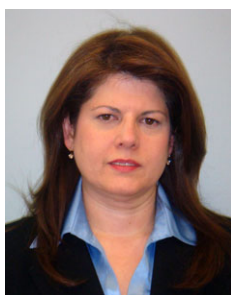




Perampanel efficacy and safety by gender: Subanalysis of phase III randomized clinical studies in subjects with partial seizures

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Epilepsia, 56(7):e90–e94, 2015
doi: 10.1111/epi.13019



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SUMMARY

The antiepileptic drug (AED) perampanel is approved in ≥ 40 countries as adjunctive therapy for drug-resistant partial seizures in patients with epilepsy. This post hoc analysis of pooled data from three phase III, double-blind, randomized studies of perampanel examines between-gender differences in perampanel efficacy and safety. Of the 1,478 subjects in the pooled analysis (719 male, 759 female), 1,109 were included in the pharmacokinetic/pharmacodynamic analysis. Perampanel oral clearance was 17% lower in female than in male patients not receiving enzyme-inducing AEDs. Pooled efficacy analysis revealed that seizure frequency was reduced with perampanel treatment regardless of gender; a greater numerical reduction in seizure frequency and increased responder rates occurred in female participants at perampanel doses of 4, 8, and 12 mg. Tolerability was similar between groups, although common adverse events such as dizziness and headache occurred more frequently in female subjects. Modest elevations in perampanel exposure in female patients may result in meaningful between-gender differences in efficacy and safety; therefore, dosing should be individualized and clinical response monitored.

KEY WORDS: Perampanel, Antiepileptic drug, Efficacy, Safety, Gender, Pharmacokinetics.

The choice of antiepileptic drug (AED) depends on multiple factors, including seizure type(s), tolerability, pharmacokinetics, and gender, highlighting the importance of individualized treatment.¹ Although the prevalence of epilepsy is similar among women and men, AED treatment considerations vary between the genders.² Differences in gender physiology, including body mass and plasma volume, can affect drug pharmacokinetics, which may ultimately

influence the clinical efficacy and tolerability of an AED.³

The efficacy and tolerability of perampanel, a noncompetitive α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist, has been demonstrated in three multinational, multicenter, randomized, double-blind, placebo-controlled, phase III studies.^{4–6} Perampanel is approved in ≥ 40 countries, including the United States and the European Union, for adjunctive treatment of partial seizures, with or without secondarily generalized seizures, in patients with epilepsy who are ≥ 12 years of age, and in Canada for patients ≥ 18 years of age. The pharmacokinetic (PK) profile of perampanel includes a half-life of ~ 105 h as well as rapid and almost complete absorption following oral administration.⁷ In addition, perampanel plasma concentrations increase in direct proportion to dose.⁷

Pooled PK data from the three phase III perampanel studies revealed a linear relationship between clinical outcomes and perampanel systemic exposure.⁸ Although it is known

Accepted April 3, 2015; Early View publication June 11, 2015.

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that gender can affect drug PK and consequently the clinical effectiveness of a treatment,³ analyses of the gender effects with perampanel have not been conducted. We sought to elucidate between-gender differences in perampanel efficacy and tolerability in this subgroup analysis of the pooled phase III studies.

METHODS

Design and subjects

Three phase III studies evaluating perampanel (clinicaltrials.gov: NCT00699972, NCT00699582, and NCT00700310) have been described in detail previously.^{4–6} All studies were conducted in accordance with the Helsinki Declaration, European Medicines Agency requirements, and the U.S. Code of Federal Regulations, as appropriate. All subjects provided written informed consent prior to participation.^{4–6}

These randomized, double-blind, placebo-controlled studies enrolled male and nonpregnant female subjects ≥ 12 years of age who experienced partial seizures with or without secondary generalization in accordance with the 1981 International League Against Epilepsy (ILAE) Classification of Epileptic Seizures, despite receiving 1–3 AEDs in the previous 2 years.^{4–6} Each study comprised three phases: pre-randomization (baseline), double-blind, and follow-up (Fig. S1). Subjects were randomized to receive once-daily doses of 2, 4, 8, or 12 mg perampanel or placebo over a 19-week double-blind phase (6-week titration; 13-week maintenance).^{4–6} During the titration period, perampanel doses were increased weekly by 2-mg increments until the randomized dose or intolerability was reached. Subjects received ongoing treatment with stable doses of 1–3 concomitant AEDs, with only one enzyme-inducing AED (EIAED) permitted.^{5,9}

Pharmacokinetic/pharmacodynamic (PK/PD) analysis

The final PK model, using a one-compartment disposition model with first-order elimination to describe perampanel plasma concentrations at steady state, yielded adequate predictions of pooled data from the perampanel phase III studies.⁸ This was considered an appropriate basis for predicting perampanel exposure in exposure–response PK/PD analyses.⁸ Plasma samples for analysis were collected during the maintenance period (visits 6 and 7) and at the discontinuation visit (visit 8).

