



Use of Perampanel for Refractory Seizures in Pediatric Patients

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Perampanel is a unique alternative to traditional antiseizure drugs for adolescents with refractory seizures. It was approved by the Food and Drug Administration (FDA) on October 22, 2012 for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients 12 years of age and older. On June 19, 2015, the FDA extended the approval to include the treatment of primary generalized tonic-clonic seizures.¹⁻³ Several recent papers have focused on the efficacy and safety of perampanel in children and adolescents, adding to our understanding of this drug in the pediatric population.

Mechanism of Action

Perampanel, 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate, is the first drug in a new class of selective non-competitive α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonists.^{2,3} Although the exact mechanism by which these drugs work is not yet fully understood, the selective blockade of AMPA receptors on post-synaptic neurons is believed to prevent generation and propagation of seizures by blocking the effects of the excitatory neurotransmitter glutamate.

Pharmacokinetics

The pharmacokinetic profile of perampanel has been studied in both adults and adolescents.²⁻⁵ Perampanel is rapidly and completely absorbed after oral administration, with no significant first-pass metabolism. Median time to the maximum plasma concentration in adults ranges from 0.5 to 2.5 hours in the fasting state. Administration with food slows absorption by 2-3 hours, but does not affect the extent of drug absorption. It is highly bound (95-96%) to albumin and α -1-acid glycoprotein. Perampanel undergoes extensive oxidative metabolism via cytochrome P450 (CYP) 3A4/5, and to a lesser extent by CYP1A2 and CYP2B6, followed by glucuronidation. The average half-life in adults is 105 hours, with a clearance of 0.6 L/hr. The half-life of perampanel is prolonged in patients with

mild to moderate hepatic impairment (approximately 300 hrs). Clearance has not been studied in patients with severe hepatic or renal impairment. The pharmacokinetic parameters of perampanel in a study of adolescents 12-17 years of age revealed a slightly faster clearance (0.73 L/hr) than that of adults. Other values were similar to adults, suggesting that adolescents can be dosed as adults.

Clinical Experience

The safety and efficacy of perampanel in adolescents and adults were determined in three multicenter randomized double-blind placebo-controlled studies which included a total of 1,178 patients, including 143 adolescents between 12 and 17 years of age.⁶⁻⁸ All three trials included a 6-week baseline evaluation period followed by a 6-week titration phase and 13-week maintenance phase. Patients continued on their baseline antiseizure drugs. Treatment was initiated with a dose of 2 mg given once daily, with titration of 2 mg every week to a maximum of 12 mg/day.

Pooled data from the maintenance phase was divided into patients who were not receiving an enzyme-inducing drug and those who were, with the second group expected to have a less robust response due to lower concentrations of perampanel resulting from potential drug interactions. In the first group, the median percent reduction in seizure frequency in the 2 mg/day group was 23% in the treatment group and 16% in the controls. The results were similar in the 4 mg/day group, with a 22% reduction in the treatment group and 16% in the controls. A greater reduction in seizure frequency was seen in the 8 mg/day group, with a 45% reduction in the treatment group, and in the 12 mg/day group with a 54% reduction in treatment group. The controls in both the 8 mg/day and 12 mg/day groups had a median reduction of 19%. In the patients already taking an enzyme-inducing antiseizure drug, the results were lower as anticipated: a 16% reduction in seizure frequency in the 2 mg/day treatment group, a 33% reduction in the 4 mg/day group, a 24%

reduction in the 8 mg/day group, and a 22% reduction in the 12 mg/day group, with all but the 2 mg/day group having a percent reduction at least twice that of the controls. Combining all studies, the percentage of patients with a 50% or greater reduction in seizure frequency was 29%, 35%, and 35% for the 4 mg, 8 mg, and 12 mg groups, compared to 19% of the controls.

Patients from these studies were eligible for enrollment into an open-label extension study.⁹ The study began with a 16-week blinded conversion phase followed by an open-label maintenance phase. A total of 1,216 patients were included in the study, with a median exposure of 1.5 years (range 1 week to 3.3 years). At the end of the study, 58% of patients had remained on therapy. Median percentage change in seizure frequency from baseline was 46% at 9 months and 60% at 2 years. Among the patients with data for more than 1 year, 5.3% were seizure-free for at least 1 year. Adverse events included dizziness, somnolence, headache, fatigue, irritability, and weight gain reported in 10% or more of patients. No serious adverse events were reported.

Earlier this year, Rosenfeld and colleagues analyzed the results of only the adolescent patients from these four studies.¹⁰ A total of 143 patients between 12 and 17 years of age were enrolled in one or more of the studies. Pooled data provided a median percent decrease in seizure frequency of 34.8% for a perampanel dose of 8 mg/day and 35.6% for a dose of 12 mg/day, significantly greater than the 18% in the controls. Responder rates were 40.9%, 45.0% and 22.2%, respectively. As in the overall results, the adolescents receiving enzyme-inducing antiseizure drugs had a smaller reduction in seizure frequency (31.6% with an 8 mg/day dose and 26.8% with a 12 mg/day dose) compared to those who did not (54.6% and 52.7%). Adverse reactions were similar to those seen in adults.

