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FULL-LENGTH ORIGINAL RESEARCH

Concentration–effect relationships with perampanel in patients with pharmacoresistant partial-onset seizures

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Summary

Purpose: Although there is a general paucity of published pharmacokinetic (PK) data for new antiepileptic drugs (AEDs), PK analyses of pooled data from clinical studies of perampanel have recently been presented. We present PK/pharmacodynamic (PD) analyses of pooled data from phase III studies of perampanel describing efficacy and safety as a function of exposure, in order to determine whether a predictable concentration–effect relationship exists for perampanel efficacy and/or adverse events (AEs). The effects of concomitant enzyme-inducing AEDs (EIAEDs) and non–enzyme-inducing AEDs on the exposure, efficacy, and safety of perampanel are also considered.

Methods: Three multicenter, randomized, double-blind, placebo-controlled phase III studies investigated the efficacy and safety of perampanel 2–12 mg in patients with uncontrolled partial-onset seizures despite prior therapy with two or more AEDs. From baseline onward, patients also received ongoing treatment with stable doses of one to three approved concomitant AEDs. AEs were monitored throughout the studies. Changes from baseline in seizure frequency and 50% responder rates were evaluated. Exposure to perampanel was predicted based on the actual (last) dose using a previously established PK model. A population PK/PD model for the relationship between perampanel exposure and seizure frequency was estimated using nonlinear mixed-effect modeling with first-order conditional estimation, whereas logistic analyses for responder rate and AEs were performed using SAS analysis software.

Key Findings: The PK/PD population included 1,109 patients. Seizure frequency decreased linearly as predicted perampanel average steady-state plasma concentrations increased. Concomitant EIAEDs (carbamazepine, oxcarbazepine, and phenytoin) reduced exposure to perampanel but had no effect on the slope of the PD model–predicted relationship between exposure and reduction in seizure frequency. The probability of patients achieving a response was predicted to increase as perampanel average plasma concentration at steady state increased. No demographic, AED, region, or study covariate had any effect on the probability of achieving a positive treatment response to perampanel or on the slope of the exposure–response curve. Across the phase III studies, there were reports of dizziness (32.9%), somnolence (21.7%), fatigue (13.9%), irritability (12.3%), gait disturbance (9.1%), weight increase (6.1%), dysarthria (4.5%), and euphoric mood (0.5%); the model-predicted probability of these AEs increased significantly at higher exposure to perampanel (all $p < 0.001$). There was no effect of demographic variables or region on the probability of experiencing any of the AEs analyzed.

Significance: PK and PD analyses have played a pivotal role in the clinical development of perampanel as an adjunctive treatment for pharmacoresistant partial-onset seizures. Phase III data suggest that a significant relationship exists between increases in perampanel plasma concentration (i.e., systemic exposure) and reductions in seizure frequency. In addition, increases in perampanel plasma concentration may potentially be associated with increases in AE rates. The model-predicted concentration-safety profile of perampanel does not appear to be affected by patient age, gender, or ethnicity. Although concomitant EIAEDs may influence perampanel PK, they do not appear to alter the relationship between perampanel plasma concentration and seizure frequency. Understanding these relationships between perampanel plasma concentration and clinical response will be valuable in utilizing this novel AED.

KEY WORDS: Adverse effects, Antiepileptic drugs, Efficacy, Epilepsy, Pharmacodynamics, Pharmacokinetics.

Despite the availability of >20 approved antiepileptic drugs (AEDs) (Perucca & Tomson, 2011), approximately 20–30% of patients have epilepsy that is considered treatment refractory (French, 2007). During the last decade, our understanding of the neurobiology of epilepsy has led to the development of AEDs that target novel molecular targets.

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In addition, drug-development efforts have led to the development of AEDs with improved pharmacokinetic (PK) and pharmacodynamic (PD) profiles.

PK/PD data can provide key insights into appropriate dosing schemes for AEDs and facilitate their integration into clinical practice, but such data are currently lacking. For example, it has long been assumed that there is a relationship between plasma concentrations of AEDs and their clinical effects (Patsalos et al., 2008), but there are limited data from randomized controlled trials to provide guidance to clinicians who wish to use PD principles to assist them in optimizing individual drug regimens. As new AEDs are developed, there is also a need for data on drug–drug interactions and adverse events (AEs) due to AED polypharmacy and the concomitant use of other prescribed medications (Johannessen & Landmark, 2010).

