

An Open-Label Evaluation of the Effect of Coadministering Desvenlafaxine 100 mg on the Pharmacokinetics of Aripiprazole in Healthy Subjects

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Abstract

Study background: The atypical antipsychotic aripiprazole is commonly coadministered with antidepressant drugs as an adjunctive treatment for depression. The goal of the current study was to assess the potential for multiple-dose treatment with the antidepressant desvenlafaxine (administered as desvenlafaxine succinate) to modify the pharmacokinetics of aripiprazole.

Methods: Healthy subjects received aripiprazole 5 mg alone and coadministered with desvenlafaxine 100 mg at steady-state in an open-label, 2-period, sequential, inpatient/outpatient study. Blood samples collected prior to aripiprazole administration and for 14 days after each aripiprazole dose were analyzed for plasma aripiprazole and dehydro-aripiprazole concentrations. Aripiprazole area under the plasma concentration curve (AUC) over infinite time (AUC_{inf}) and peak plasma concentration (C_{max}) were determined for aripiprazole administered alone and co-administered with desvenlafaxine. Lack of an interaction was concluded if the 90% confidence intervals (CIs) for the ratio of adjusted geometric means for AUC_{inf} and C_{max} fell wholly within a prespecified acceptance range of 80% to 125%. Safety and tolerability were also assessed.

Results: Aripiprazole AUC_{inf} in the presence of steady state desvenlafaxine was 1584 ng·h/mL, compared with 1494 ng·h/mL for aripiprazole alone. The ratio of adjusted geometric mean (90% CI) was 106.0%, with CIs (101.4%, 110.8%) falling wholly within the prespecified acceptance range. The geometric mean C_{max} of aripiprazole was 24.7 ng/mL for aripiprazole administered alone or with desvenlafaxine (ratio of adjusted geometric means [90% CI], 101.1% [92.9% to 109.9%]). Coadministration of desvenlafaxine with aripiprazole did not alter dehydro-aripiprazole AUC_{inf} or C_{max} (ratio of adjusted geometric means [90% CI], 102.9% [94.2%, 112.5%], and 106.3% [101.0%, 111.9%], respectively).

Conclusions: Median plasma aripiprazole concentration-time profiles for single-dose administration of aripiprazole 5 mg alone and with steady-state desvenlafaxine 100 mg/d were nearly superimposable indicating that coadministration of multiple-dose desvenlafaxine 100 mg does not significantly alter aripiprazole pharmacokinetics.

Keywords: Desvenlafaxine; Aripiprazole; Pharmacokinetics; Drug interactions

Introduction

Major depressive disorder (MDD) has a lifetime prevalence in the United States of approximately 17% and is associated with significant disability [1]. High rates of incomplete response with first-line antidepressant therapy have been observed in a number of large scale studies [2,3]. Treatment options for patients with residual symptoms despite antidepressant treatment include dose optimization, combining two antidepressants, and augmentation with a psychotropic agent from another therapeutic class, such as lithium or an atypical antipsychotic [4]. Results of double-blind, placebo-controlled clinical trials of atypical antipsychotics used adjunctively with an antidepressant in patients with incomplete response to antidepressant treatment support the efficacy of this treatment option for further alleviating depressive symptoms and improving outcomes [4-8].

Aripiprazole is an atypical antipsychotic that is a partial D_2 dopamine and serotonin_{1A} agonist that is approved by the US Food and Drug Administration (FDA) as an adjunctive treatment for MDD [9,10]. Aripiprazole is primarily metabolized by dehydrogenation and hydroxylation through the cytochrome P450 (CYP) 3A4 and -2D6 enzymes, as well as N-dealkylation via CYP3A4 [10]. As a result of this metabolic profile, concomitant administration of aripiprazole with a drug that inhibits or induces CYP2D6 or -3A4 may affect the metabolism of aripiprazole [11]. For example, quinidine 166 mg/d,

a significant CYP2D6 inhibitor, has been shown to increase the area under the plasma concentration curve (AUC) of aripiprazole by 112% and decreased the AUC of dehydro-aripiprazole by 35% when coadministered with a single dose of aripiprazole 10 mg [10]. The clinical effect of aripiprazole is thought to be primarily driven by the parent compound but is also partially dependent on the primary metabolite, dehydro-aripiprazole, so inhibition of CYP3A4 and/or -2D6 may impact the efficacy or tolerability of aripiprazole [10].

