



Original Article

An open-label, randomized, cross-over bioequivalence study of montelukast 10 mg tablets in healthy Thai volunteers

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Abstract

To determine bioequivalence of a generic 10 mg montelukast tablet formulation. A 2-period, 2- sequence crossover study was designed. It included 28 healthy subjects, each subject received a single dose of the randomly assigned formulation with 240 ml water after 10-hr fasting, and 14 blood samples (6 mL each) were drawn at predose, and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 7, 10, 12 and 24 hr post-dose. The procedure was repeated after a 7-day washout period. Plasma samples were stored at -20°C until analysed using LC-MS/MS, LLOQ 5 ng/mL. The mean \pm SD for the test and the reference were: C_{max} 568 \pm 185 and 570 \pm 205 ng/mL; and $AUC_{0-\infty}$ 3864 \pm 1228 and 4022 \pm 1331 ng.hr/mL, respectively. The log-transformed ratios (90% CI) were: C_{max} : 99.64% (92.80% - 109.66%); and $AUC_{0-\infty}$: 99.79 (92.25% - 102.37%). The two formulations were bioequivalent as the 90% CI for the log-transformed ratios for the mean C_{max} , and $AUC_{0-\infty}$ were within the 80-125%.

Keywords: bioequivalence, montelukast, pharmacokinetics, LC/MS/MS, allergic rhinitis, asthma

1. Introduction

Montelukast, a cysteinyl leukotriene type-1 receptor antagonist, is an anti-inflammatory agent that was initially developed for asthma therapy and is increasingly being applied for the treatment of seasonal and perennial allergic rhinitis (Virchow & Bachert, 2006). Montelukast, 10-mg film-coated tablet, has demonstrated efficacy and tolerability in the treatment of allergic rhinitis and asthma in adult patients (Knorr *et al.*, 2001). Despite its effectiveness in asthma and seasonal and perennial allergic rhinitis, the use of Singulair[®], the original product, is limited as it is very expensive. Availability of the cheaper locally made generic drug formulations

will increase patient accessibility, but it requires bioequivalence data to establish that the generic drug product is therapeutically equivalent to and can be used interchangeably with the original product. Thai FDA has recommended that a bioequivalence study in human is needed for registration of generic drug products. This study is therefore designed to determine the bioequivalence of two film-coated tablet formulations of montelukast 10 mg in healthy Thai male volunteers under fasted condition.

2. Materials and Methods

2.1 Drugs

The pharmaceutical equivalent test montelukast formulation was manufactured by Unison Laboratories, Co., Ltd., Thailand (batch number T25/11-076, manufacture date

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January 18, 2011, and expiry date January 18, 2013). The reference Singulair® film-coated tablet formulation was manufactured by Merck Sharp & Dohme Ltd., Northumberland, England (batch number R1785, manufacture date May 07, 2010, and expiry date May 07, 2013). According to Asian Guideline on Stability of Drug Product (2013) and requirements of the Thai FDA, the shelf-life proposed for labeling of the test montelukast formulation (R&D batch) should be not longer than 24 months. Each film-coated tablet of both formulations contained montelukast equivalent to 10 mg. The clinical study was conducted at Clinical and Pharmacological Research Unit, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Thailand, and was sponsored by Unison Laboratories, Co., Ltd., Thailand.

2.2 Study subjects

The study was carried out in accordance with the current revision of the Declaration of Helsinki concerning medical research in humans. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (EC: 55-025-19-2-2).

Twenty eight healthy male subjects, including 4 subjects as standby to replace dropouts, were included in the study. All volunteers gave a written informed consent prior to participation, after they had been informed of the nature and details of the study which they thoroughly understood. Subject screening examinations were performed by a clinical investigator at Songklanagarind Hospital, a medical teaching hospital. All clinical laboratory tests were performed by the ISO 15189 certified laboratories, Department of Pathology, Songklanagarind Hospital. The daily results of the clinical laboratory tests including the quality control data were verified by its own independent quality assurance personnel before reporting. Subject inclusion criteria included Thai male, aged between 18-45 years, no consumption of drugs or food supplements for 4 weeks prior to the study, and no participation in any bioavailability or bioequivalence study at least 30 days prior to the present study.

