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Effect of enzyme inhibition on perampanel pharmacokinetics: Why study design matters

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ABSTRACT

Objectives: Perampanel, a selective, noncompetitive AMPA receptor antagonist, is indicated as adjunctive therapy for the treatment of partial seizures with or without secondarily generalized seizures and primary generalized tonic-clonic seizures in patients with epilepsy aged 12 years and older. In vitro studies and Phase I trials indicate that perampanel is metabolized almost exclusively by CYP3A, with an elimination half-life ($t_{1/2}$) averaging approximately 105 h. Understanding of pharmacokinetic (PK) interactions—enzyme inhibition or induction—and anticipating their occurrence are important for management of patients with epilepsy. Here we report PK results from a Phase I drug-drug interaction (DDI) study (Study 005) combining perampanel with the CYP3A inhibitor ketoconazole, as well as supplementary in silico predictions further exploring this interaction.
Methods: A Phase I, randomized, open-label, two-period, two-treatment, two-way crossover study was conducted in 26 healthy adult male volunteers. Subjects were randomized to 1 of 2 treatment sequences. In one period, subjects received a single 1-mg fasting dose of perampanel (Day 1); in the other period, subjects received ketoconazole 400 mg once daily for 10 days with a single 1-mg perampanel dose while fasting (Day 3). Blood samples were drawn at multiple time points up to 288 h after the perampanel dose. Pharmacokinetic parameters of perampanel were calculated by noncompartmental analysis, and safety was recorded. An integrated, physiologically based PK model built in Simcyp® provided additional insight into this interaction. Drug-drug interaction intensity was measured by the ratio of systemic exposure (area under plasma concentration-time curve [AUC]) of perampanel in the presence or absence of concomitant ketoconazole.
Results: Single oral doses of 1 mg perampanel and once-daily oral doses of ketoconazole 400 mg were safe and well tolerated. Maximum perampanel plasma concentration (C_{max}) and time to C_{max} showed no apparent differences when perampanel was administered alone versus with ketoconazole. Ketoconazole co-administration resulted in an approximate 20% increase in perampanel AUC ($P < 0.001$). This increase, although statistically significant, was a < 2.0-fold AUC change and alone would suggest a modest effect of ketoconazole. To further explore these results, DDI simulations were performed to query the findings and test additional study conditions. Using the actual trial conditions of Study 005, the simulations also predicted an AUC ratio increase < 2-fold, providing verification of the simulation assumptions and the modest effect of ketoconazole for 10 days. Simulations further suggested that an interaction effect of ketoconazole on perampanel exposure (> 2-fold) of potential clinical significance could be predicted when using larger doses of ketoconazole (e.g., 200 mg every 6 h) coadministered for a greater time period (e.g., 30 days), with AUC ratio as high as 3.36. Additionally, simulations suggested that a significant interaction with co-administration of perampanel and an inhibitor more

Abbreviations: AED, antiepileptic drug; ANOVA, analysis of variance; AUC, area under the concentration–time curve; $AUC_{0\text{-inf}}$, area under the concentration-time curve extrapolated to infinity; BCRP, breast cancer resistance protein; BID, twice per day; CI, confidence interval; CL_{int}, intrinsic retrograde-calculated clearance; C_{max}, maximum plasma concentration; C_{min}, trough concentration; DDI, drug-drug interaction; ECG, electrocardiogram; FDA, US Food and Drug Administration; PBPK, physiologically based PK; PER, perampanel; PGTC, primary generalized tonic-clonic; PK, pharmacokinetics; QD, once per day; $t_{1/2}$, half-life; t_{max}, time to C_{max}

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potent than ketoconazole (such as itraconazole) could not be ruled out.
Conclusions: Selecting an appropriate study design is critical to fully characterize the PK interaction for drugs such as perampanel that have a long $t_{1/2}$. Although a negligible effect on perampanel PK was observed following co-administration of ketoconazole 400 mg/day for 10 days, this is likely due in part to the relatively brief co-administration period of ketoconazole and perampanel (< 3 times the $t_{1/2}$ of perampanel). While short-term administration of a CYP3A inhibitor may not significantly increase perampanel exposure, such increases may be expected following chronic and larger dosing or with a more potent inhibitor.

1. Introduction

Perampanel is an orally active, noncompetitive, selective AMPA receptor antagonist that is approved as adjunctive therapy for the treatment of both partial seizures, with or without secondarily generalized seizures, and primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy aged 12 years and older (Fycompa Prescribing Information, 2016; Rogawski and Hanada, 2013).

Perampanel is a low-extraction ratio drug, meaning that it has minimal first-pass metabolism (Fycompa Prescribing Information, 2016). Perampanel does not appear to be a substrate for P-glycoprotein (Patsalos, 2015). Following oral administration, absorption of perampanel is rapid and almost complete, with peak plasma concentrations being achieved in approximately 1 h (Franco et al., 2013). Perampanel is extensively protein bound (95–96%), primarily to albumin and α1-acid glycoprotein (Fycompa Prescribing Information, 2016; Patsalos, 2015).