Perampanel is a highly selective, orally active, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist (Hanada et al., 2011; Ceolin et al., 2012) that has recently been approved by the European Medicines Agency and the U.S. Food and Drug Administration (FDA) as an adjunctive treatment for partial-onset seizures with or without secondary generalization, in patients aged ≥12 years (European Medicines Agency, 2012; Food & Drug Administration, 2012). Following oral administration, perampanel is rapidly and almost completely absorbed, with high bioavailability (Templeton, 2009; Franco et al., 2013; Rektor, 2013). Plasma protein binding averages approximately 95% (European Medicines Agency, 2012; Food & Drug Administration, 2012; Franco et al., 2013). Perampanel is eliminated primarily by hepatic metabolism via cytochrome P450 (CYP)3A4, with an elimination half-life of approximately 100 h (European Medicines Agency, 2012; Food & Drug Administration, 2012; Franco et al., 2013). As might be expected, the apparent oral clearance (Cl/F) of perampanel is influenced by concomitant enzyme-inducing AEDs (EIAEDs), including carbamazepine, oxcarbazepine, and phenytoin, which can increase Cl/F two- to threefold (Laurenza et al., 2012). However, perampanel does not appear to induce or inhibit the CYP isozyme system (Laurenza et al., 2012).

Two phase II, randomized, double-blind, placebo-controlled, dose-escalation studies of perampanel were conducted in patients with partial-onset seizures (with or without secondary generalization) that were inadequately controlled despite prior treatment with at least three different AEDs within the previous 2 years (Krauss et al., 2012a). Findings from these studies demonstrated that perampanel 2–12 mg was well tolerated and provided preliminary evidence of antiseizure efficacy in this patient population. An analysis of pooled PK data from these studies found that a one-compartment disposition model with first-order absorption and elimination adequately described perampanel plasma concentrations (Fuseau et al., 2011). Moreover, preliminary PK/PD analyses demonstrated that the probability of achieving a therapeutic response increases as exposure to perampanel is increased. This relationship was used to select doses of perampanel for the phase III studies (predicted "no-effect," "low-effective," "mid-effective," and "high-effective," doses were 2, 4, 8, and 12 mg, respectively).

Clinical findings from the three pivotal phase III studies of adjunctive perampanel in patients with pharmacoresistant partial-onset seizures have been reported previously (French et al., 2012; Krauss et al., 2012b; French et al., 2013). Consistent with the phase II data, PK data derived from the three phase III studies have collectively suggested that there is a predictable dose–concentration relationship for perampanel (Laurenza et al., 2012). We suggest that it is also important to determine whether a similar relationship exists between perampanel predicted concentration and clinical effect, as this information could be valuable for the optimization and individualization of therapy. With this in mind, we present an overview of concentration–effect analyses of pooled data from the phase III studies and explore the impact of systemic exposure to perampanel on clinical measures of both efficacy and safety.

Methods

Study designs

Consistent with the phase II data, analyses of pooled PK data from the phase III studies also supported the use of a one-compartment disposition model with first-order elimination to describe perampanel plasma concentrations (Laurenza et al., 2012). These observations were used to develop a final PK model, which yielded adequate predictions of pooled data from the phase III studies of perampanel, and was considered an appropriate basis for predicting perampanel exposure in exposure–response PK/PD analyses.

Studies 304, 305, and 306 were multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III studies (French et al., 2012; Krauss et al., 2012b; French et al., 2013). In each study, patients were randomized to receive once-daily treatment over a 19-week double-blind phase, which consisted of a 6-week titration period followed by a 13-week maintenance period. All studies included a placebo group and a perampanel 8 mg group. Studies 304 and 305 both included an additional perampanel 12 mg cohort, whereas study 306 included additional perampanel 2 and 4 mg cohorts. Patients were uptitrated to their randomized dose in weekly increments of 2 mg. Throughout the maintenance period, patients continued treatment with the dose of perampanel achieved during the titration period. Dose reductions due to intolerability were permitted at the discretion of the investigator.