Efficacy end points

The primary end point in the United States and other non-EU countries for the phase III studies was percent change in seizure frequency per 28 days during the double-blind treatment phase relative to baseline (secondary end point in EU countries). The secondary end point was the 50% responder rate (primary end point in EU countries), defined as the proportion of subjects experiencing a $\geq 50\%$ reduction in seizure frequency per 28 days in the

maintenance period versus baseline with last-observation-carried-forward (LOCF) imputation.

Safety

Safety assessments included treatment-emergent adverse events (TEAEs) and reasons for discontinuation. Adverse events (AEs) were reported using Medical Dictionary for Regulatory Activities (MedDRA) standardized terms.

Statistical analyses

The baseline seizure frequency per 28 days and the percentage change during treatment were rank-transformed separately prior to regression analysis due to the skewed distribution of the seizure frequency data. An analysis of covariance was then conducted on the rank-transformed data with treatment as a factor and the ranked baseline seizure frequency per 28 days as a covariate. For the secondary end point, responder rates were analyzed over the maintenance period (LOCF) using the chi-square test.

RESULTS

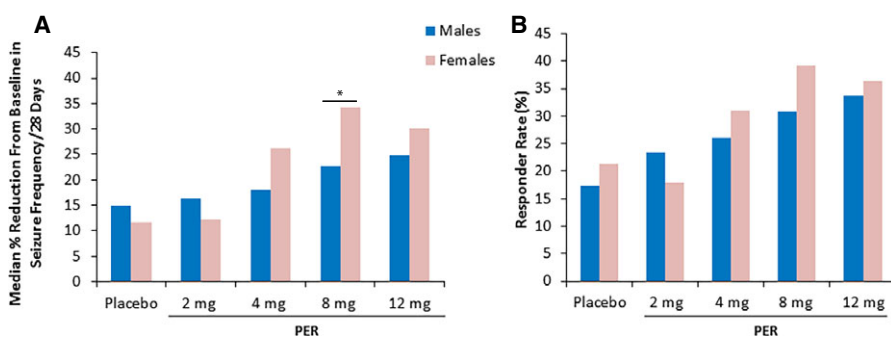
Demographics and baseline characteristics

Of the 1,478 subjects in the three phase III studies, 719 were male and 759 were female. Demographic and epilepsy-specific medical histories were similar for male and female participants at baseline: mean time since diagnosis (20.4 and 21.7 years, respectively); mean age (34.1 and 35.5 years, respectively); mean body mass index (25.1 and 24.9 kg/m², respectively); and seizure type (83.2% and 87.7%, respectively, had complex partial seizures with or without secondary generalization). Mean weight was 75.4 kg for male and 64.9 kg for female participants (Table S1).

Approximately one half received two AEDs (51.9% male, 49.5% female), and approximately one third received three AEDs (36.4% male, 34.4% female). EIAEDs were taken by 60.9% of male and 56.1% of female subjects (Table S1). Oral contraceptives were taken by 7.1% (n = 38) of perampanel-treated and 9.5% (n = 21) of placebo-treated female subjects. Other hormone therapy medications were taken by 6.7% (n = 36) of perampanel-treated and 7.7% (n = 17) of placebo-treated female subjects.

