EXPERT REVIEWS

Perampanel: newly approved, novel antiepileptic medication for partial-onset seizures

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Evaluation of: French JA, Krauss GL, Steinhoff BJ *et al*. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global Phase III study 305. *Epilepsia* doi:10.1111/j.1528-1167.2012.03638.x (2012) (Epub ahead of print).

Epilepsy is characterized by two or more unprovoked seizures. The number of individuals burdened by recurrent seizures in the USA alone is approximated at around 2 million, with the vast majority of patients maintained on chronic medical management for appropriate seizure control. Perampanel is an oral, noncompetitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid-type glutamate receptor that has been approved by the European Medicines Agency and the US FDA under the trade name Fycompa® (Eisai Medical Research Laboratories, Hatfield, UK) as an adjunct treatment of partial-onset seizures in patients aged ≥12 years. The article under review is a Phase III randomized, placebo-controlled, double-blind study that demonstrates the efficacy and safety of an 8- and 12-mg daily oral dose of perampanel with greater mean percentage seizure frequency reduction at 8-mg daily dose. The study is discussed in relation to the current understanding of cellular mechanisms of neuronal excitability leading to epileptogenicity, as well as clinical application of novel and established antiepileptic agents.

Keywords: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid • Fycompa® • glutamate • novel antiepileptic drug • partial seizures • perampanel • refractory epilepsy

Epilepsy is defined as a condition characterized by two or more unprovoked seizures. Prevalence of epilepsy in the USA is estimated to be between 4 and 9 per 1000 people [1], and may be twice as high in developing countries. Excluding the small percentage of people who underwent successful epilepsy surgery, the vast majority of patients are maintained on chronic medical management for appropriate seizure control [2]. Despite the advent of new antiepileptic drugs (AEDs) over the past two decades, approximately 30% of epilepsy patients still experience recurrent seizures, and many experience undesirable side effects, underscoring the ever-present necessity for novel therapeutic agents with the potential to reduce seizure frequency and improve their safety and tolerability [3,4].

Perampanel

Perampanel is an oral, noncompetitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type glutamate receptor. It is a result of the screening project among potential compounds by Eisai Medical Research Laboratories (Hatfield, UK) [5,6]. Based on the preclinical pharmacological and toxicological data observed in animal models and two Phase II studies, three Phase III efficacy and safety trials have been conducted [7–12]. Perampanel was approved by the European Medicines Agency in July 2012 and by the US FDA in October 2012 under the trade name Fycompa® (Eisai Medical Research Laboratories) as an adjunct treatment for partial-onset seizures in patients aged ≥12 years. Perampanel is rapidly absorbed following oral administration, reaching peak plasma concentrations after 15 min and up to 2 h [6]. The half-life is estimated to be approximately 70 h, allowing once-daily dosing. The distribution volume is approximately 77 l with high protein binding of 95%. Following oral administration of radiolabeled perampanel, 70% was excreted via the feces in the unchanged form, and the remaining 30% through the

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kidney. *In vitro* studies indicated that the CYP 3A4 pathway is the primary route of CYP-mediated metabolism of platelet-rich plasma [6].

Methods & results

The Phase III randomized, double-blind study by French *et al.* was designed to assess the efficacy and safety of 8- and 12-mg daily oral doses of perampanel [11]. The trial was conducted in 78 centers across the USA, Australia, South Africa, Europe, India and Israel. Patients older than 12 years of age with a diagnosis of refractory partial seizures were assessed during 29 weeks divided into baseline (6 weeks), titration (6 weeks), maintenance (13 weeks) and follow-up (4 weeks) periods. Most patients in the study (89%) were taking two or three AEDs when perampanel was added; subjects had at least five partial seizures during baseline period. Patients were randomized to daily administration of placebo or perampanel 8 or 12 mg. Perampanel was started at 2 mg/day and increased by 2 mg every week up to the target dose. Exclusion criteria included patients with nonpartial or complex partial epilepsies, progressive CNS disease, substance dependence or suicide attempts within last 2 years, vagus nerve stimulator implanted for ≤5 months, progressive cause of epilepsy, scheduled epilepsy surgery and use of more than two liver enzyme inducers.