The studies were performed in accordance with the Declaration of Helsinki, European Medicines Agency requirements, and the U.S. Code of Federal Regulations.

The trial protocol, amendments, and informed consent were reviewed by national regulatory authorities in each country and independent ethics committees or institutional review boards for each site. Before trial participation, all subjects gave written informed consent.

Patients

Eligible patients were ≥12 years of age with uncontrolled simple or complex partial-onset seizures (with or without secondary generalization), despite prior therapy with two or more AEDs within the previous 2 years.

During the studies, patients received ongoing treatment with stable doses of one to three approved AEDs, only one of which was permitted to be a recognized EIAED, defined a priori as carbamazepine, phenytoin, phenobarbital, or primidone. The drug–drug interactions of perampanel were not fully established at the time of phase III study initiation, and therefore these EIAEDs were selected based on their known effects on other AEDs. However, subsequent analysis of perampanel plasma concentrations and PK modeling of the pooled phase III data showed that clinically important induction of perampanel metabolism was observed only with carbamazepine, oxcarbazepine, and phenytoin (based on presence versus absence of each concomitant treatment; Laurenza et al., 2012). Although topiramate was associated with statistically significant induction of perampanel, its effect on perampanel exposure was small and not deemed clinically relevant.

Key exclusion criteria included presence of non-motor simple partial seizures only, primary generalized seizures, diagnosis of Lennox-Gastaut syndrome, or history of status epilepticus in the previous year.

Pharmacodynamic assessments: efficacy and safety

Median percent change from baseline in overall seizure frequency per 28 days in the double-blind phase was the primary efficacy end point in the three phase III studies in all regions outside the European Union. The primary efficacy end point within the European Union was 50% responder rate (proportion of patients with ≥50% reduction from baseline in seizure frequency per 28 days in the maintenance period). Seizures were recorded daily in a patient diary and AEs were monitored throughout the studies.

Pharmacokinetic/pharmacodynamic modeling

The PK/PD population included all patients in the PK population plus all placebo-treated patients with total seizure frequency data (efficacy) and dosing/sampling history (safety) during the maintenance period (data from placebo-treated patients were included in the PK/PD model to account for placebo and time effects in addition to the active treatment, in order to lead to an unbiased effect of perampanel on the reduction in seizure frequency). The plasma concentrations of perampanel and each concomitant AED were measured. Predictions of perampanel exposure were based on modeled data derived from previous PK analyses (Laurenza et al., 2012).

Population PK/PD models for log-transformed seizure frequency were estimated by nonlinear mixed-effect modeling using NONMEM v5.1 (Icon Development Solutions, Ellicott City, MD, U.S.A.) with first-order conditional estimation. Models were validated using NONMEM objective function value, precision of parameter estimates, and visual inspection of goodness-of-fit. The probability of response and occurrences of AEs were analyzed by logistic regression using SAS v8.2 (SAS Software, Cary, NC, U.S.A.). A linear predictor (logit) was estimated as a function of exposure to perampanel. The influence of demographic covariates and concomitant AEDs or EIAEDs (presence/absence) on this relationship was examined on the logit and on the PK/PD analysis for log-transformed seizure frequency.

The population models used in these analyses comprised four basic components: (1) structural model; (2) interpatient variance; (3) covariate model; and (4) residual error model.

Based on the individual perampanel apparent clearance (Cl/F) from the final population, PK model average perampanel plasma concentrations at steady state (C_{avSS}) were calculated at visits 6, 7, and 8, as follows:

$$C_{avSS} = (\mathrm{DOSE}/24) * 1,000/(\mathrm{Cl/F})$$

Where DOSE is daily dose in mg and Cl/F is perampanel apparent oral clearance. At baseline, DOSE = 0 and C_{avSS} = 0. For the placebo-treated patients, C_{avSS} = 0.

Analysis of the relationship between perampanel dose and the predicted exposure/efficacy model was based on the actual (last) dose of perampanel achieved by patients completing the maintenance period of the phase III studies rather than the randomized dose. This approach was adopted given that randomized dose analyses may underestimate efficacy at higher doses in standard AED clinical trials as a consequence of fixed-flexible dosing paradigms, which allowed for downward dose titration in the setting of intolerability.