A number of antidepressants are known to inhibit the activity of CYP2D6 to varying degrees [12]. As a result, dose adjustments are recommended when aripiprazole and CYP2D6 inhibiting antidepressants are used concomitantly; however, no dose adjustments are recommended when using aripiprazole adjunctively

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Received November 04, 2013; **Accepted** November 25, 2013; **Published** December 02, 2013

Citation: Nichols AI, Lubaczewski S, Liang Y, Matschke K, Braley G, et al. (2013) An Open-Label Evaluation of the Effect of Coadministering Desvenlafaxine 100 mg on the Pharmacokinetics of Aripiprazole in Healthy Subjects. J Bioequiv Availab 5: 253-259. doi:10.4172/jbb.1000169

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in MDD patients [10]. Desvenlafaxine (administered as desvenlafaxine succinate) is a serotonin-norepinephrine reuptake inhibitor approved by the FDA for the treatment of MDD at a dose of 50 mg/d [13] and has demonstrated efficacy in a number of randomized, placebo-controlled clinical trials [14-16]. The metabolic profile of desvenlafaxine suggests that it has a low risk for CYP mediated drug-drug interactions because this agent does not substantially inhibit or induce the activity of these enzymes; instead, the metabolism of desvenlafaxine primarily occurs through phase II glucuronidation and to a lesser degree through CYP3A4 [13,17,18]. The objective of the current study was to assess the potential of desvenlafaxine to interfere with the pharmacokinetics of aripiprazole and dehydro-aripiprazole when administered concomitantly using a population of healthy, nondepressed subjects.

Methods

Study design

This open-label, single-center, 2-period, sequential, inpatient/outpatient study was performed with a population of healthy subjects that did not meet criteria for MDD. A screening period occurred during the 28 days prior enrollment (Table 1). During period 1, subjects entered the inpatient setting for 3 days and 2 nights and received a single oral dose of aripiprazole 5 mg followed by blood sampling for pharmacokinetic analyses over the subsequent 14 days. During period 2, subjects reentered the inpatient setting for 9 days and 8 nights and received desvenlafaxine 100 mg once daily for 19 days until steady state concentrations were reached. On day 7 of period 2, subjects were coadministered a single dose of aripiprazole 5 mg followed by 14 days of blood sampling for pharmacokinetic analyses.

Inclusion criteria

Eligible study participants were required to be physically healthy, 18 to 55 years of age, and have body mass index (BMI) 17.5 to 30.5 kg/m² with a total body weight >50 kg. Physical health was defined as having no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead electrocardiogram and clinical laboratory tests. In addition, eligible subjects were required to be nonsmokers or smokers of <5 cigarettes daily and be able to abstain from tobacco use during the inpatient period.

Exclusion criteria

Subjects were ineligible to participate in this study if they had any evidence or history of clinically significant disease that would interfere with study completion or collection of accurate results in this study, including alcohol abuse or a positive urine drug screen. Pregnant or nursing females or females of childbearing potential who are unwilling or unable to use an acceptable method of nonhormonal contraception \geq 14 days before the first dose of study medication were excluded. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) before the first dose of study medication was prohibited. Eligible subjects could not have donated blood of approximately 1 pint (500 mL) within 56 days before dosing. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation, or use of an investigational product administration that may interfere with the interpretation of study results would make the subject ineligible for enrollment.