The exclusion criteria included history of hypersensitivity to montelukast and/or related chemical structure and/or any of the components of the product, history or concurrent symptoms of cardiovascular, liver, kidney, gastrointestinal or hematological disorders and/or any disease that might affect the bioavailability of the study drug, subjects with malignancy, allergy, vital sign abnormalities, or clinically significant abnormal values during pre-study screening, smoker (> 10 cigarettes/day) or smoker of < 10 cigarettes/day who could not quit at least 7 days prior to study initiation and throughout study (including washout period), regular alcohol consumption (more than 1 time/week) or alcohol consumption within 7 days prior to the study, coffee consumption within past 7 days, or drug addiction.

2.3 Study design

The study was conducted as an open label, randomized two-period, two-sequence, single-dose crossover bioequivalence study under fasting condition, with a wash-out period of 7 days. All subjects arrived at the clinical research laboratory, at least 11 h prior to the start of the study. They were housed in an air-conditioned facility and were given a standard dinner, which was finished at least 10 h before dosing in each period of the study. On the day of drug dosing in period 1, volunteers were randomly assigned to one of two treatment sequences (TR (sequence 1) or RT (sequence 2)), as indicated in a pre-printed randomization scheme, which was generated using block randomization with the blocks of size 4 and 6, and the allocation ratio of 1:1. Subjects in sequence 1 received treatment T at the first dosing period and then crossed over to receive treatment R at the second dosing period (after the 7-day washout period). Subjects in sequence 2 received treatments in the order of R and T at the two dosing periods. The subjects were administered the assigned montelukast formulation with 240 mL of plain drinking water. After the intake of the study formulations, the oral cavity was checked to ensure completion of the administration process. Subjects were required to refrain from lying down during the first 4 h after dosing.

No meal was permitted until 4 h after dosing. Drinking water was restricted from 1 h before dosing till 2 h after dosing and *ad libitum* thereafter. Excess water intake (> 100 mL/h) was not permitted. Lunch, snacks, and dinner were served as per the scheduled time. All subjects abstained from any xanthine-containing food or beverages for at least 72 h and alcoholic products for at least 7 days prior to formulation administration and throughout the sampling schedule during each period. They were informed not to take any drug at least 30 days prior to the study, especially phenobarbital, rifampicin or gemfibrozil. Subjects abstained from the use of tobacco- or nicotine-containing products for 7 days prior to dosing and during confinement in the clinical research laboratory. No concomitant medication was permitted during the study period.

2.4 Blood sampling

Blood samples (6 mL) were collected from an antecubital vein by an indwelling venous catheter and transferred into coded 15-mL polypropylene centrifuge tube containing CPD-A1 as an anticoagulant. The tubes were covered with aluminum foil to protect samples from exposure to light. Blood samples were obtained at pre-dosing (0.00 h), and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 7, 10, 12 and 24 h after dosing. Blood samples were centrifuged at 4000 rpm (g force = 3717 x g) at approximately 4°C for 10 min, within 30 min of the sample collection. The plasma was separated, transferred into

2 (2- and 1.5-mL) opaque microcentrifuge tubes and stored frozen at -20°C until shipment on dry ice to All Research Laboratories (Bangkok, Thailand). During the sample collection, all subjects were under medical supervision. Vital signs were examined at scheduled time as described in the protocol.

2.5 Analytical procedure

A validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method was used for determination of montelukast concentration in human plasma. Equipment used was a LC-MS/MS 6490 Triple Quad (Agilent Technologies, Singapore). Column type used was a Zorbax SB-C18 column (2.1x50 mm, 1.8 μm) (Agilent Technologies, USA), and the mobile phase used was 0.5% formic acid in water and acetonitrile delivered at the flow rate of 0.3 mL/min with a gradient elution system. Procedures of validation and acceptance criteria were based on "FDA Bio-analytical Method validation guidelines" (Food and Drug Administration [FDA], 2001).

Calibration curve of montelukast was prepared within the concentration range of 5-800 ng/mL (5, 10, 20, 50, 100, 200, 400, 800 ng/mL) ($r^2 > 0.998$). The calibration curve consisted of one replicate of 8 non-zero standards. The concentrations of quality control (QC) samples were 15, 360 and 600 ng/mL for low (LQC), medium (MQC) and high (HQC) concentrations, respectively. The calibration standards and QC samples were prepared in 230 μL of blank plasma by spiking with 20 μL of respective working standard solutions. The lower limit of quantification was 5 ng/mL, with $S/N > 5$. The average values of accuracy percentages of within-run and between-run accuracy were 97.37-102.98% and 98.27-102.20%, respectively. The percentages of coefficient of variation of within-run and between-run precision for QC samples were 1.26-4.97% and 0.30-2.81%, respectively. The mean extraction recovery was 77.79%.