Logistic regression analysis for the relationship between exposure to perampanel and safety was conducted based on AEs of special interest (decreased appetite, dizziness, dysarthria, euphoric mood, fatigue, gait disturbance, increased appetite, irritability, and weight increase) and/or AEs that occurred most frequently (≥30 patients). In this analysis, C_{avSS} was used as a marker of systemic drug exposure.

Laboratory measurements

Total plasma concentrations of perampanel were analyzed by both liquid chromatography-fluorescence (LC-Fl), and liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) on a triple quadrupole mass spectrometer under positive ion mode. LC-Fl methodology

utilized liquid–liquid extraction with reverse-phase chromatography. In all LC-Fl methods, the fluorescence detector wavelength was 290 nm excitation and 430 nm emission. The assay range was between 0.25 and 1,000 ng/ml and required assay volumes of between 0.05 and 1 ml.

Accuracy and precision for all bioanalytical methods used were within 15%.

Results

Patient populations

Data from a total of 1,109 patients were included in the PK/PD analysis. Study cohorts were well balanced in terms of demography and clinical characteristics at baseline (Table 1). The mean (range) age was 34.5 (12–76) years, 51.2% of patients were female, and the majority of patients were white or Asian (75.5% and 12.0%, respectively). Baseline laboratory findings were indicative of normal renal and liver functions. Overall, median seizure frequency at baseline was 11.3 seizures per 28 days. The majority of patients (71.1%) were being treated with at least one EIAED at baseline (carbamazepine, 34.2%; oxcarbazepine, 18.1%; phenytoin, 8.2%).

Overall efficacy

Findings from each of the core individual phase III studies (studies 304, 305, and 306) demonstrated the efficacy of perampanel 4–12 mg/day as adjunctive therapy in patients with treatment-resistant partial-onset seizures (French et al., 2012; Krauss et al., 2012b; French et al., 2013). Compared with placebo, significantly greater changes from baseline in median seizure frequency per 28 days were observed with perampanel 4 and 8 mg in study 306 ($p < 0.01$ and $p < 0.001$, respectively) and with perampanel 8 and 12 mg in study 305 ($p < 0.001$ and $p < 0.05$, respectively) and study 304 (both $p < 0.05$). Significantly higher 50% responder rates versus placebo were observed with perampanel 4 and 8 mg in study 306 ($p < 0.05$ and $p < 0.001$, respectively) and with perampanel 8 and 12 mg in study 305 ($p < 0.01$ and $p < 0.001$, respectively); however, no significant differences in 50% responder rate were found with perampanel 8 and 12 mg in study 304.

It is important to note that the responder rate in the placebo cohort of study 304 was higher than that reported in study 305 or study 306 (26.4% vs. 14.7% and 17.9%, respectively) (French et al., 2012; Krauss et al., 2012b; French et al., 2013). A subanalysis of patients in study 304 identified a significant treatment-by-region interaction in this one study with higher rates of placebo response observed in Central/South America regions compared with North America (33.3% vs. 21.9%; $p = 0.04$) (French et al., 2012).

Concentration–effect relationship: efficacy

Seizure frequency

The final PK/PD model–predicted log-transformed median seizure frequency per 28 days (LTSF/28) in perampanel-treated patients was based on the sum of $\log_e$ seizure frequency at baseline plus a constant placebo/time effect, and a perampanel effect that was proportional to C_{avSS}, as follows:

Table 1. Patient demography and clinical characteristics at baseline in pivotal phase III studies of perampanel (PK/PD population)