The primary assessment of efficacy was based on the change in partial-onset seizure frequency and was evaluated in two ways: the change in seizure frequency during 28 days from baseline to the maintenance period and the proportion of patients experiencing a 50% or greater reduction in seizure frequency from baseline to maintenance period (50% responder rate). The primary efficacy analysis was conducted on the intent-to-treat population, which is defined as all randomized patients who received at least one dose of the trial medication and had at least one postbaseline efficacy assessment. A total of 386 patients were enrolled in the study, with 136 patients randomized to placebo, 129 patients to perampanel 8-mg and 121 patients to perampanel 12-mg groups. Overall completion rate was 83.2%, and the most common reason for discontinuation was adverse effects. Discontinuation rates were lowest in the placebo group and highest in the perampanel 12-mg group.

The efficacy outcomes for the 50% responder rates were essentially the same for the perampanel 8-mg and perampanel 12-mg groups with 33.3 ($p = 0.002$) and 33.9% ($p < 0.001$), respectively, with significant difference from placebo administration. The mean percentage seizure reduction was higher in the perampanel 8-mg group (30.5%; $p < 0.001$) than the 12-mg group (17.6%; $p = 0.011$), versus 9.7% in the placebo group. However, the seizure freedom rate was higher in 12-mg dosing (5%) as compared with 8 mg (2.3%) and placebo (1.5%).

The most common adverse events were dose-related dizziness, somnolence, fatigue and headache. Less common side effects included irritability, nausea, falls and weight increase. No significant worsening of seizures, cases of sudden unexpected death in epilepsy or severe rashes were reported with administration of perampanel.

Discussion & significance

The primary target of currently available anticonvulsants can be divided into two main mechanisms: suppression of neuronal excitation or enhancement of the inhibition. Glutamate receptors play an integral role in neuronal excitation, and suppression of such activity could be an important target for seizure control. Currently, three distinct types of inotropic glutamate receptors are known, which include AMPA, the kainic acid and the *N*-methyl-D-asparate (NMDA) receptors [13]. Since neurons' excitatory NMDA receptors become operative in the setting of partial cell depolarization, AMPA receptor activation is a required initial step [14]. This concept of excitatory neurotransmission led to consideration of the AMPA receptor as a potential pharmacological target, promoting the discovery of AMPA antagonists, such as perampanel.

Preclinical studies of perampanel were promising in chronic and acute seizure models, including maximal electroshock seizure model, audiogenic seizure model, pentylenetetrazole-induced seizure model, as well as 6-Hz electroshock-induced and amygdala-kindling seizure models. Based on favorable preclinical and Phase I trials, two Phase II trials exploring tolerability and efficacy toward seizure control were performed: study 206 was a randomized, double-blind, placebo-controlled trial with oral perampanel up to 4 mg/day; study 208 was a dose-escalation trial up to 12 mg/day. The subsequent three Phase III pivotal studies (304, 305 and 306) had provided further evidence of perampanel's efficacy against partial epilepsy. Studies 304 and 305 had identical study design and target doses (8 and 12 mg/day). Study 304 included subjects only from the Americas, whereas study 305 had included multiple geographic regions as discussed earlier. Study 306 was conducted in 25 different countries and targeted lower doses (2, 4 and 8 mg/day). All three studies had demonstrated seizure improvement and adverse effect profile similar to previous Phase II trials, with the most common being dose-proportional dizziness, headache and somnolence.