The safety and efficacy of perampanel in adolescents with primary generalized tonic-clonic seizures were established in a single multicenter randomized double-blind, placebo-controlled trial of 162 adolescents and adults.¹¹ Patients underwent an 8-week baseline evaluation period prior to randomization. They then entered a 4-week titration period followed by a 13-week maintenance period. The maximum dose for the study was 8 mg once daily. The primary endpoint for the study was the percent change from baseline in seizure frequency per 28 days during the treatment period. Perampanel produced a median percent reduction in seizure frequency of 76% versus a 38% reduction in the placebo group ($p < 0.0001$) with a higher percentage of patients with a 50% or greater reduction in seizure frequency (64.2% versus 39.5% in the controls, $p = 0.0019$).

In 2015, Biró and colleagues published the results of a collaborative observational study conducted at eight centers throughout Europe.¹² A total of 58 patients between 2 and 17 years of age were included (mean age 10.5 ± 4.2 years). Thirty-six patients had focal seizures, 12 had generalized tonic-clonic seizures, five had Lennox-Gastaut syndrome, three had West syndrome, and two had Dravet syndrome. Fifty-two of the patients were receiving other antiseizure drugs, most often valproic acid and lamotrigine. Dosing was initiated with 2 mg once daily at bedtime in patients 12 years of age and older and 1 mg once daily in younger patients. After 3 months of treatment, 18 patients (31%) had achieved a $\geq 50\%$ reduction in seizures. Five patients (9%) had complete resolution. Five had a worsening of their seizures. The most frequent adverse reactions were fatigue or inattention in 16 patients (28%), a change in behavior or aggression in 14 (24%), and dizziness, gait instability, or changes in appetite, each in 6 patients (10%).

An additional case of perampanel use in pediatrics was published by Dirani and colleagues at the American University of Beirut Medical Center.¹³ The authors describe a 15-year-old girl with a history of seizures since the age of 12. She had generalized tonic-clonic seizures along with multifocal myoclonic jerks, which worsened to include dysarthria, ataxia, and cognitive regression. After failing treatment with lamotrigine and topiramate, she was treated with levetiracetam and clonazepam without improvement. Following an evaluation off all medications, she was diagnosed with Lafora disease and started on perampanel. The dose was titrated to 10 mg once daily over 12 days. Within 2 weeks there was a significant reduction in both the myoclonus and generalized tonic-clonic seizures. She was discharged after placement of a vagus nerve stimulator which further reduced her myoclonus. Seven months after starting treatment she was able to run, write, and perform all activities of daily living. Her parents reported no significant adverse effects. The authors suggest that the patient's response, as well as that of a 21-year-old woman previously reported¹⁴, suggest that the loss of GABAergic cortical neurons seen with Lafora disease may be offset by the antagonism at AMPA receptors by perampanel, with improvement in the balance of inhibitory to excitatory neurotransmitters.

Warnings and Precautions

The prescribing information for perampanel includes a black box warning for the development of serious psychiatric and behavioral reactions, including aggression, hostility, anger, and suicidal or homicidal ideation or behavior.² In pooled data from clinical trials, hostility and aggression were reported in 12% in patients on an 8 mg/day regimen and 20% in those on a 12 mg/day

regimen, compared to 6% of placebo.^{2,14} Rates were not increased in patients receiving doses less than 8 mg/day. Homicidal ideation or threat was exhibited in 0.1%. Close monitoring is needed for changes in mood, behavior, or personality during initiation or with dose adjustment. Symptoms typically occur within the first 6 weeks of therapy, but may occur later. Patients with pre-existing psychiatric disorders may be at greater risk for these adverse effects. Perampanel should be discontinued or the dose reduced if symptoms occur.

Perampanel is classified as a schedule III (CIII) controlled drug.^{2,3} In studies of the abuse potential of perampanel, doses of 8 mg (within the normal dosing range), 24 mg, and 36 mg (double and triple the recommended maximum daily dose) were compared to alprazolam at 1.5 mg and 3 mg doses and a 100 mg oral dose of ketamine. Responses in the 24 mg and 36 mg groups for euphoria and a feeling of being “high” were similar to those of the subjects given 3 mg alprazolam or 100 mg ketamine. Study subjects also rated perampanel 24 mg and 36 mg doses higher than the other agents for “bad drug effects” and sedation.

Adverse Effects

The incidence of adverse effects in adolescents is similar to that seen in adults.^{2,6-9,15} In the analysis of adolescent patient data from the premarketing clinical trials, the most frequently reported adverse effects in adolescents included dizziness (20.4%), somnolence (15.3%), aggression (8.2%), decreased appetite (6.1%), and rhinitis (5.1%). In adolescent patients enrolled in the extension study, aggression was more common in males. Of the 22 patients with aggression, 21 were taking more than 8 mg/day; 73% of the reports involved a single episode. There was no clear relationship between the development of aggressive behavior and length of treatment or patient age. The most frequent reasons for discontinuation were dizziness (13.2%), somnolence (11.6%), and aggression (6.6%).