PK assessment by gender

When analyzed by gender, perampanel apparent oral clearance (CL/F) was 17% lower in female than in male participants (0.605 L/h vs. 0.730 L/h), assuming a fatty body mass of 17.1 kg and no concomitant EIAEDs. For both genders, the CL/F of perampanel increased significantly when perampanel was concomitantly administered with EIAEDs (carbamazepine, oxcarbazepine, or phenytoin; Table S2). Although clearance was increased with these EIAEDs, it remained somewhat lower in female than in male participants. When analyzed by gender, the CL/F of clobazam,

**Figure 1.**

Median percent reduction in seizure frequency (A) and responder rates (B) by gender. PER, perampanel. * $p < 0.05$ female versus male. Epilepsia © ILAE

levetiracetam, and oxcarbazepine was lower in female compared to male subjects. The addition of perampanel increased clobazam CL/F (<5% in male and <8% in female subjects); had no effect on levetiracetam CL/F; and decreased oxcarbazepine CL/F (26% in male and 35% in female subjects; Table S2). Overall, the population PK models show no clinically relevant effect of perampanel on the pharmacokinetics of carbamazepine, lamotrigine, clobazam, clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide. The population PK/PD model showed no difference in the perampanel concentration–therapeutic response relationship based on gender.

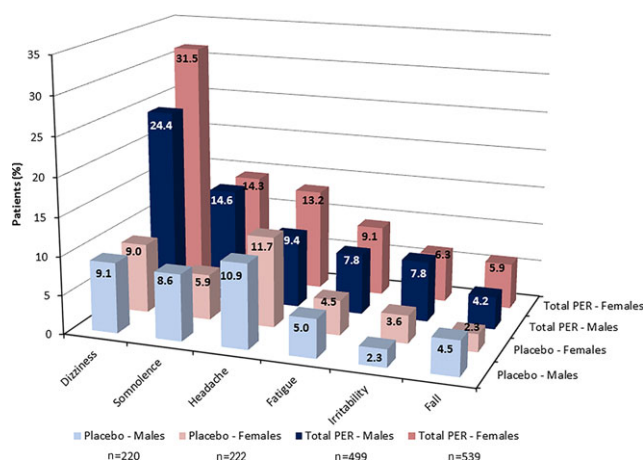
Efficacy

Median percent change in seizure frequency per 28 days and responder rates by gender are shown in Figure 1. With perampanel treatment, both genders displayed improved seizure control; however, female participants experienced consistently greater numerical reductions in seizure frequency (Fig. 1A) and increases in responder rates (Fig. 1B) at therapeutic perampanel doses (4–12 mg). A significant difference between genders was observed only for the median percent change at the 8 mg dose (Fig. 1A; $p < 0.05$). The magnitude of the treatment effect relative to placebo (placebo-adjusted) for the median percent change in seizure frequency (all partial seizures and complex partial plus secondarily generalized seizures) for perampanel 4, 8, and 12 mg doses was numerically higher for female than for male participants (Table S3).

Safety

Very common TEAEs ($\geq 10\%$ of any treatment group) occurred at similar rates in perampanel-treated male and female patients, except for dizziness and headache, which occurred at a slightly higher rate in female than in male participants (Fig. 2). Aggression was higher in male (perampanel $n = 12$, 2.4%; placebo $n = 1$, 0.5%) compared to female (perampanel $n = 5$, 0.9%; placebo $n = 1$, 0.5%) subjects, but the overall incidence was low for both genders.

Regardless of gender, AEs were the main reason for discontinuation; however, the percentage was higher for perampanel-treated female (10.9%) than for male subjects

**Figure 2.**

Common treatment-emergent adverse events (TEAEs) in male and female subgroups. Very common TEAEs are those that occurred in $\geq 10\%$ of the subjects in any treatment group and were similar for both gender subgroups. PER, perampanel; TEAE, adverse event that either begins on or after first dose date and up to 30 days after last dose date of study drug, or begins before first dose date and increases in severity during treatment period. Subjects treated during double-blind study; dose is based on the last dose treatment. A subject with two or more adverse events in the same system organ class (or with same preferred term) is counted only once for that class (or term). n = total number of subjects in each dose group in this pool. Males: placebo $n = 220$, PER 0 mg $n = 2$, PER 2 mg $n = 93$, PER 4 mg $n = 93$, PER 6 mg $n = 35$, PER 8 mg $n = 184$, PER 10 mg $n = 16$, PER 12 mg $n = 76$. Females: placebo $n = 222$, PER 0 mg $n = 2$, PER 2 mg $n = 104$, PER 4 mg $n = 94$, PER 6 mg $n = 45$, PER 8 mg $n = 193$, PER 10 mg $n = 21$, PER 12 mg $n = 80$. Epilepsia © ILAE

(6.8%) (Table S4). For both genders, AEs leading to discontinuation appeared dose related. TEAEs leading to discontinuation in more than three subjects included dizziness (2.4%), somnolence (1.3%), fatigue (0.9%), and vertigo (0.7%) for female, and dizziness (1.8%), convulsion (1.4%), ataxia (0.8%), and vertigo (0.8%) for male participants.

