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Potential protein-binding displacement interactions with perampanel: An in vitro analysis

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ABSTRACT

Plasma protein binding and effects on volume of distribution and pharmacologically active, circulating-drug concentrations are complex issues. Protein-binding displacement often underlies drug–drug interactions. Perampanel is a once-daily oral anti-seizure drug for focal seizures and primary generalized tonic-clonic seizures. Perampanel is also indicated for monotherapy use for focal seizures in the United States. Perampanel is extensively but slowly metabolized via CYP3A4. Its elimination $t_{½}$ is about 100 h, and it displays substantial plasma protein binding (> 95%). Here, we examine perampanel's potential to displace highly bound anti-seizure drugs and the ability of warfarin, a standard highly protein-bound drug, to displace perampanel. Protein binding of perampanel, phenytoin, valproate, and warfarin was assessed using equilibrium dialysis. Plasma samples containing each compound were dialyzed against phosphate buffered saline. For phenytoin, valproate, and warfarin, plasma samples were also dialyzed in the presence of perampanel. After 24 h equilibrium dialysis, amounts of test compounds were analyzed to calculate plasma protein binding. At clinically relevant concentrations, perampanel did not displace other highly bound drugs or vice versa. Protein-binding displacement may confound therapeutic drug monitoring of extensively protein-bound medications. Without empirical data, clinicians might be concerned that addition of perampanel could alter unbound concentrations of other medications, resulting in adverse effects. Our data indicate perampanel has low potential for drug interactions resulting from protein-binding displacement.

1. Introduction

While over the past several decades a number of new anti-seizure drugs (ASDs) have been introduced into the global market, the situation remains that a substantial number of patients will require treatment with multiple ASDs in order to adequately control their seizures. In addition, many patients with epilepsy suffer from comorbid psychiatric and medical conditions, making polytherapy with non-ASDs common clinical practice (Gidal et al., 2009). Given this, pharmacokinetic (PK) interactions have the potential to complicate, and at times confound, the management of patients with epilepsy (Brodie et al., 2013; Patsalos, 2013a, b).

Protein-binding displacement is perhaps one of the more misunderstood PK interactions. For example, many clinicians intuitively believe that if a drug is displaced from a protein-binding site, this will result in increased concentrations of free or unbound drug, with the likely result of an increased or potentially toxic pharmacological effect (Benet and Hoener, 2002). However, for most drugs, protein-binding-displacement–related interactions are likely to be clinically irrelevant unless there is also a coexisting alteration in drug metabolism (Benet and Hoener, 2002; Roberts et al., 2013). Nevertheless, even the potential for a clinically meaningful PK interaction is cause for concern.

Perampanel, a selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, is a once-daily oral ASD for focal seizures and primary generalized tonic-clonic seizures (European Medicines Agency, 2017; Food and Drug Administration, 2017). Perampanel is also indicated for monotherapy

Abbreviations: ASD, anti-seizure drug; C'$_{ss}$, unbound concentration; CL_H, hepatic drug clearance; CL_{int}, intrinsic metabolic clearance; CL_T, total clearance; C_{ss}, steady-state plasma concentration; CYP, cytochrome P450; F, bioavailability; Fu, unbound fraction; LC–MS/MS, liquid chromatography with tandem mass spectrometry; *m/z*, mass-to-charge ratio; PAR, peak area ratio; PBS, phosphate buffered saline; PK, pharmacokinetic; Q_H, hepatic blood flow; T, dose interval; $t_{1/2}$, half-life; V_d/F, volume of distribution

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use for focal seizures in the United States (Food and Drug Administration, 2017). Perampanel has a favorable — albeit unique — PK profile. Perampanel is well absorbed with a bioavailability (F) of approximately 100% (European Medicines Agency, 2012), with no evidence of marked first-pass metabolism (European Medicines Agency, 2017). Perampanel does not appear to be a substrate for efflux transporters, including P-glycoprotein, breast cancer resistance protein, or organic anion transporters (Patsalos, 2015). Perampanel displays extensive binding (95–96%) to plasma proteins. Binding in human subjects is mainly to albumin, alpha-1-acid glycoprotein and, to a lesser extent, gamma-globulin (Patsalos et al., 2017). Binding to albumin is constant over a concentration range of 20–2000 ng·mL^{-1}, whereas saturable binding to alpha-1-acid glycoprotein was seen at this same concentration range.