		Perampanel			
	Placebo (n = 339)	2 mg (n = 134)	4 mg (n = 136)	8 mg (n = 324)	12 mg (n = 176)
Mean (SD) age, years	34.3 (13.7)	33.2 (12.9)	33.4 (12.0)	35.6 (13.4)	35.0 (14.1)
Gender, n (%)					
Female	169 (49.9)	76 (56.7)	68 (50.0)	161 (49.7)	94 (53.4)
Race, n (%)					
White	261 (77.0)	86 (64.2)	86 (63.2)	256 (79.0)	148 (84.1)
Asian	36 (10.6)	27 (20.1)	28 (20.6)	30 (9.3)	12 (6.8)
Chinese	23 (6.8)	20 (14.9)	21 (15.4)	21 (6.5)	–
Black	10 (2.9)	–	–	7 (2.2)	7 (4.0)
Other	9 (2.7)	1 (0.7)	1 (0.7)	10 (3.1)	9 (5.1)
Mean (SD) BMI, kg/m^2	25.4 (5.6)	23.7 (4.5)	24.7 (4.9)	25.8 (5.7)	26.6 (6.1)
Mean (SD) FBM, kg	19.9 (11.4)	16.7 (8.1)	18.6 (9.5)	20.6 (11.5)	22.3 (13.4)
Mean (SD) CLCR, ml/min	120.5 (29.4)	115.0 (27.1)	117.0 (27.7)	118.8 (26.6)	124.1 (27.8)
Mean (SD) ALT, IU	20.8 (11.7)	20.0 (10.6)	22.8 (20.1)	21.3 (12.2)	20.0 (10.7)
Mean (SD) AST, IU	21.3 (8.5)	20.7 (7.1)	23.2 (16.1)	21.1 (7.1)	20.1 (6.8)
Median seizure frequency (min, max)	11.6 (3.2, 572.1)	9.8 (3.3, 438.0)	10.0 (3.3, 4504.0)	12.0 (3.2, 1022.6)	13.3 (2.9, 591.8)
Concomitant perampanel-inducer AEDs,[a] n (%)	231 (68.1)	94 (70.1)	97 (71.3)	225 (69.4)	141 (80.1)

AED, antiepileptic drug; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CLCR, creatinine clearance; FBM, fat body mass; PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation.

[a]Defined as carbamazepine, oxcarbazepine, phenytoin, or topiramate (note that the induction of perampanel associated with topiramate was small and not considered clinically important).

$$\text{LTSF}/28 = \text{LTSF}/28 \text{ at baseline} - 0.368 - 0.000595 \times C_{avSS} \text{ (ng/ml)}$$

The model-predicted reduction in seizure frequency by perampanel plasma concentration (C_{avSS}) is shown in Fig. 1. The slope for the linear decrease in $\log_e$ seizure frequency with an increase in exposure to perampanel was unaffected by concomitant AED administration, age, gender, race, study, or region, suggesting a consistent profile across a range of patients.

During the maintenance period, the model predicted an average placebo/time effect of −0.368 on the $\log_e$ scale (Table 2). Interpatient variability in the placebo/time effect was very large, with a standard deviation of 0.670 (182% coefficient of variation [CV]), indicating very high variability in the response of subjects receiving placebo.

Log_e seizure frequency decreased linearly as perampanel C_{avSS} increased. Perampanel-treated patients were predicted to achieve a decrease in total seizure frequency equivalent to −0.000595 on the $\log_e$ scale per 1 ng/ml increase in C_{avSS}. In other words, based on the final PK/PD model, a typical patient treated with perampanel is predicted to achieve improvements leading to a reduction in seizure frequency from 11.3 seizures per 28 days at baseline to 7.5,