Incidence of TEAEs among the 38 perampanel-treated female participants taking concomitant oral contraceptive medications was 94.7% ($n = 36$), versus 81.0% ($n = 17$) of placebo-treated subjects. Similarly, incidence of TEAEs in

perampanel-treated female patients receiving hormone therapy was 94.4% (n = 34) versus 82.4% (n = 14) of placebo-treated female patients.

DISCUSSION

The results of this pooled analysis of the three phase III perampanel studies support the efficacy and safety of perampanel and were generally consistent with previous pooled data analyses for perampanel.⁹ However, the current subgroup analysis highlights potentially relevant between-gender differences in pharmacokinetics, efficacy, and, to a lesser extent, tolerability.

Compared to men, women in general have lower body weight, slower gastrointestinal motility, and slower glomerular filtration rates.³ These physiologic gender differences need to be considered when evaluating the PK of drugs, including AEDs. For example, the CL/F of the AEDs pregabalin, vigabatrin, and gabapentin, which are primarily eliminated by renal excretion,¹⁰ was found not to be affected by gender in PK analysis.^{11–15} Based on population PK modeling, perampanel apparent clearance was 17% lower in female than in male participants not receiving concomitant EIAEDs, and it remained somewhat lower with concomitant EIAEDs, implying greater perampanel systemic exposure in females. The PK of perampanel includes a half-life of ~105 h as well as rapid and almost complete absorption following oral administration.^{7,16} Physiologic gender differences may contribute to the lower perampanel CL/F in female patients and may be associated with greater perampanel systemic exposure. The lower clearance and corresponding increase in perampanel plasma concentrations in female subjects may provide a basis for the slightly greater seizure reduction seen in female subjects with therapeutic doses (4–12 mg) of perampanel. A linear relationship has indeed been demonstrated between perampanel systemic exposure and its PD effects.⁸ At all doses of perampanel studied, both male and female participants exhibited reductions in seizure frequency compared to placebo, although at the 8 mg dose, a significant difference was observed between genders for the median percent change.

Consistent with the overall population,⁹ dizziness and headache were two of the most common AEs experienced by perampanel-treated male and female participants, occurring slightly more frequently in female participants. The discontinuation rate due to AEs was also somewhat higher for female (~11%) than for male (~7%) subjects. Women with epilepsy should be aware of special considerations associated with AEDs, including effects on reproductive and bone health, risk of fetal malformations, and drug interactions with oral contraceptives.^{17,18} Use of oral contraceptives and other hormone therapies can alter AED pharmacokinetics in a variable manner, decreasing exposure to some AEDs and increasing exposure to others.^{19–21} With concomitant use, perampanel (12 mg) reduces the concentration of the oral

contraceptive levonorgestrel, which can ultimately render it less effective.²² In the current study, although the concentration of oral contraceptives was not analyzed, the incidence of TEAEs in women receiving an oral contraceptive was found to be similar between those receiving placebo and those receiving perampanel.

These results suggest that the modest increase in perampanel plasma concentration in female subjects may explain between-gender differences in efficacy, although perampanel reduced seizure frequency for both genders. The recommended perampanel starting doses and titration regimens are appropriate for both men and women, and no dosage adjustments are required based on gender.²² However, dosing should be individualized according to clinical response and tolerability, and clinical response should be carefully monitored.

ACKNOWLEDGMENTS

This study was funded by Eisai Inc. Editorial support was funded by Eisai Inc. and provided by Imprint Publication Science, New York, NY.

DISCLOSURE OF CONFLICTS OF INTEREST

Blanca Vazquez has served as a consultant for Acorda, Eisai Inc., UCB Pharma, and Upsher-Smith, and has served as a consultant and a speaker for Sunovion and Supernus. Haichen Yang, Betsy Williams, Sharon Zhou, and Antonio Laurenza are employees of Eisai Inc. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study design for the three phase III perampanel pivotal studies.

Table S1. Baseline characteristics by gender.

Table S2. Perampanel and concomitant AED clearance by gender.

Table S3. Magnitude of the treatment effect relative to placebo for the median percent change in seizure frequency per 28 days, by gender.

Table S4. Study TEAEs and discontinuation by gender.