The analytical method was modified from the method of Bharathi *et al.*, 2009; Challa *et al.*, 2010; Papp *et al.*, 2007; Sripalakit *et al.*, 2008. Extraction of montelukast and amlodipine (internal standard, IS) from human plasma was performed by exploring optimized protein precipitation using acetonitrile. Aliquots of 250 μL plasma samples spiked with standard solutions and QC samples were taken in microcentrifuge tubes. Then the tubes were added with 50 μL of IS working solution (400 ng/mL amlodipine) and 1,000 μL of acetonitrile. The tubes were vortex-mixed for 60 s and centrifuged at 13,000 rpm (g force = $15870 \times g$) at 4°C for 10 min. A 2- μL aliquot was injected into the LC-MS/MS system. Blank sample was carried out by adding 1000 μL of acetonitrile into 250 μL blank plasma in microcentrifuge tube while zero blank sample was prepared by adding 1000 μL of acetonitrile and 50 μL of IS working solution into 250 μL blank plasma. The extraction procedure was done in the same manner as plasma samples.

Mass spectra were obtained using an Agilent Technologies 6490 Triple Quad LC-MS/MS equipped with elec-

troscopy ionization (ESI) source. The positive ion multiple reaction monitoring (MRM) mode was chosen for quantification. The capillary voltage was set at 3500 V and the mobile phase was nebulized using drying gas flow at 18 L/min, gas temperature at 200°C and nebulizer pressure at 35 psi. Sheath gas temperature and flow were set at 350°C and 11 L/min. The mass transitions were monitored from m/z 586.1 to 422.1 with collision energy of 21 V for montelukast and from m/z 409.2 to 283.3 with collision energy of 5 V for amlodipine. The fragmentor voltage of both montelukast and amlodipine was 380 V. The dwell time for all analytes was set to 200 ms. The data acquisition was ascertained by MassHunter software version B.04.01. For quantification the peak area ratios of the target ions of montelukast to those of amlodipine were compared with weighted ($1/x^2$) calibration curves in which the peak area ratios of the calibration standards were plotted against their concentrations, using Agilent MassHunter^a Quantitative Analysis software version B04.00.

2.6 Tolerability assessments

Throughout the study, subjects were monitored by a clinician, a clinical pharmacist, and 4 nurses. Tolerability was determined by monitoring of vital signs (sitting blood pressure, heart rate, and axillary body temperature), and physical examinations at baseline and at the end of each study period. Subject interviews were also conducted regarding the potential occurrence of adverse events (AEs) at each montelukast study period.

Serious AEs (SAEs) were considered to be when the subject outcome was death, life threatening, requiring hospitalization, leading to disability, or requiring medical intervention to prevent permanent impairment or damage. Any AEs or SAEs were recorded in the source data record form and on the case-report form, and their relationship to the study drug was determined by the study physician who was blinded to the randomization schedule.

2.7 Pharmacokinetic analyses

The primary pharmacokinetic parameters compared between treatments were maximum plasma concentration (C_{max}), the area under the concentration time curve (AUC) from time zero to 24 hr or to the last quantifiable time point after dosing ($\text{AUC}_{0\text{-}t_{\text{last}}}$), and the AUC from time zero to infinity ($\text{AUC}_{0\text{-}\infty}$). Other pharmacokinetic parameters examined were time to C_{max} (T_{max}), apparent terminal half-life ($t_{1/2}$) and elimination rate constant (k_{el}). All pharmacokinetic parameters were determined by non-compartmental methods. Values below the quantification limit (< 5.00 ng/mL) were set to zero for calculation purposes. The C_{max} and the T_{max} were obtained by visual inspection of individual plasma concentration-time profiles. The $\text{AUC}_{0\text{-}t_{\text{last}}}$ was calculated using linear-log trapezoidal approach. The k_{el} was estimated by a slope of linear regression line of log-transformed data. The $t_{1/2}$ was obtained by dividing 0.693 by k_{el} . The $\text{AUC}_{0\text{-}\infty}$ was calculated from the

sum of $AUC_{0-t_{last}}$ and C_{last}/k_{el} , where C_{last} is the last measurable concentration of montelukast in plasma. The pharmacokinetic parameters were calculated using WinNonlin® software version 5.3 (Pharsight®, North Carolina, USA).

The test and the reference formulations were considered to be equivalent if the calculated 90% confidence interval (CI) of geometric means for the log transformed ratios (test/reference) of the C_{max} , $AUC_{0-t_{last}}$, and $AUC_{0-\infty}$ were within the bioequivalence criteria range of 80.00-125.00 as established by the US FDA (FDA, 2001), and Thai FDA (FDA, 2009).