Pharmacokinetic analyses

Blood samples of 4 mL, to provide a minimum of 1.5 mL plasma for pharmacokinetic analysis, were collected at specified times and stored in appropriately labeled tubes containing K2-EDTA. Blood samples were placed in an ice-water bath immediately then centrifuged at 1700 g for 10 minutes at 4°C. Plasma samples were stored at -20°C within 1 hour of collection and analyzed for aripiprazole and dehydro-aripiprazole concentrations by Cetero Research (Houston, TX) using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. Calibration responses were linear over the range of 0.100 to 80.0 ng/mL for both aripiprazole and dehydro-aripiprazole using a weighted linear least squares regression with a lower limit of quantification of 0.100 ng/mL. Desvenlafaxine concentrations were also assayed using a validated LC/MS/MS method; calibration responses were linear over the range of 2.0 to 500.0 ng/mL.

The primary pharmacokinetic end point for this study was aripiprazole area under the plasma concentration curve (AUC) over infinite time (AUC_{inf}). Secondary end points included dehydro-aripiprazole AUC_{inf} , aripiprazole and dehydro-aripiprazole AUC to the last measurable concentration (AUC_{last}), peak plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F).

Plasma analyte concentrations at time 0 (C_0) of period 2, immediately before administration of the second dose of aripiprazole, were evaluated for possible carry-over effect by numerically adjusting AUC_{inf} and AUC_{last} based on pharmacokinetic superposition methods [19], and comparing original and corrected AUC_{inf} and AUC_{last} values. The equations used to calculate corrected AUC_{inf} ($AUC_{infcorr}$) and corrected AUC_{last} ($AUC_{lastcorr}$) are:

$$AUC_{infcorr} = AUC_{inf} - (C_0/k_{el})$$

$$AUC_{lastcorr} = AUC_{last} - (C_0/k_{el})$$

where, k_{el} is the terminal phase rate constant for period 2, calculated by a linear regression of the log-linear concentration-time curve.

Pharmacogenomic analyses

On study day 1, a 5 mL blood sample was collected to determine each subject's CYP2D6 phenotype to ensure that genetically derived variations in the activity of this metabolic enzyme will not impact the results of this study. A CYP2D6 genotype suggesting an intermediate metabolizer (IM), extensive metabolizer (EM), ultrarapid metabolizer (UM), and poor metabolizer (PM) phenotype predicted based on genotyped CYP2D6 alleles *1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *14, *17, *21, *36, *41 and gene duplication were analyzed. CYP2D6 genotyping was used to evaluate the potential impact of genetic polymorphism for any outliers (characterized by IM and UM status) and to exclude PM subjects from statistical analyses.

Safety analyses

An adverse event (AE) was defined as any untoward medical occurrence, defined using abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity, or progression/worsening of underlying disease. Additionally, AEs may include the signs or symptoms resulting from drug overdose, drug withdrawal, drug interactions, extravasation, and exposure in utero. A serious AE (SAE) was an event that resulted in death, was life threatening, required inpatient hospitalization

In addition, the difference between original and corrected AUC values was minimal, on average approximately 1.3% and 9.3% for AUC_{inf} and AUC_{last} , respectively. Due to the small contribution of carryover for C_{max} and AUC values, the uncorrected values were used for statistical analyses.

Similar to the observed plasma aripiprazole concentration-time profile, median plasma concentrations of dehydro-aripiprazole were equivalent whether aripiprazole was administered alone or with steady-state desvenlafaxine (Figure 2). The other pharmacokinetic parameters for dehydro-aripiprazole were also similar (Table 2). Dehydro-aripiprazole geometric mean C_{max} was comparable whether aripiprazole was administered alone (3.01 ng/mL) or with desvenlafaxine (3.20 ng/mL); however, median t_{max} increased with the coadministration of desvenlafaxine (59.9 hours vs 71.9 hours). Results of statistical comparisons of pharmacokinetic parameters for dehydro-aripiprazole are shown in Table 4. As AUC_{inf} could only be calculated for 18 of 38 subjects in period 1 and 14 of 35 subjects in period 2, AUC_{last} rather than AUC_{inf} was determined to be a more appropriate measure of exposure. Geometric means for dehydro-aripiprazole AUC_{last} was 599.6 ng•h/mL for aripiprazole alone and 630.9 ng•h/mL when desvenlafaxine was coadministered. Coadministration of