Both absorption and elimination pharmacokinetics (PK) of perampanel are linear, predictable and essentially complete over the clinically relevant dosing range of 2–12 mg/day (Patsalos, 2015). In vitro studies demonstrate that perampanel is not a substrate for multidrug efflux transporters including P-glycoprotein, BCRP, or human anion transporters (OAT1-4) (Patsalos, 2015). Perampanel is extensively metabolized (> 90%) via hepatic oxidation and sequential glucuronidation of inactive metabolites (Patsalos, 2015). Specifically, the principal enzymes involved are cytochrome P4503A4 (CYP3A4) and/or CYP3A5 (Patsalos, 2015). Although CYP3A-mediated metabolism of this agent is the primary route of elimination, perampanel apparent oral clearance is relatively slow. Population PK analyses from the perampanel Phase 1 program, which included pooling data from > 20 separate studies, determined that the mean elimination half-life ($t_{1/2}$) is approximately 105 h. Based on this, if one accepts that steady-state is achieved in 4–5 half-lives, then steady-state would require approximately16–20 days of repeat dosing.

It is well recognized that understanding PK interactions both between AEDs and between AEDs and non-AED medications is important in optimizing therapy in patients with epilepsy (Zaccara and Perucca, 2014). Based on in vitro and population PK data, it would not be anticipated that perampanel will itself perpetrate significant PK interactions (Patsalos, 2015). However, given its extensive metabolism via CYP3A, it is well documented that the oral clearance of perampanel can be markedly affected by enzyme-inducing AEDs such as phenytoin, carbamazepine, and oxcarbazepine (Fycompa Prescribing Information, 2016; Gidal et al., 2013, 2015). Indeed, these three inducers may increase perampanel clearance by two- to threefold (Gidal et al., 2013).

Although the impact of enzyme induction on perampanel plasma concentrations and expected therapeutic response are well known (Gidal et al., 2015), the potential effect of enzyme inhibition on perampanel is not as well understood. Conceptually, because its elimination is largely controlled by CYP3A-mediated metabolism, inhibition of CYP3A may result in an increase in the systemic exposure of perampanel, possibly leading to adverse effects. Indeed, in vitro studies using human liver microsomes revealed that the CYP3A4 0.3 μM of ketoconazole inhibited 60–65% of the metabolite formation of M1 (the most abundant metabolite formed), M3, M4, and M19. Similarly, ketoconazole also inhibited the in vitro formation of M6, M7, and M8 (Data on file, Eisai, Study B07001). The formation of all perampanel metabolites was inhibited by ketoconazole in a concentration-dependent manner. Curiously, however, a dedicated drug- interaction study conducted in healthy volunteers using this same strong CYP3A4 inhibitor resulted in only a negligible increase in perampanel exposure. Clearly, given these seemingly conflicting findings, a more complete understanding of the potential for inhibitory interactions is important in optimizing the clinical use of this AED.

The objectives of this manuscript are two-fold. First, we describe the results of a standard, Phase 1 drug-drug interaction (DDI) study that was conducted in healthy subjects using the potent CYP3A inhibitor ketoconazole (U.S. Department of Health and Human Services, 2012). Second, we further explore and discuss the larger clinical implications of this potential DDI using in silico predictions as a way to reconcile the healthy volunteer data with in vitro metabolic findings.

2. Methods

2.1. Phase I drug-drug interaction study

2.1.1. Subjects and design

This open-label, randomized, two-period, two-treatment, two-way crossover, DDI study included 26 healthy male subjects, aged 18–45 years. Subjects were randomized to one of two study groups (Group A or B), each consisting of 13 subjects (Fig. 1). Each study group participated in two treatment periods. During Period 1, subjects in Group A received oral ketoconazole 400 mg once daily from Day 1 to Day 10 and a single oral dose of perampanel 1 mg on Day 3; subjects in

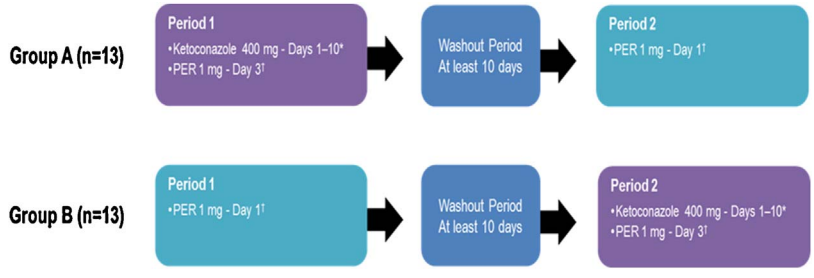

Fig. 1. Drug-drug interaction study design. *For pharmacokinetic (PK) parameters of ketoconazole, blood samples were drawn before dosing on Days 2, 3, and 4. †For PK parameters of PER, blood samples were drawn predose, then 15 and 30 min, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 240, and 288 h after PER dosing in Period 1 for Group A and Period 2 for Group B. PER = perampanel.