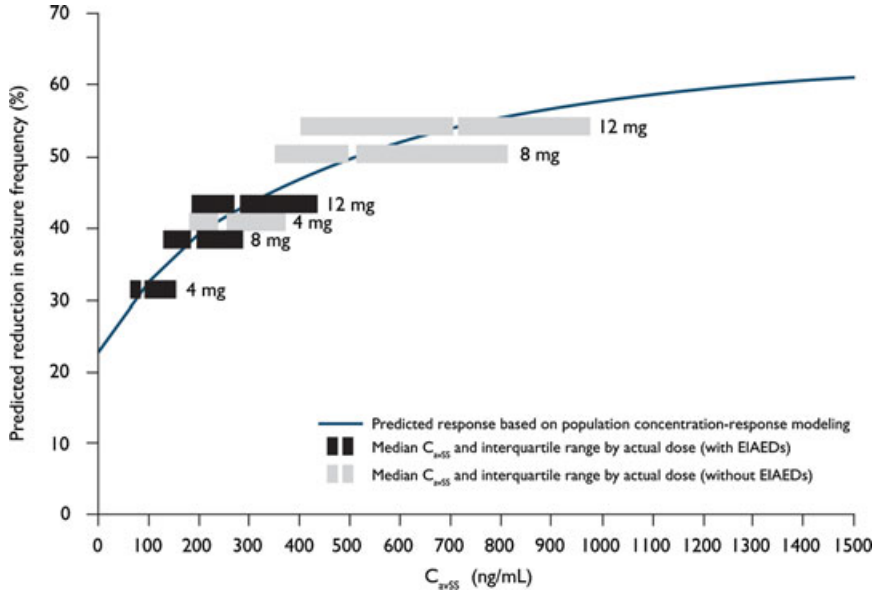

Figure 1.
PK/efficacy model-predicted response based on population concentration–response modeling. Doses shown are based on the actual (last) dose achieved by patients at the end of the maintenance period. The percentage change in seizure frequency corresponding to each actual median dose represents the model-predicted value. C_{avSS}, average plasma concentration at steady state; EIAED, enzyme-inducing antiepileptic drug; PK, pharmacokinetic.
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Table 2. Concentration of perampanel and primary efficacy outcomes across three phase III studies of perampanel during the maintenance period (visits 6, 7, and 8) (PK/PD efficacy/seizure population)

		Perampanel			
	Placebo (n = 339)	2 mg (n = 134)	4 mg (n = 136)	8 mg (n = 324)	12 mg (n = 176)
Visit 6					
Geometric mean concentration of perampanel[a]	–	73.7	141.5[c]	280.5	364.6[d]
Median change from baseline in seizure frequency per 28 days, %	−17.1	−18.0	−28.1[c]	−33.0	−33.3[d]
50% responder rate,[b] %	27.4	23.9	29.6[c]	37.0	37.0[d]
Visit 7					
Geometric mean concentration of perampanel[a]	–	73.9[f]	142.6[g]	279.9[h]	355.6[i]
Median change from baseline in seizure frequency per 28 days, %	−17.2[e]	−18.9[f]	−35.5[g]	−37.6[h]	−38.0[i]
50% responder rate, %	21.8[e]	28.2[f]	35.8[g]	39.8[h]	42.4[i]
Visit 8					
Geometric mean concentration of perampanel[a]	–	75.6[k]	146.1[g]	281.1[l]	358.6[m]
Median change from baseline in seizure frequency per 28 days, %	−18.7[j]	−21.0[k]	−31.6[g]	−40.4[l]	−39.1[m]
50% responder rate, %	22.0[j]	29.5[k]	38.8[g]	42.0[l]	43.5[m]

[a]Perampanel concentration is the predicted average at steady state.
[b]Response defined as ≥50% reduction from prerandomization period in seizure frequency per 28 days.
[c]n = 135; [d]n = 173; [e]n = 330; [f]n = 131; [g]n = 134; [h]n = 319; [i]n = 172; [j]n = 327; [k]n = 129; [l]n = 312; [m]n = 170.

7.2, 6.7, and 6.4 seizures per 28 days during the maintenance period at median C_{avSS} of 73.5, 146.3, 264.2, and 336.5 ng/ml, respectively (i.e., median C_{avSS}, based on individual observed concentrations pooled from visits 6, 7, and 8, for the 2, 4, 8, and 12 mg treatment groups, respectively). Interpatient variability in the slope for the effect of perampanel C_{avSS} on seizure frequency was large (132% CV).

Although EIAEDs reduced the overall systemic exposure of perampanel, they had no effect on the slope for the relationship between systemic exposure and reduction in seizure frequency. In addition, population PK analyses indicated that perampanel had no clinically relevant effect on the PK of the 10 most commonly coadministered AEDs.

50% Responder rate

Fifty percent Responder rate increased as perampanel C_{avSS} increased. Model predictions of 50% responder rates during the maintenance period are shown in Table 2. In the final logistic regression model, the probability of patients achieving a response was predicted to increase as perampanel concentration increased. This increase was equivalent to a slope of +0.00156 on the logit scale per 1 ng/ml increase in C_{avSS}, indicating that nonresponders will benefit from higher exposure to perampanel, by increasing their dose, to increase their chance of being responders.