Population PK analyses of data derived from regulatory clinical trials suggest that perampanel is not expected to cause significant PK interactions. There are no data suggesting that perampanel induces the activity of major cytochrome P450 (CYP) enzymes or uridine diphosphate-glucuronosyltransferases, although perampanel at high doses may affect oral contraceptives, possibly via a CYP3A4-independent mechanism (European Medicines Agency, 2012; Patsalos, 2013a). In contrast, because perampanel is extensively and essentially exclusively metabolized by CYP3A4 (Food and Drug Administration, 2017), perampanel oral clearance and elimination half-life ($t_{½}$) are markedly influenced by concomitant treatment with enzyme-inducing ASDs (EIASDs) (e.g. carbamazepine, oxcarbazepine, and phenytoin) (Gidal et al., 2013, 2015; Majid et al., 2016; Patsalos et al., 2016).

It is well recognized that understanding PK interactions — both between ASDs and between ASDs and other non-epilepsy medications — is important in optimizing therapy in patients with epilepsy (Zaccara and Perucca, 2014). Perampanel has essentially complete F and is extensively metabolized (> 90%) via hepatic oxidation and sequential glucuronidation of inactive metabolites, with CYP being the principal enzyme involved (Patsalos, 2015). While CYP3A4-mediated metabolism of this agent is extensive, oral clearance is relatively slow, indicating that perampanel is a low-extraction-ratio drug. Data from Phase I studies suggest an average oral clearance of 11.0–13.5 mL·min^{-1} (Patsalos, 2015) and an average elimination $t_{½}$ of 88–103 h. Consistent with its metabolic scheme, three commonly used EIASDs — carbamazepine, oxcarbazepine, and phenytoin — can increase perampanel clearance by two- to three-fold (Gidal et al., 2013, 2015).

While the impact of enzyme induction and inhibition (Gidal et al., 2017) on perampanel PK is well recognized (Gidal et al., 2015), the potential confounding effect of protein-binding interactions on perampanel is not. As it is generally believed that drug distribution into the brain is driven by unbound or free fraction of a drug (Mandula et al., 2006), it would seem important to explore if concomitant medications can alter perampanel protein binding. Similarly, as several commonly used ASDs (including valproate and phenytoin, which are also categorized as low-extraction-ratio drugs) are, themselves, highly protein bound and commonly observed by use of therapeutic drug monitoring, it is important that potential displacement interactions are described. Therefore, our objective was to assess the potential impact of perampanel on the binding of the commonly used (and potentially toxic) ASDs, phenytoin and valproate, as well as the highly protein-bound, narrow-therapeutic-index drug, warfarin. In addition, potential protein-binding displacement of perampanel by the aforementioned drugs was explored, using an in vitro experimental design.

2. Materials and methods

2.1. Equilibrium dialysis

Solutions of test compounds were prepared using 50% methanol (distilled water/methanol [1:1, v/v]) and added at a 1:99 ratio to individual human plasma. Spiked concentrations of test compounds as free base were set at 0.5 and 2 μg·mL^{-1} for perampanel, 10 and 20 μg·mL^{-1} for phenytoin, 50 and 150 μg·mL^{-1} for valproate, and 1 and 5 μg·mL^{-1} for warfarin. Plasma samples (300 μL) spiked with test compounds were transferred into one side (donor chamber) of the dialysis device (Rapid Equilibrium Dialysis Device, molecular weight cut-off: 8 kDa; Thermo Scientific [Rockford, IL, United States]) and 500 μL of phosphate buffered saline (PBS; pH 7.4) was transferred into the other side (receiver chamber) of the dialysis device. The dialysis device was sealed with a Breathe-Easy® sealing membrane and incubated at 37 °C for 24 h on a shaker (Recipro Shaker NA-201, Speed 5; Nissin Scientific Corporation, Tokyo, Japan) in the CO_2 incubator (5% CO_2). Plasma samples spiked with phenytoin, valproate, or warfarin were also dialyzed in the presence of perampanel to evaluate protein-binding displacement interactions. After incubation, 15 μL of dialyzed plasma sample and 150 μL of dialyzed PBS sample were individually collected from each side of the dialysis device, and 15 μL of blank plasma and 150 μL of PBS were added to dialyzed PBS and plasma samples, respectively. Before and after incubation, 15 μL of plasma samples spiked with each test compound was collected and mixed with 150 μL of PBS. These samples were used for stability assessment during incubation. A volume of 15 μL of 50% methanol was added to all the samples and deproteinized with 150 μL of acetonitrile containing 10 ng·mL^{-1} niflumic acid as internal standard. The mixture was centrifuged, and the resulting supernatant was filtered and subjected to a liquid chromatography with tandem mass spectrometry (LC–MS/MS) analysis.