desvenlafaxine with aripiprazole did not significantly impact the geometric means of dehydro-aripiprazole AUC_{last} and C_{max} , as reflected by the ratio of adjusted geometric means (90% CI) of 105.2% (101.3%, 109.3%) and 106.3% (101.0%, 111.9%), respectively, which were within the bioequivalence range. Dehydro-aripiprazole AUC_{last} for the 4 subjects with an IM genotype ranged from 381 to 500 ng•h/mL, which was lower than the average AUC_{last} value. In contrast, the AUC_{last} for dehydro-aripiprazole for the subject with the UM genotype was higher (725 ng•h/mL) than the average AUC_{last} value.

Desvenlafaxine plasma concentrations: Predose plasma concentrations of desvenlafaxine were quantified for samples obtained prior to the second administration of aripiprazole. Quantifiable concentrations of desvenlafaxine were observed in all 35 subjects and ranged from 47.6 to 389 ng/mL.

Safety analyses

There were no deaths or other SAEs and no discontinuations, temporary discontinuations, or dose reductions due to an AE in this study (Table 5). The majority of AEs throughout the study were considered treatment-related, but most were mild in severity; no severe AEs were reported. The most frequent AE was nausea, reported by 6 subjects who received aripiprazole alone, 2 subjects who received desvenlafaxine alone, and 5 subjects who received aripiprazole with desvenlafaxine. Hot flushes were reported by 7 subjects while receiving aripiprazole. Of the treatment-related AEs, nausea (n=1), vomiting (n=2), headache (n=1), and presyncope (n=1) were moderate in severity; all AEs occurred during administration of aripiprazole. All other AEs were mild in severity.

Discussion

The present study examined the effect of desvenlafaxine 100 mg on the pharmacokinetics of aripiprazole 5 mg when coadministered to a population of healthy subjects. The results demonstrate that steady-state desvenlafaxine at twice the recommended dose for treating MDD did not significantly alter the pharmacokinetics of either aripiprazole or its active metabolite dehydro-aripiprazole. In conjunction with previously conducted pharmacokinetic studies that coadministered desvenlafaxine with the CYP2D6 substrates desipramine and tamoxifen and the CYP3A4 substrate midazolam, the results of the current study demonstrate that desvenlafaxine does not significantly affect the activity of the CYP2D6 and -3A4 enzymes [20].

In contrast to the results observed here with desvenlafaxine, a previously conducted study demonstrated that the coadministration of aripiprazole with the potent CYP2D6 inhibiting antidepressants fluoxetine and paroxetine significantly increased the steady-state dose-adjusted serum concentrations of aripiprazole by approximately 45% ($P < 0.05$) compared to aripiprazole alone [21]. In addition, when paroxetine was administered concomitantly with aripiprazole to genotyped CYP2D6 EMs, clearance of aripiprazole decreased by 58%, C_{max} increased 39%, and AUC_{inf} increased 140% compared to when aripiprazole was administered alone [22]. The effect of concomitant paroxetine was smaller in IM individuals (-23%, +27%, and +30%, respectively). A therapeutic drug monitoring analysis of aripiprazole suggests that concentrations of aripiprazole and dehydro-aripiprazole are associated with efficacy and tolerability, and individuals with particularly low or high levels of either or both compounds may be at risk for a lower therapeutic response or increased side effects, respectively [23]. A post hoc analysis conducted by Nelson et al. [24]