An interesting result of study 305 was a lack of significant therapeutic benefit of 12-mg/day compared with 8-mg/day dosing. In fact, when efficacy was measured by median percentage reduction, 8-mg/day dosing was better than 12-mg/day, raising a question whether there is a maximal therapeutic threshold for perampanel at 8 mg/day. Nonetheless, seizure freedom was higher with 12 mg/day, perhaps indicating a therapeutic benefit of the dose increase, presuming its tolerance.

Expert commentary & five-year view

When a new AED is introduced, many questions are raised: what is 'new' about the new medication? Is it better than other medications on the market? Does it work for both generalized and partial epilepsy? These questions ultimately lead to a more important question: does it improve the overall seizure control and quality of life for patients with epilepsy? The strengths of perampanel are a unique mechanism of action, allowing once-daily dosing and a favorable side-effect profile. In light of current understanding of excitatory synaptic transmission underlying seizure generation, the glutamate antagonists are logical targets for the development of

novel antiepileptic agents, with perampanel being the first in its class. Even though perampanel is approved as an adjunct therapy for partial seizures, animal studies demonstrated the effectiveness of perampanel against absence- and myoclonic-type seizures. In addition, AMPA receptors have been implicated in the initiation and maintenance of status epilepticus [15,16] in the setting of gradual internalization of inhibitory GABA receptors. Elucidation of these mechanisms makes AMPA antagonists promising candidates for use in the benzodiazepine-resistant status epilepticus.

Perampanel is highly protein bound (95%) and mainly metabolized by liver enzymes, which predispose it to potential drug–drug interactions. In fact, perampanel concentrations can be reduced by 50% when used with carbamazepine [6]. Perampanel does not affect the plasma concentration of carbamazepine, topiramate, oxcarbazepine, levetiracetam, lamotrigine or valproic acid. The impact of perampanel on the effectiveness of oral contraceptives has not been established.

When combination therapy is considered, using AEDs with different mechanisms of action may provide better efficacy and tolerability and a synergistic effect. On the other hand, using AEDs with similar mechanisms of action may result in simple additive or even antagonistic effects. For perampanel, a synergistic effect has been reported in 6-Hz electroshock mice seizure model when combined with phenytoin, carbamazepine and valproate [7]. Nonetheless, it is not yet clear how these combinations would impact the seizure control in clinical practice.

In summary, perampanel is a new antiepileptic medication with a novel mechanism of action. Results from clinical studies demonstrate that perampanel was well tolerated and effective in reducing partial-onset seizures as an adjunctive therapy. The potential of perampanel as an antiepileptic agent with broad-spectrum coverage, as well as its effectiveness as a pharmacological rescue therapy for status epilepticus will be clarified as it is utilized in greater number of patients.

Financial & competing interests disclosure

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Key issues

- The prevalence of epilepsy in the USA is estimated to be between 4 and 9 per 1000 people, and may be twice as high in developing countries. Despite the advent of new antiepileptic drugs over the past two decades, approximately 30% of epilepsy patients still experience recurrent seizures, and many experience undesirable side effects underscoring the ever-present necessity to develop novel therapeutic agents with the potential to reduce seizure frequency and improve their safety and tolerability.
- Perampanel is an oral, noncompetitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid-type glutamate receptor. Perampanel was approved by the European Medicines Agency in July 2012 and by the US FDA in October 2012 under the trade name Fycompa® as an adjunct treatment for partial-onset seizures in patients aged ≥12 years and older.
- The perampanel study by French *et al.* is a Phase III randomized, placebo-controlled, double-blind study designed to assess the efficacy and safety of 8-mg and 12-mg daily oral dose of perampanel.
- The efficacy outcomes for the 50% responder rates were essentially the same for perampanel 8-mg and perampanel 12-mg groups. The mean percentage seizure reduction was higher in the perampanel 8-mg group than in the 12-mg group.
- Seizure freedom was higher with a dose of 12 mg/day, perhaps supporting a notion that for those who responded, 12 mg/day may provide more complete seizure control, as long as they can tolerate perampanel.

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