Concentration–effect relationship: adverse events

The most frequently reported AEs (occurring in ≥30 patients [2.7%] in the overall PK/PD population) were dizziness (32.9%), somnolence (21.7%), fatigue (13.9%), irritability (12.3%), gait disturbance (9.1%), headache (6.8%), weight increase (6.1%), and dysarthria (4.5%). AEs of special interest that occurred less frequently included decreased appetite (2.3%), increased appetite (0.9%), and euphoric mood (0.5%).

Our analysis indicated that median predicted perampanel concentrations (C_{avSS}) would be higher in patients who experienced specific AEs compared with those who did not. The predicted probability of euphoric mood, dysarthria, weight increase, gait disturbance, irritability, fatigue, somnolence, and dizziness increased significantly at higher plasma concentrations of perampanel ($p < 0.001$ vs. lower plasma concentrations, each). Marked differences in plasma concentrations of perampanel (>150 ng/ml) were predicted between patients who experienced the following AEs versus those who did not: increased appetite (615 vs. 215 ng/ml), euphoric mood (607 vs. 215 ng/ml), gait disturbance (383 vs. 211 ng/ml), and dysarthria (368 vs. 214 ng/ml), respectively. Patients experiencing any of the other frequently reported AEs or AEs of special interest were predicted to have higher perampanel concentrations compared with those who did not; however, the differences were less pronounced (<150 ng/ml; Fig. 2). Despite differences in exposure, the predicted probability of headache and increased or decreased appetite was not significantly affected by an increase in perampanel plasma concentration.

There was no effect of demographic variables or region on the probability of experiencing any of the AEs analyzed.

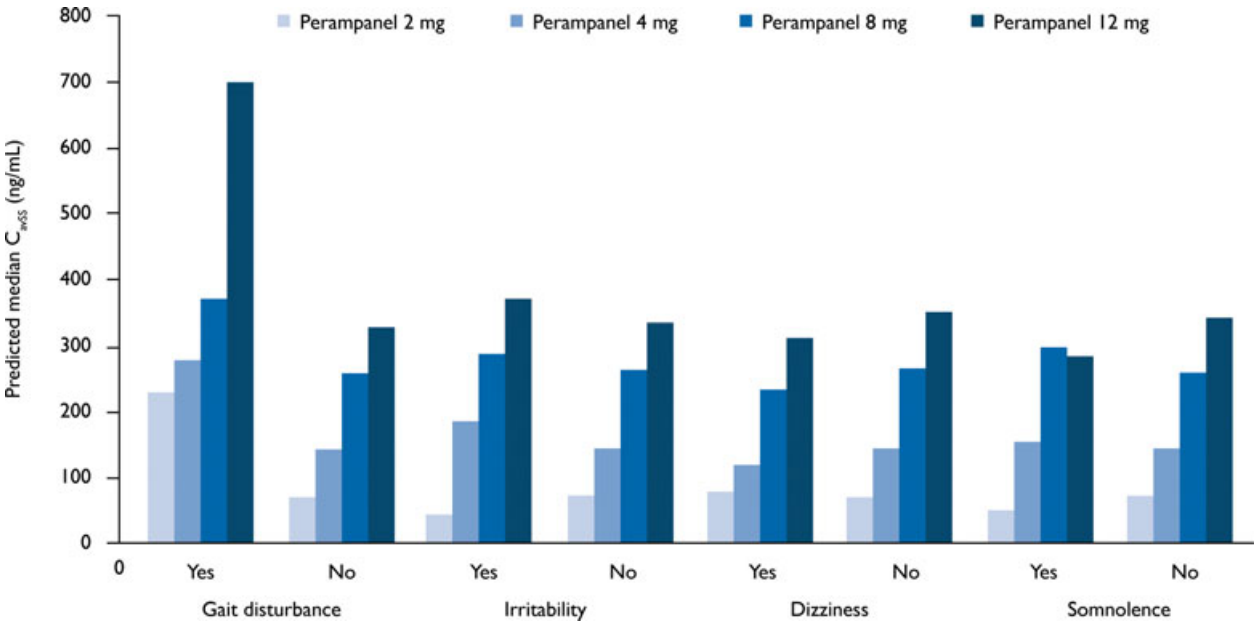

Figure 2.
Final PK/PD model predictions of median perampanel exposure (C_{avSS}) in patients with or without AEs of special interest. AE, adverse event; C_{avSS}, average plasma concentration at steady state; PD, pharmacodynamic; PK, pharmacokinetic.