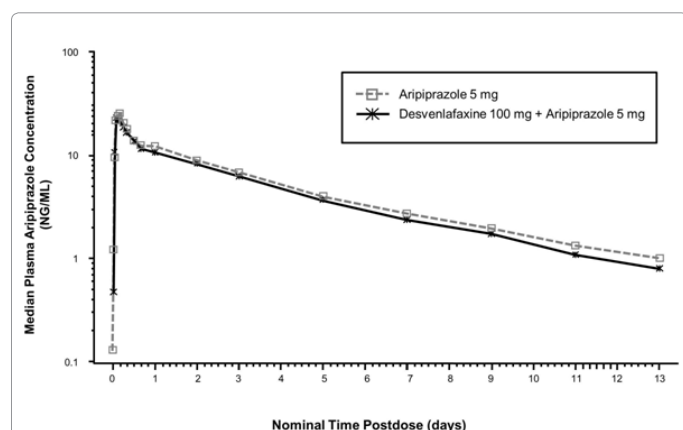


Figure 1: Median plasma aripiprazole concentration-time profiles following single oral dose of 5-mg aripiprazole alone and with 100 mg once daily oral desvenlafaxine. Aripiprazole concentrations are shown without corrections for carry-over.

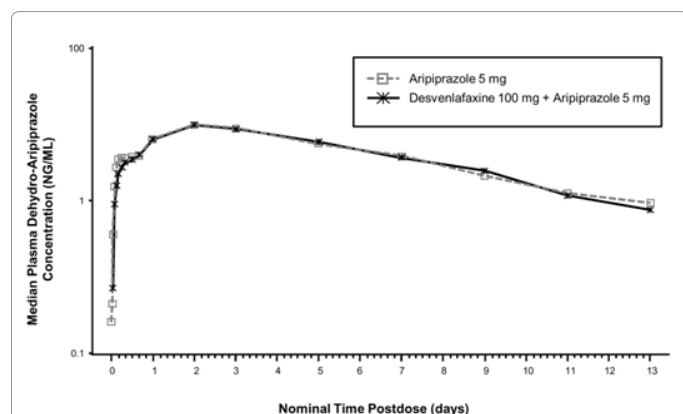


Figure 2: Median plasma dehydro-aripiprazole concentration-time profiles following single oral dose of 5-mg aripiprazole alone and with 100 mg once daily oral desvenlafaxine. Dehydro-aripiprazole concentrations are shown without corrections for carry-over.

	Aripiprazole		Dehydro-aripiprazole	
	Aripiprazole 5 mg (Reference)	Desvenlafaxine 100 mg + Aripiprazole 5 mg (Test)	Aripiprazole 5 mg (Reference)	Desvenlafaxine 100 mg + Aripiprazole 5 mg (Test)
N, n	38, 37	35, 35	38, 18	35, 14
AUC _{inf} (ng·h/mL)*	1494 (43)	1604 (33)	695.9 (21)	685.8 (21)
C _{max} (ng/mL)*	24.66 (29)	24.69 (29)	3.007 (34)	3.185 (30)
t _{max} (h) [†]	3.00 (2.00-8.00)	4.00 (2.00-8.00)	59.9 (23.9-120)	71.9 (23.9-168)
t _{1/2} (h) [‡]	85.17 (26)	84.18 (24)	97.78 (17)	94.27 (17)

AUC_{inf} = area under the plasma concentration curve over infinite time; C_{max} = peak plasma concentration; N= number of subjects in the treatment group; n= number of subjects where AUC_{inf} was determined for aripiprazole, and where t_{1/2} and AUC_{inf} were determined for dehydro-aripiprazole; t_{1/2} = half-life; t_{max} = time to peak plasma concentration
 *Geometric mean (geometric %CV)
[†]Median (range)
[‡]Arithmetic mean (%CV)

Table 2: Summary of Pharmacokinetic Parameters for Aripiprazole and Dehydro-aripiprazole Following Single Oral Dose of 5 mg Aripiprazole Alone and With 100 mg Once Daily Desvenlafaxine.

