Pharmacokinetic Comparison of 2 Formulations of Anastrozole (1 mg) in Healthy Korean Male Volunteers: A Randomized, Single-Dose, 2-Period, 2-Sequence, Crossover Study

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ABSTRACT

Background: Anastrozole is an aromatase inhibitor used to treat advanced breast cancer in postmenopausal women. A generic 1-mg tablet of anastrozole was recently developed.

Objective: The study was designed to provide data to submit to Korean regulatory authorities to allow marketing of the test formulation. We evaluated the comparative bioavailability and tolerability of the test and reference formulations in healthy male adult volunteers.

Methods: This single-dose, randomized, double-blind, 2-way crossover trial was conducted in the Clinical Trial Center at the Asan Medical Center (Seoul, Korea). A total of 24 healthy male Korean volunteers were enrolled. Subjects were randomized to receive 1 mg of the test or reference formulation, and pharmacokinetic (PK) parameters were measured. After a 3-week washout period, the other formulation was administered, and PK parameters were measured again. C_{max} and AUC_{last} were determined from blood samples obtained at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 168, and 216 hours after drug administration. The formulations were considered bioequivalent if the 90% CIs of the geometric mean ratios of test-to-reference formulations for AUC_{last} and C_{max} were within the bioequivalence limits of 0.8 to 1.25. Nonlinear mixed-effect modeling and Monte Carlo simulations for both formulations were also conducted, and the results were used to characterize and compare the PK properties. Safety profile and tolerability were assessed using measurements of vital signs, clinical chemistry tests, and interviews.

Results: All enrolled subjects completed the study. A total of 8 adverse events (AEs) were reported (2 on test formulation, 6 on reference formulation) in 7 of 24 participants. These AEs were headache (n = 1), hordeolum (n = 1), and abnormal laboratory test values (n = 6). Both formulations were well tolerated, and there were no serious AEs. Both formulations were best described by a 2-compartment disposition model with lag phase. The 90% CIs of the geometric mean ratios of test formulation to reference formulation were 0.96 to 1.08 for C_{max} and 0.93 to 1.0 for AUC_{last}.

Conclusion: The test and reference formulations had similar PK parameters and similar plasma concentration-time profiles. The test formulation of anastrozole met the Korean regulatory criteria (AUC and C_{max}) for assuming bioequivalence. ClinicalTrials.gov identifier: NCT01105299. (*Clin Ther*. 2012;34: 305–313)

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Key words: anastrozole, bioequivalence, formulation, nonlinear mixed-effect modeling, pharmacokinetic properties, simulation.

INTRODUCTION

Numerous aromatase inhibitors are approved for the treatment of estrogen-sensitive breast and ovarian cancers[1,2] and have potential for the treatment of other conditions. Estrogen synthesis occurs primarily in the ovaries of premenopausal women and also occurs in the fat, muscle, skin, normal breast stromal cells, and many breast tumors.[3,4] After ovarian failure, adipose tissues and muscles continue to synthesize estrogens.[5,6] In peripheral tissues, the aromatization of androstenedione to estrone and testosterone to estradiol are the final and rate-limiting steps in estrogen synthesis.[7–10]

Anastrozole and other third-generation aromatase inhibitors provide nearly complete inhibition of this reaction in the peripheral tissues of postmenopausal women. Anastrozole, 2,2′-[5-1H-1,2,4,-triazole-1-y-methyl)-1,3-phenylene]bis(2-methylpropiononitrile), is a selective nonsteroidal aromatase inhibitor developed by AstraZeneca Pharmaceutical Company.[11] Third-generation aromatase inhibitors are recommended as first-line treatment for breast cancer in postmenopausal women with estrogen-sensitive breast cancer that is early stage or metastatic.[12,13] Anastrozole is well tolerated, has a long half-life, and hence can be given as a daily oral dose of 1 mg.[14–16] A generic, once-daily 1-mg formulation of anastrozole was recently developed for the Korean market. Data on the pharmacokinetic (PK) properties and comparative bioavailability of this new formulation are required before marketing in this region.[17]

The present bioequivalence study was designed to provide data to submit to regulatory authorities to allow marketing of the test formulation, which is the first generic anastrozole formulation approved in Korea. This study compares the PK properties, safety profiles, and relative bioavailability of generic (test)* and branded (reference)† anastrozole tablets in healthy male Korean volunteers.

*Manufactured by CJ Cheiljedang Corporation, Seoul, Korea.
†Trademark: Arimidex® (AstraZeneca, Wilmington, Delaware).

SUBJECTS AND METHODS

Subjects

All enrolled subjects were healthy, male, Korean volunteers aged 19 to 55 years, who weighed >50 kg and were within 20% of ideal body weight. None of the subjects had significant cardiac, hepatic, renal, pulmonary, neurologic, gastrointestinal, or hematologic disorders as determined by medical history and physical examination that included assessment of vital signs, electrocardiography, and clinical laboratory tests (hematology, blood chemistry, urinalysis, and testing for HIV and hepatitis B virus surface antigens). None of the subjects had a history of alcohol or drug abuse, and all had negative urine test results for drugs of abuse (eg, amphetamines, barbiturates, cocaine, opioids, benzodiazepines) and alcohol. All laboratory tests other than PK analysis were performed at the Department of Laboratory Medicine, Asan Medical Center, which has been accredited by the Korean Association of Quality Assurance for Clinical Laboratories. The Institutional Review Board of Asan Medical Center approved the study protocol, and all procedures were performed in accordance with the Good Clinical Practice guidelines[18] and the Declaration of Helsinki and its amendments.[19] All participants provided written, informed consent before the screening test for eligibility.

Study Design and Materials

There were 2 treatment periods separated by a 3-week washout period, which is more than 5 times the half-life of 42.5 hours determined in previous studies.[20,21] Twenty-four eligible men were randomly assigned to 2 sequence groups in order of passing the eligibility tests using the 1:1 randomization method before initiation of the study. A table of random numbers generated by R version 2.7.2 (R Foundation for Statistical Computing, Vienna, Austria) was used to assign subjects in a 1:1 ratio to receive the test drug or the reference drug. Each envelope for a given (numbered) subject concealed the subject's matched treatment sequence until administration.

Participants were instructed not to take other medications, including over-the-counter and herbal products, from 2 weeks before the study's onset (study drug administration day) to the end of the study and were asked to abstain from smoking and use of alcohol- and caffeine-containing foods and beverages from 2 days before the study's onset to the end of the study. All subjects were admitted to the Clinical Trial Center