In most cases, concomitant AED use had no effect; however, some exceptions were noted. The likelihood of developing fatigue was increased in perampanel-treated patients receiving concomitant levetiracetam. Coadministration of phenobarbital led to a predicted increased probability of irritability in perampanel-treated patients, whereas co-therapy with oxcarbazepine or primidone was associated with an elevated risk of decreased appetite.

Discussion

Analysis of pooled data from phase III studies of perampanel allowed the investigation of PK/PD relationships with this new AED. It is important to note that the analysis demonstrated a positive correlation between perampanel plasma concentration and therapeutic response in patients with pharmacoresistant partial-onset seizures. Although it would be premature to propose a specific initial target concentration, or therapeutic range for perampanel, these data suggest that steady-state plasma concentrations of about 70 ng/ml and above are more likely to be associated with a positive therapeutic response. Increasing plasma concentrations do seem to be associated with increased response; however, our model does not allow for a precise determination of a plateau concentration for therapeutic response.

Based on analyses of randomized dose, phase III data have suggested that perampanel 12 mg provides no additional clinical benefit over the 8 mg dose (French et al., 2012; Krauss et al., 2012b; French et al., 2013). However, this is inconsistent with our PK/PD analysis based on actual (last) dose that predicted a linear exposure/efficacy relationship across the 2–12 mg dose range. This suggests that randomized dose analyses likely underestimate efficacy at higher doses due to intrinsic study design factors discussed previously. Of note, efficacy analyses based on actual dose have shown that patients who tolerate perampanel 12 mg do achieve additional clinical benefit compared with those receiving lower doses (Kramer et al., 2012).

Despite lower perampanel plasma concentrations in patients receiving concomitant EIAEDs, the slope for the relationship between predicted perampanel exposure and efficacy in terms of seizure frequency was not meaningfully affected. In other words, the same correlation between plasma concentration and therapeutic response exists regardless of concomitant medications. It is important to note, that due to the effects of enzyme induction on perampanel plasma concentrations, initial dosages of perampanel will likely need to be increased and a more frequent uptitration schedule may be more appropriate in patients receiving a concomitant EIAED compared with those receiving non-EIAEDs (European Medicines Agency, 2012; Food & Drug Administration, 2012).

There has been increasing interest in potential "rational polytherapy" combinations of AEDs. In the present analysis, no consistent relationships between specific AED combinations and efficacy or tolerability measures were identified.

Although our data clearly suggest increasing efficacy with increased exposure, clinicians need to be mindful that increased perampanel plasma concentrations might translate into an increased side effect burden. Specifically, higher plasma concentrations were significantly associated with increased risks of dizziness, somnolence, fatigue, irritability, gait disturbance, weight increase, dysarthria, and euphoric mood, in that order. The model-predicted probability of these AEs increased significantly at higher exposure to perampanel (all $p < 0.001$), although it should be noted that the overall incidences were 0.5–28.1% across the phase III studies, with most AEs of mild or moderate intensity and no cases of sudden unexpected death in epilepsy (French et al., 2012; Krauss et al., 2012b; French et al., 2013). Nonetheless, such data on the relationship between plasma concentration and AEs will enable the clinician to better guide and individualize treatment.

Clinicians have long recognized the need to individualize pharmacotherapy in patients with epilepsy. The observation that a relationship between perampanel dose, plasma concentration, and expected clinical response seems to exist should be of clinical utility in this respect. Although it is a common clinical approach to dose an AED to clinical effect, it is not always clear whether there is an associated marginal benefit: does the AED have a predictable, linear concentration–response relationship, or does the concentration–response curve flatten out? Our findings show that, in the case of perampanel, seizure response may be improved by increasing plasma concentration. In addition, incorporating focused PK/PD analyses into future clinical trial design may further our understanding of how best to optimize use of this novel medication.

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Disclosures

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