2.2. LC–MS/MS analysis

The LC–MS/MS system consisted of ACQUITY UPLC™ system (Waters) equipped with an Atlantis T3 column (5 μm, 2.1 mm × 50 mm, Waters), Quattro Premier XE™ (Waters), and MassLynx™ 4.0 software (Waters). The mobile phases for chromatography were (A) distilled water containing 0.1% formic acid and (B) acetonitrile containing 0.1% formic acid. The injection volume was 2 μL, and the run time was 6.0 min using an isocratic flow rate of 0.4 mL·min^{-1} (mobile phase composition: A = 60%, B = 40%). The temperature in the column heater and auto-sampler was set at 40 °C and 4 °C, respectively. The mass spectrometer was operated in positive electrospray ionization mode. The capillary voltage was 3.10 kV, the source temperature was 120 °C, the desolvation temperature was 400 °C, the cone gas flow rate was 300 L·h^{-1}, and the desolvation gas flow rate was 850 L·h^{-1}. The transition ions (mass-to-charge ratio; m/z) were 350.24 > 219.23 for perampanel, 253.21 > 182.07 for phenytoin, 144.94 > 70.87 for valproate, 309.19 > 251.20 for warfarin, and 283.07 > 264.99 for niflumic acid.

2.3. Determination of plasma protein binding

In this assay, peak area ratios were used for the calculation of plasma protein binding. All samples were analyzed in one batch only. The stability of each analyte in processed samples at 4 °C was also evaluated, and all analytes were stable for more than 24 h.

Protein binding (%) of each compound was determined in triplicate and calculated using the following equation:

$$Protein\ binding\ (\%) = 100 - \frac{PAR_{PBS}}{V_{PBS}} \div \frac{PAR_{plasma}}{V_{plasma}} \times 100$$

where PAR_{plasma} and PAR_{PBS} represent peak area ratios of the test drug to internal standard (niflumic acid) in dialyzed plasma and PBS samples, respectively; and V_{plasma} and V_{PBS} are collected volumes of dialyzed plasma (15 μL) and PBS (150 μL) samples, respectively. Mean and standard error of the mean of protein binding at each concentration were calculated.

Table 1
Molecular weights and spiked plasma concentration ranges of perampanel, phenytoin, valproate, and warfarin.

Compound	Molecular weight ($g \cdot mol^{-1}$)	Spiked plasma concentration range (low, high) ($\mu g \cdot mL^{-1}$)	(μM)
Perampanel	349.38	0.5, 2	1.43, 5.72
Phenytoin	252.27	10, 20	39.64, 79.28
Valproate	144.21	50, 150	346.72, 1040.15
Warfarin	308.33	1, 5	3.24, 16.22

2.4. Materials

Human plasma (containing sodium heparin as anticoagulant) was freshly obtained from three healthy volunteers following an overnight fast and in the absence of other medications. Informed consent was obtained from all the volunteers before blood collection. Perampanel was synthesized at Eisai Co., Ltd. (Ibaraki, Japan). Phenytoin sodium, warfarin, and niflumic acid were purchased from Sigma-Aldrich (St. Louis, MO, United States). Sodium valproate was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All other chemicals and reagents used were commercially available.

Clinicians are accustomed to interpreting drug plasma concentration data in units of $\mu g \cdot mL^{-1}$ for ASDs such as phenytoin or valproate, or perhaps $ng \cdot mL^{-1}$ for agents such as perampanel. However, when considering drug–protein-binding competition between different agents, actual molar concentrations of each drug (which account for the molecular weight of each chemical species in solution) need to be compared.

3. Results

3.1. Sample analysis of plasma concentration ranges

Spiked plasma concentration ranges for perampanel, phenytoin, valproate, and warfarin are presented alongside their molecular weights in Table 1.

No interference peaks were observed on mass chromatograms of blank samples at retention times of perampanel, phenytoin, valproate, warfarin, or niflumic acid. Linearity of test compounds was confirmed within the range covering peak area ratios of dialyzed samples, and the correlation coefficients were greater than 0.99. The test compounds were stable in human plasma during incubation at 37 °C for 24 h.