Post-marketing data for perampanel includes a case of drug reaction with eosinophilia and systemic symptoms (DRESS).¹⁶ Shimabukuro and colleagues described a 13-year-old girl who developed rash and fever 5 weeks after starting perampanel for refractory seizures. She had been receiving a maintenance dose of 4 mg once daily at bedtime. Her reaction progressed to erythroderma and superficial exfoliation, with acute renal failure, increased serum transaminases, and an elevated C-reactive protein. A skin biopsy revealed lymphocytic and eosinophilic infiltrates, suggesting a diagnosis of DRESS. Her antiepileptic drugs were stopped and she was treated with methylprednisolone and intravenous immunoglobulin with significant improvement. She was discharged after 3 weeks with full resolution of her symptoms.

Drug Interactions

The concomitant use of drugs which induce CYP enzymes, including carbamazepine, phenytoin, and oxcarbazepine, may decrease perampanel plasma levels by 50% to 67%.^{2,3} In a study evaluating the effect of carbamazepine use in patients given perampanel, the half-life of perampanel was shortened to 25 hours, with reduction in the area under the concentration-time curve (AUC) of 64%. Oxcarbazepine produced a 48% reduction in AUC, while phenytoin produced a 43% reduction. The effect of eslicarbazepine on perampanel clearance has not been studied, but would be expected to be similar. Topiramate produced a smaller effect, with a reduction in AUC of 19%.

In patients currently taking an enzyme-inducing antiepileptic drug, the initial dose of perampanel should be increased (see Dosing Recommendations).^{2,3} Strong CYP3A4 inducers such as rifampin or St. John’s wort greatly increase the clearance of perampanel and may significantly reduce plasma concentrations. Conversely, use with strong CYP3A4 inhibitors may increase the risk of toxicity. Administration of ketoconazole, with perampanel for 8 days prolonged the half-life perampanel by 15% and increased AUC by 20%.

Perampanel has a weak inhibitory effect on CYP2C8, CYP3A4, UGT1A9, and UGT2B7. At doses of 12 mg/day, perampanel did not alter the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide. Perampanel produced a small but measureable (< 10%) decrease in the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid. Coadministration of perampanel with oxcarbazepine resulted in a 26% decrease in oxcarbazepine clearance and an increase in oxcarbazepine serum concentrations. Perampanel has also been found to increase the clearance of midazolam, decreasing its AUC by 13%.²

Use of perampanel at a 12 mg daily dose may reduce serum concentrations of levonorgestrel by 40%.² It is recommended that patients requiring an oral or implantable contraceptive be changed to an alternative hormonal preparation or use an additional non-hormonal form of contraception. Administration of perampanel with other central nervous system (CNS) depressants may increase their effects.² The use of alcohol, benzodiazepines, opioids, barbiturates, or sedating antihistamines should be avoided until the degree of CNS depression produced by perampanel is known.

Availability

Perampanel (Fycompa[®]) is available in 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets.² The average retail price of the drug ranges from \$10-15 per tablet. The manufacturer provides both a patient assistance program and a savings

program. Information on these programs is available at <http://www.eisairimbursement.com/Fycompa/PatientAssistance.aspx>.

Dosing Recommendations

In patients starting therapy who are not already receiving enzyme-inducing antiseizure drugs, perampanel should be started at a dose of 2 mg once daily at bedtime.² The dose may be increased as needed, based on seizure response and tolerability, in increments of 2 mg at weekly intervals. The recommended dose for partial-onset seizures is 8-12 mg once daily, but some patients may respond to lower doses. In patients with primary generalized tonic-clonic seizures, a maintenance dose of 8 mg once daily is recommended. A dose of 12 mg once daily may be considered in patients requiring further seizure control. Patients taking a dose greater than 8 mg should receive close monitoring for adverse effects.

For patients taking enzyme-inducing antiseizure drugs (carbamazepine, phenytoin, and oxcarbazepine), perampanel can be initiated at 4 mg once daily. The dose should be titrated as described earlier, with a maximum daily dose of 12 mg. If the enzyme-inducing drug dose is reduced or discontinued, the patient should be monitored for adverse effects and the need for a reduction of their perampanel dose. In patients requiring rapid discontinuation of the drug, the long half-life allows a gradual fall in perampanel plasma levels, reducing the risk for an increase in seizure frequency.²

In patients with mild to moderate hepatic impairment, the recommended starting dose of perampanel is 2 mg, with titration by 2 mg increments no more frequently than every 2 weeks. In patients with mild hepatic impairment, the recommended maximum dose is 6 mg, with a 4 mg maximum in patients with moderate impairment. Patients with mild to moderate renal impairment may receive perampanel at standard doses, but with a slower titration based on clinical response. Perampanel is not recommended for use in patients with severe hepatic or renal impairment.²

Summary

Perampanel offers a unique mechanism of action and a once-daily alternative for adjunctive therapy in patients with treatment-resistant partial-onset or generalized tonic-clonic seizures. At doses of 8-12 mg/day, it produces significant reductions in seizure activity in approximately 50% of patients. While generally well tolerated, there is a risk for significant neurologic and behavioral adverse effects, particularly in adolescent males.

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