2.8 Statistical analysis

WinNonlin® software version 5.3 (Pharsight®, North Carolina, USA) program was used for statistical evaluation of the pharmacokinetic parameters. The pharmacokinetic parameters were statistically analyzed by analysis of variance (ANOVA) test, and Schuermann's two one-sided *t*-test. Descriptive analyses including mean, standard deviation (SD), median, and range were performed for variables such as age, weight, height, and BMI. Pharmacokinetic parameters C_{max} , $AUC_{0-t_{last}}$, and $AUC_{0-\infty}$ were analyzed using a four-way ANOVA accounting for sequence, subjects, period, and treatments, and the statistical significance was evaluated at 95% confidence level ($p < 0.05$). A non-parametric test, Wilcoxon signed rank test, was performed on T_{max} and considered significant when $p < 0.05$.

3. Results

Twenty eight healthy male subjects, including 4 subjects as standby to replace dropouts, were included and completed the study. All 28 subjects were included in the pharmacokinetic and statistical analyses.

The mean±SD of age, weight, height, and BMI were 21.4±1.9 years (range 18-25), 61.7±7.1 kg (range 50-76), 1.71±0.05 m (range 1.63-1.82), and 20.9±1.9 kg/m² (range 18.3-24.8). The mean plasma concentrations of montelukast versus time for the test and reference formulations were similar after administration of the 10 mg montelukast film-coated tablet (Figure 1). Both formulations were well tolerated, No deaths

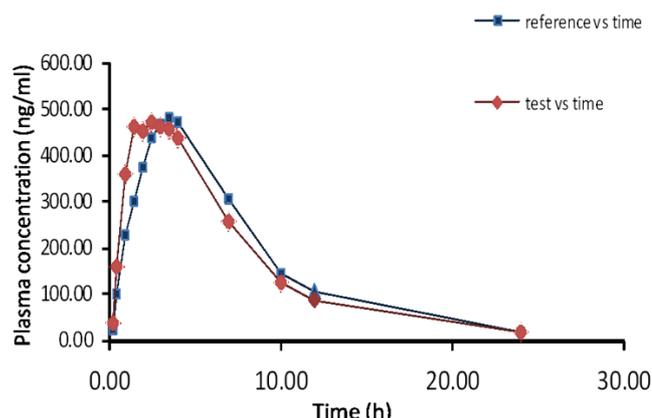


Figure 1. Mean plasma concentration versus time curves of the test and reference of 10 mg montelukast film-coated tablets (n = 28). The lower limit of quantitation was 5 ng/mL.

or serious AEs occurred during the conduct of this study. The only AE reported was drowsiness in 1 (3.6%) of 28 subjects receiving the test formulation. The AE was assessed to be mild in intensity and was not related to the study drug.

The average pharmacokinetic parameters of 10 mg montelukast film-coated tablets for test and reference products are presented in Table 1. The means±SD of C_{max} for the test and reference formulations were 568.08±185.03 ng/mL and 570.54±205.00 ng/mL, respectively. The means±SD of $AUC_{0-t_{last}}$ for the test and reference formulations were 3759.18±1197.00 ng·h/mL and 3906.53±1296.71 ng·h/mL, respectively. The respective values for $AUC_{0-\infty}$ were 3864.61±1228.26 ng·h/mL and 4022.01±1331.63 ng·h/mL. The mean extrapolated AUC for the test and reference were 2.75% (range 1.29-2.38%) and 2.94% (range 1.28-2.91%), suggesting blood sampling collection was performed during a sufficiently long period.

It was observed that absorption of both formulations was similar with the median (range) of the time to reach the T_{max} 2.75 (1-7) h for the test formulation and 3.5 (1.5-7) h for the reference formulation. The mean±SD of $t_{1/2}$ for the test formulation was 4.69±0.68 h, which was very similar to that of the reference formulation (mean±SD 4.56±0.42 h). The

Table 1. Mean pharmacokinetic parameters of the test and the reference formulations

Parameter	Test (mean ± SD)	Reference (mean ± SD)
C_{max} (ng/mL)	568.08 ± 185.03	570.54 ± 205.00
$AUC_{0-t_{last}}$ (ng·h/mL)	3759.18 ± 1197.00	3906.53 ± 1296.71
$AUC_{0-\infty}$ (ng·h/mL)	3864.61 ± 1228.26	4022.01 ± 1331.63
T_{max} (h)*	3.13 ± 1.63, [2.75]	3.79 ± 1.64, [3.50]
k_{el} (h ⁻¹)	0.15 ± 0.02	0.15 ± 0.01
$t_{1/2}$ (h)	4.69 ± 0.68	4.56 ± 0.42
$AUC_{0-t_{last}} / AUC_{0-\infty}$	97.25 ± 1.38	97.06 ± 1.17