3.2. Effect of perampanel on protein binding of phenytoin, valproate, and warfarin in human plasma

Protein-binding values at the spiked concentrations of phenytoin (10 and 20 $\mu g \cdot mL^{-1}$), valproate (50 and 150 $\mu g \cdot mL^{-1}$), and warfarin (1 and 5 $\mu g \cdot mL^{-1}$) in human plasma in the absence and presence of perampanel are shown in Fig. 1. In the presence of perampanel at 0.5 and 2 $\mu g \cdot mL^{-1}$, protein-binding values of phenytoin, valproate, and warfarin were comparable with those in the absence of perampanel.

3.3. Effect of phenytoin, valproate, or warfarin on protein binding of perampanel in human plasma

Protein-binding values of perampanel in human plasma in the absence and presence of phenytoin, valproate, or warfarin are shown in Fig. 2.

In the presence of phenytoin (10 and 20 $\mu g \cdot mL^{-1}$), valproate (50 and 150 $\mu g \cdot mL^{-1}$), or warfarin (1 and 5 $\mu g \cdot mL^{-1}$), protein-binding values of perampanel (0.5 and 2 $\mu g \cdot mL^{-1}$) were comparable with those in the absence of these concomitant drugs.

4. Discussion

Understanding whether or not the protein binding of drugs is altered during concomitant administration of other medications is important for several quite pragmatic reasons. For drugs acting in the central nervous system, only unbound fractions of drugs are able to pass across the blood–brain barrier; thus, potential displacement, even if only transiently, might result in exaggerated pharmacological effects. The same might be said for non-ASDs such as warfarin, where again a transient increase in the unbound portion of this highly protein-bound drug might result in short-term variability in response with potentially

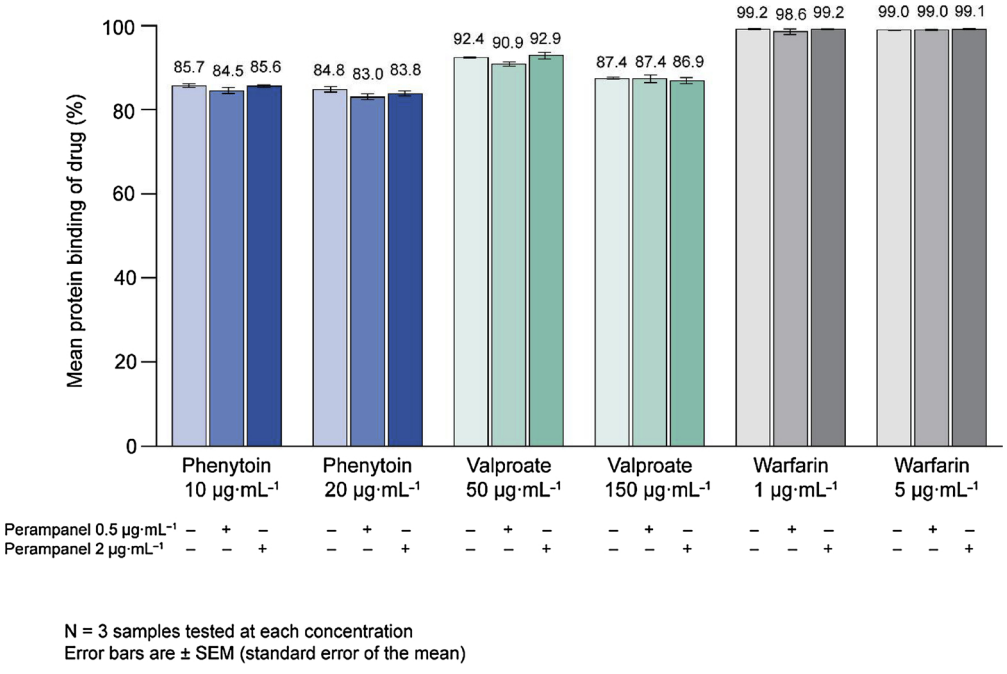

Fig. 1. Effect of perampanel on the protein binding of phenytoin, valproate, and warfarin in human plasma in vitro.

