and 47.6%, respectively.

50.0 percent and 100.0 percent are respondents. In individuals with both focal and generalized onset seizures, PER monotherapy has proven to be a viable and well-tolerated treatment.

Nagel et al. [20] divided their research into two categories: study 504 and study 506. PER monotherapy was started for (n=60) participants in Study 504. The seizure freedom rate was reported to be 55.0% at 3 months, with retention rates of 55.6% at 12 months and 60.6% at 24 months, with a mean dosage of 7.3 (2.8) mg/day. For (n=47) participants in Study 506 With a mean dose of 7.2 (2.7) mg/day, the seizure freedom rate was found to be 100% after 12 months, with retention rates 48.7% at 12 months and 45.5% at 24 months. Seizure independence reached at 4-mg maintenance period (n=73) is 63.0% at 4 mg/day and 74% at 4-8 mg/day for patients with 1 post-dose effectiveness measurement. Safety of PER monotherapy studied and found to be efficacious for focal onset seizure, with or without secondarily generalized seizures and refractory epilepsy, using clinical trial data and real-world research.

Conclusion

PER is a newer antiepileptic drug with a unique mechanism of action and specialized pharmacokinetics permitting once daily dosage, minimal ADR`s, high efficacy in a wide range of seizures types in both adults and children over 4 years. While initially used as an add-on anti-epileptic, it is also found to be effective as monotherapy. On the basis of the patient's clinical response, adverse drug reactions, and tolerance, dosing should be personalized. The current evidence on monotherapy has been a breakthrough by realizing its great potential of therapeutic relevance into clinical practice. Larger double-blinded, prospective, randomized control trials can answer its long-term efficacy in treating different seizure types.

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Conflict of Interest

No conflict of interest.

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