Plasma Aripiprazole Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means*	90% CI for Ratio
	Aripiprazole 5 mg With Desvenlafaxine 100 mg QD (Test)	Aripiprazole 5 mg (Reference)		
AUC _{inf} (ng·h/mL)	1584	1494	105.97	101.39, 110.76
AUC _{last} (ng·h/mL)	1465	1377	106.38	101.96, 110.99
C _{max} (ng/mL)	24.92	24.66	101.05	92.94, 109.87

AUC_{inf} = area under the plasma concentration curve over infinite time; AUC_{last} = area under the plasma concentration curve to the last measurable concentration; CI= confidence interval; C_{max} = peak plasma concentration; QD= once daily
 *The ratios (and 90% CIs) are expressed as percentages

Table 3: Statistical Summary of Treatment Comparisons (Aripiprazole).

Plasma Aripiprazole Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means*	90% CI for Ratio
	Aripiprazole 5 mg With Desvenlafaxine 100 mg QD (Test)	Aripiprazole 5 mg (Reference)		
AUC _{inf} (ng·h/mL)	699.2	679.3	102.93	94.21, 112.46
AUC _{last} (ng·h/mL)	630.9	599.6	105.23	101.32, 109.29
C _{max} (ng/mL)	3.195	3.007	106.27	100.97, 111.85

AUC_{inf} = area under the plasma concentration curve over infinite time; AUC_{last} = area under the plasma concentration curve to the last measurable concentration; CI= confidence interval; C_{max} = peak plasma concentration; QD= once daily
 *The ratios (and 90% CIs) are expressed as percentages

Table 4: Statistical Summary of Treatment Comparisons (Dehydro-aripiprazole).

	Aripiprazole 5 mg (n=38) [†]		Desvenlafaxine 100 mg (n=36) [†]		Desvenlafaxine 100 mg + Aripiprazole 5 mg (n=35) [†]	
	All	TR	All	TR	All	TR
Number of adverse events	32	27	8	6	19	17
Subjects with adverse events	14	12	5	4	9	9
Subjects with severe adverse events	0		0		0	
Subjects discontinued due to adverse events	0		0		0	
Subjects with dose reduced or temporary discontinuation due to adverse events	0		0		0	
Treatment-Emergent Adverse Events Occurring in ≥2 Subjects in Any Treatment Category[†]						
Gastrointestinal disorders	9	8	3	2	6	6
Nausea	6	6	2	2	5	5
Vomiting	3	3	0		2	2
General disorders and administration site conditions	1	1	0		2	2
Chills	0		0		2	2
Nervous system disorders	6	6	3	3	5	5
Dizziness	3	3	0		1	1
Headache	1	1	2	2	1	1
Presyncope	2	2	0		1	1
Vascular disorders	8	7	0		0	
Hot flush	7	7	0		0	

Except for the number of adverse events row, subjects are counted only once per treatment in each row
 All= all causality; MedDRA= *Medical Dictionary for Regulatory Activities*; TR= treatment related

[†]Subjects evaluable for adverse events

[†]If the same subject in a given treatment had >1 occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row. Includes all data collected since first dose of study drug. MedDRA (version 13.1) coding applied

Table 5: Summary of Treatment-Emergent Adverse Events.