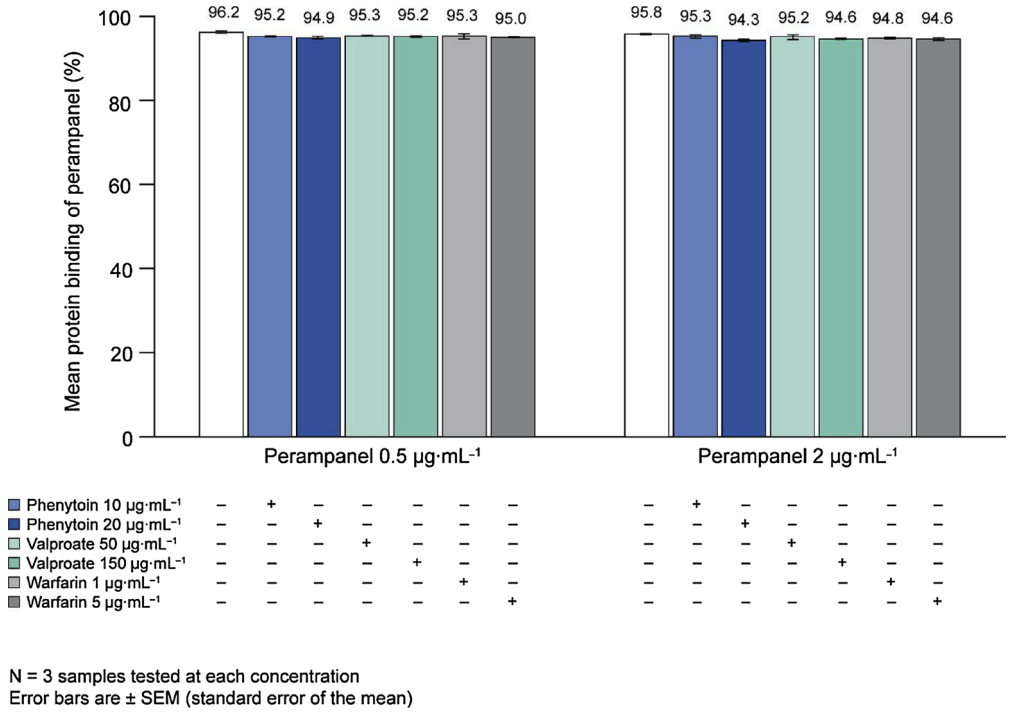

Fig. 2. Effect of phenytoin, valproate, and warfarin on the protein binding of perampanel in human plasma in vitro.

clinically important consequences. Also, given that monitoring of total plasma concentrations of ASDs, such as phenytoin and valproate, is commonly performed in order to optimize therapy, any displacement of these medications may lead to misinterpretation of plasma-concentration data.

Our data demonstrate that plasma protein binding of phenytoin, valproate, and warfarin was not affected by the presence of perampanel, indicating that perampanel is not a displacer of these drugs at clinically relevant concentrations (Gidal et al., 2013). Likewise, perampanel was not displaced from serum proteins by clinically relevant concentrations of phenytoin, valproate, or warfarin.

These results are consistent with the key properties of perampanel. First, for a drug to act as a displacer of another drug, one needs to consider the relative molar concentrations of the two agents that may reasonably be expected in vivo. Drug displacement from plasma protein is typically a result of competition for the same binding site or allosteric displacement due to microenvironmental changes at the binding site (Kragh-Hansen et al., 2002). Perampanel hemisesquihydrate has a molecular weight of 362.9 $g{\cdot}Mol^{-1}$ (Eisai Australia Proprietary Limited, 2017). At 2000 $ng{\cdot}mL^{-1}$ (a high, yet achievable, plasma concentration), this would equal 7.26 $\mu Mol{\cdot}L^{-1}$. In the case of phenytoin, for example, at what many would consider a low plasma concentration of 5 $\mu g{\cdot}mL^{-1}$, the equivalent molar concentration would be 19.8 $\mu Mol{\cdot}L^{-1}$. This suggests that, even at low concentrations, molar concentrations of phenytoin would greatly exceed those of perampanel.

Secondly, clinical evidence generated in Phase III clinical trials of perampanel shows that the PK profile of perampanel is altered in the presence of CYP3A4-inducing drugs, such as the highly protein-bound (90%) ASD, phenytoin.

However, in these trials, plasma concentrations of phenytoin and valproate (both low-extraction, extensively metabolized, and highly albumin-bound drugs) were unchanged. This is relevant in that, as a low-extraction-ratio drug, perampanel total clearance (CL_T) is dependent upon its unbound fraction (Fu) and its intrinsic metabolic clearance (CL_{int}).

