Pharmacokinetics of a New Orally Disintegrating Tablet Formulation of Aripiprazole 15 mg Administered Without Water in Healthy Middle-aged Korean Subjects

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ABSTRACT

Purpose: The main objective of this study was to compare the pharmacokinetic properties and relative bioavailability of two 15-mg aripiprazole formulations (an orally disintegrating tablet [ODT] as the test drug and a conventional tablet as the reference drug) in healthy middle-aged Korean subjects.

Methods: This study was conducted in a population of healthy middle-aged Korean subjects as a randomized, open-label, single-dose, 2-sequence, 2-period crossover trial. After administration of a single dose of a 15-mg aripiprazole standard tablet with 240 mL water or an aripiprazole 15-mg ODT without water, blood samples were collected at specific time intervals from 0 to 240 hours. Concentrations of aripiprazole in plasma were analyzed by using a LC-MS/MS method of detection. Data on the pharmacokinetic parameters were recorded, and the 90% CIs of the ratios of the geometric means of the parameters were determined from the logarithmically transformed data by using an ANOVA model.

Findings: Thirty-nine healthy middle-aged Korean subjects were enrolled (mean age, 52.7 years; mean height, 167 cm; mean weight, 67.6 kg); 33 participants completed the study (29 male subjects and 4 female subjects). The 90% CIs of the geometric means ratio (test drug/reference drug) of C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ values were 0.95 to 1.14, 0.98 to 1.09, and 0.97 to 1.08, respectively. All of the subjects who experienced adverse events recovered without sequelae, and no serious adverse events were observed.

Implications: The aripiprazole pharmacokinetics was similar for the ODT and standard tablet of 15-mg aripiprazole in these healthy middle-aged Korean subjects. The aripiprazole ODT formulation is therefore expected to offer a convenient alternative for patients who have difficulty swallowing tablets without water. The study was registered at http://cris.nih.go.kr (registration number: KCT0001677). (*Clin Ther*. 2015;37:2772–2779) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: aripiprazole, middle-aged healthy subjects, orally disintegrating tablet, pharmacokinetics.

INTRODUCTION

Schizophrenia is a severe mental disorder characterized by a range of negative symptoms, positive symptoms, and cognitive dysfunctions, as well as a decline in psychosocial functioning.[1] The etiology of schizophrenia is unclear, but it is believed that the dopaminergic neuron system is involved in the pathophysiology and symptoms of the disease.[2] Because the causes of schizophrenia are not fully known, the focus of treatment is on eliminating the symptoms of the disease. First-generation antipsychotic agents such as chlorpromazine, haloperidol, and perphenazine have antagonistic properties at postsynaptic dopamine$_2$ (D_2) receptors in the mesolimbic and neocortical dopaminergic tracts, thus demonstrating efficacy for the treatment of positive symptoms.[3] However, due to their antagonism at D_2 receptors, these first-generation agents are also associated with adverse effects and a substantial risk of causing extrapyramidal symptoms, tardive dyskinesia, impaired cognition, and potential exacerbation of

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negative symptoms. Second-generation antipsychotic agents, such as clozapine, risperidone, and olanzapine, have less affinity for dopaminergic D_2 receptors and a greater affinity for antagonism at serotonin$_{2A}$ receptors than the first-generation antipsychotic agents. They demonstrate at least equal efficacy and better tolerability than typical antipsychotic agents.[3,4]

Aripiprazole*, a second-generation antipsychotic agent, was the top-selling drug in the United States in 2013.[5] It has been approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia, bipolar disorder, major depressive disorder, autism, and Tourette's syndrome.[6] Unlike other antipsychotic agents, aripiprazole is considered a partial dopamine agonist, acting on both postsynaptic D_2 receptors and presynaptic autoreceptors.[7,8] The partial agonist activity at the D_2 receptor of aripiprazole may explain its efficacy in the treatment of both positive and negative symptoms of schizophrenia and its lower propensity to cause extrapyramidal symptoms.[9] Elimination of aripiprazole is primarily through the hepatic metabolism involving the cytochrome P450 (CYP) 3A4 and CYP2D6 enzyme systems, resulting mainly in the formation of the active metabolite dehydro-aripiprazole.[10–12]

Aripiprazole has extensive extravascular distribution, and >99% of aripiprazole and dehydro-aripiprazole is bound to plasma protein. The mean elimination t½ values are ~75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. There were no differences in the pharmacokinetics of aripiprazole between healthy elderly subjects and younger adult subjects, nor was there any detectable effect of age, in a population pharmacokinetic analysis in patients with schizophrenia.[13] However, adults aged <35 years reportedly have a 15-fold higher rate of neuroleptic-induced dystonia compared with patients 60 to 80 years of age, according to the "Draft Guidance on Aripiprazole" of the FDA's Product-Specific Recommendations for Generic Drug Development[14]; this higher rate of dystonia resulted in potentially life-threatening laryngeal dystonia. Consequently, patients aged <45 years were not included in the present study of an orally disintegrating tablet (ODT) formulation. Aripiprazole is recommended at a dosage between 10 and 15 mg/d in the treatment of schizophrenia, with a dose range considered to be effective between 10 and 30 mg/d.

ODT, a relatively new dosage formulation, provides the benefits of a liquid medication in a solid dosage form. It differs from a conventional tablet in that it is designed to be dissolved on the tongue or in the mouth rather than be swallowed whole. ODT is therefore ideal for patients who cannot have continuous access to water or who have difficulty swallowing conventional tablets. Based on these properties, aripiprazole ODT has been developed to disintegrate in the subject's mouth without the need for water or other liquids. The ODT is placed on the tongue and disintegrates rapidly upon contact with saliva, providing the convenience of a tablet compared with a standard tablet. The dosing for aripiprazole ODT is the same as for the oral tablets. The present study was designed to compare the pharmacokinetic profiles of the newly developed ODT of aripiprazole taken without water with those of a conventional tablet of aripiprazole taken with water in healthy middle-aged Korean subjects.

PATIENTS AND METHODS

The study was approved by the Ministry of Food and Drug Safety and the institutional review board of Chonbuk National University Hospital (Jeonju, Republic of Korea). It was conducted according to the Declaration of Helsinki for biomedical research involving human subjects and the Guideline for Good Clinical Practice. A detailed explanation of the study was provided, and written informed consent was obtained from all participants before screening.

Subjects

Healthy male and female volunteers aged 45 to 64 years were enrolled in the study. The subjects' health was confirmed by physical examination, measurement of vital signs, 12-lead ECG, serology (hepatitis B virus surface antigen, hepatitis B virus surface antibody, hepatitis C virus antibody, and anti-HIV antibody), and routine laboratory assessments (hematology, chemistry, and urinalysis). Results of urine human chorionic gonadotropin testing were used to exclude pregnant women from the study. Subjects were excluded if they had participated in another clinical study within the 3 months preceding the first dose of study medication and had taken any prescription

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