found that adjunctive therapy with aripiprazole plus fluoxetine or paroxetine produced a numerically but not statistically significant greater risk of akathisia (32.2%) compared to those associated with escitalopram, venlafaxine, and sertraline (22.7%; OR 1.27 [95% CI: 0.37, 4.28] $P=NS$) which are less substantial CYP2D6 inhibitors [25,26]. Different elimination pathways account for the majority of desvenlafaxine (renal elimination and glucuronidation [13]) and aripiprazole (CYP2D6 and CYP3A4 metabolism [10], clearance, and coadministration of desvenlafaxine does not significantly impact the pharmacokinetics of aripiprazole. Desvenlafaxine therefore may be a safer and better tolerated option than several other antidepressants that inhibit CYP2D6 for adjunctive therapy with aripiprazole to treat MDD in patients not adequately responding to treatment with an antidepressant. No new or unexpected safety concerns related to administration of desvenlafaxine 100 mg were observed in this study. Furthermore, the coadministration of desvenlafaxine with aripiprazole appeared to be safe and generally well tolerated.

A study limitation was the use of a design that did not allow sufficient wash-out between doses of aripiprazole to exclude the presence of the drug and metabolite at the time of administration of the second dose. This shortcoming was primarily due to the limited information available in the literature for the $t_{1/2}$ for aripiprazole and dehydro-aripiprazole at the time the study design was developed [10,27-29] and a desire to not unnecessarily prolong study duration. However, the terminal log-linear elimination for both aripiprazole (Figure 1) and dehydro-aripiprazole (Figure 2) was well established by 6 days following aripiprazole administration. The second dose of aripiprazole was administered after a 14- to 21-day washout plus the 7-day period during which steady-state desvenlafaxine concentrations were attained, giving a total of 21 to 28 days between aripiprazole doses. The impact of this carryover can be determined based on calculation of corrected values for AUC_{last} and AUC_{inf} . Based on the calculation of corrected values, the mean percentage increase in these AUC values was 1.6% to 1.8% for aripiprazole and 1.3% to 9.3% for dehydro-aripiprazole. As this carryover was minimal, it was determined that calculation of PK parameters for the second treatment period did not need to be modified before making statistical comparisons of aripiprazole and dehydro-aripiprazole PK with and without coadministration of desvenlafaxine. If carry-over were to affect the statistical comparison between aripiprazole and aripiprazole plus desvenlafaxine, it would be to increase concentrations of aripiprazole and metabolite following the second aripiprazole dose. Thus, a conservative approach in testing for bioequivalence between the 2 doses was followed. The statistical comparisons between pharmacokinetic profiles demonstrated bioequivalence for both aripiprazole and dehydro-aripiprazole without and with the presence of desvenlafaxine, even though no adjustments for the presence of minor concentrations of aripiprazole and dehydro-aripiprazole were made.

Generalization of results to an MDD patient population that may be using multiple medications is limited by the use of healthy subjects in this study. In addition, because the study was primarily conducted to assess pharmacokinetic outcomes, the sample size was relatively small for fully assessing safety. Further analyses will need to assess the efficacy and safety of coadministering desvenlafaxine and aripiprazole in patients with MDD.

Conclusion

Using the assessed pharmacokinetic parameters of both

aripiprazole and its metabolite dehydro-aripiprazole, bioequivalence criteria were met when aripiprazole 5 mg was administered alone and coadministered with steady-state desvenlafaxine 100 mg. Thus, it appears that desvenlafaxine (at twice the dose recommended for treatment of MDD) does not significantly alter the pharmacokinetics of aripiprazole, lending support for the safety of using these agents in combination.

Acknowledgment

Medical writing support for this manuscript was provided by Marci Mikesell, MA, at Embryo, LLC, A division of Advanced Health Media, LLC and Kathleen M. Dorries, Ph.D, of Peloton Advantage. This study was sponsored by Wyeth Research, Collegeville, Pennsylvania, which was acquired by Pfizer Inc in October 2009.

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Citation: Nichols AI, Lubaczewski S, Liang Y, Matschke K, Braley G, et al. (2013) An Open-Label Evaluation of the Effect of Co-administering Desvenlafaxine 100 mg on the Pharmacokinetics of Aripiprazole in Healthy Subjects. *J Bioequiv Availab* 5: 253-259. doi:10.4172/jbb.1000169

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