The general hepatic clearance equation (i.e. 'well-stirred model') is a PK model of hepatic drug clearance (CL_H) that is physiologically based and incorporates hepatic blood flow (Q_H), Fu, and CL_{int} (Eq. 1), and can be used as a model to assess the theoretical impact of altered protein binding (Benet and Hoener, 2002).

$$CL_H = Q_H \times (Fu \times CL_{int})/Q_H + (Fu \times CL_{int}) \quad (1)$$

$$CL_T = Fu \times CL_{int} \quad (2)$$

As the unbound or free fraction increases (as one might expect in the presence of hypoalbuminemia or following the addition of a protein-binding displacer), CL_T will increase (Eq. 2) resulting in a decrease in average total steady-state plasma concentrations (C_{ss}) (Eq. 3).

$$C_{ss} = F \times dose/(T \times CL_T) \quad (3)$$

Pharmacological effect, however, is mediated by unbound-drug concentration. Unbound concentration at steady state is dependent upon CL_{int}, dose interval (T), and F. Importantly, in the event of protein displacement, even as total plasma concentration will decrease as unbound fraction increases, the pharmacologically relevant unbound concentration (C'_{ss}) will remain unchanged (Eq. 4).

$$C'_{ss} = F \times dose/T \times CL_{int} \quad (4)$$

Based upon these relationships, if perampanel was found to act as a protein displacer, even in the absence of any effects upon CL_{int}, a decline in either phenytoin or valproate plasma concentrations would be predicted. In fact, the results summarized here confirm that this is not seen. Consistent with this finding, our data further indicate no protein-binding displacement is observed, a finding consistent with the observation that no clinically meaningful international normalized ratio changes have been noted in patients receiving perampanel (data on file).

Finally, our experiments were also designed to assess potential displacement of perampanel by these commonly used drugs. Again, no changes were seen. Referring back to both the Phase III clinical trial data and post-marketing clinical experience (Patsalos et al., 2016) (since it is known that valproate exerts minimal inhibitory effects on CYP3A4 within the 50–1000-$\mu Mol{\cdot}L^{-1}$ range (Wen et al., 2001)), if this ASD were acting as a displacer, one would have predicted a decline in total perampanel plasma concentrations based upon the kinetic relationships. Again, this was not evident, confirming the overall consistency of in vitro and in vivo findings.

The above equations are based upon assumptions made at steady state. It may be argued that, acutely, should displacement occur, the drug would not only be available for metabolism but also to interact with a receptor. The extent that this (theoretically) could occur would be dependent upon redistribution and the victim drug's apparent volume of distribution (V_d/F), with the impact being most evident for drugs with small V_d/F (Rolan, 1994). In humans, a V_d/F greater than about 42 L (body water) indicates that the drug is highly distributed in tissues. In the case of perampanel, V_d/F is about 77 L. Therefore, one would expect a minimal 'acute effect'.

In summary, although our series of experiments were conducted in vitro, they are consistent with evidence from clinical trials. While no effects on perampanel by test study drugs were seen in this experiment, we unfortunately do not have unbound perampanel concentrations derived from clinical trial samples. In addition, our experiments were conducted using the simulation of normal serum albumin concentrations. Whether clinically significant hypoalbuminemia in patients would confound these observations is unknown. Taken in total, however, the data summarized here indicate that drug–drug interactions between perampanel and other common ASDs due to protein-binding displacement are unlikely.

Author contributions

Barry Gidal, Antonio Laurenza, and Takashi Ueno proposed the study concept and design, and were involved in the analysis and interpretation of the data. Takashi Ueno was also responsible for conducting the experiments. Jim Ferry was involved in the analysis and interpretation of the data. All authors contributed to the writing of the manuscript, critically reviewed each draft, approved the final manuscript for submission, and were involved in the decision to submit the article for publication. All authors also confirm accountability for the accuracy and integrity of the work.

Consent

Informed consent was obtained from all volunteers before sample collection in this study.

Conflicts of interest

Barry Gidal receives honoraria from serving as a speaker for Eisai, UCB, and Sunovion, and from consulting for Eisai, Lundbeck, Sunovion, and GW Pharmaceuticals.

Jim Ferry is an employee of Eisai Inc.

Antonio Laurenza is a former employee of Eisai Inc.

Takashi Ueno is an employee of Eisai Co., Ltd.

Prior publication

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