*[Median]

Table 2. Ratios (Test/Reference), 90% CI and intrasubject coefficient of variation (CV) of C_{\max} , $AUC_{0-t_{\text{last}}}$, and $AUC_{0-\infty}$ following the administration of 10 mg montelukast film-coated tablet formulations

Test/Reference	Ratio (90% CI) (log transformed data, %)	Intrasubject CV (log transformed data, %)
C_{\max}	99.64 (92.80-109.66)	18.47
$AUC_{0-t_{\text{last}}}$	100.16 (92.36-102.63)	11.61
$AUC_{0-\infty}$	99.76 (92.25-102.37)	11.46

means \pm SD of k_{el} for the test and reference formulations were $0.15\pm 0.02\text{ h}^{-1}$ and $0.15\pm 0.01\text{ h}^{-1}$, respectively.

Table 2 presents the geometric mean ratios between the test and the reference formulations (T/R) of C_{\max} , $AUC_{0-t_{\text{last}}}$ and $AUC_{0-\infty}$ for log-transformed data, as well as the intrasubject coefficient of variations (CVs). The 90% CI ratios of geometric mean C_{\max} , $AUC_{0-t_{\text{last}}}$ and $AUC_{0-\infty}$ were within the range of 80-125%, which meet the regulatory criteria for bioequivalence. The intrasubject CVs for C_{\max} , $AUC_{0-t_{\text{last}}}$ and $AUC_{0-\infty}$ were 18.47%, 11.61, and 11.46%, respectively. The study had sufficient power to detect bioequivalence between the two formulations i.e., 95% for C_{\max} and 99% for both $AUC_{0-t_{\text{last}}}$ and $AUC_{0-\infty}$. The T_{\max} of the test and the reference products compared using Wilcoxon signed rank test revealed a significant difference ($p=0.0421$).

The ANOVA results revealed that period, sequence and treatment had no statistically significant effects on C_{\max} , $AUC_{0-t_{\text{last}}}$ and $AUC_{0-\infty}$. Since the sequence or carry-over effect was not significant, the ANOVA test was valid. Statistically significant subject nested within sequence effects on C_{\max} , $AUC_{0-t_{\text{last}}}$ and $AUC_{0-\infty}$ were observed as are usually seen in small sample size studies such as in crossed over phase I and bioequivalence studies.

4. Discussion

Bioequivalence between the 10-mg film-coated tablet formulations of montelukast under fasting condition was demonstrated by the 90% CI of the geometric mean ratios of C_{\max} , $AUC_{0-t_{\text{last}}}$ and $AUC_{0-\infty}$ lying within the acceptable criteria of 80-125%. The T_{\max} of the test formulation was slightly shorter than that of the reference product. The test and reference formulations had very similar $t_{1/2}$ at approximately 4-5 h. Period, sequence and treatment had no significant effects on C_{\max} , $AUC_{0-t_{\text{last}}}$ or $AUC_{0-\infty}$.

The C_{\max} , $AUC_{0-t_{\text{last}}}$ and $AUC_{0-\infty}$, T_{\max} , and $t_{1/2}$ of both formulations obtained in the present study were consistent with those previously reported (Zhao *et al.*, 1997). Despite similar T_{\max} and $t_{1/2}$, the present study demonstrated relatively higher C_{\max} and $AUC_{0-\infty}$ than some other studies using the equivalent dose of oral montelukast (Cheng *et al.*, 1996; Kim, Song, Lee, Park, & Kim, 2012). A bioequivalence study of 10 mg montelukast tablets conducted among 24 healthy Thai males reported very similar C_{\max} , $AUC_{0-t_{\text{last}}}$, $AUC_{0-\infty}$, and T_{\max} ,

but a slightly lower $t_{1/2}$ of montelukast (Sripalakit, Maphanta, & Saraphanchotiwitthaya, 2010).

Montelukast exhibits anti-inflammatory effects by blocking at leukotriene D_4 receptors. It has an onset of action at 3-4 h after dosing, which may be strongly related with the rate of absorption. The shorter T_{\max} for the test formulation observed in the present study may thus indicate a faster onset of action of montelukast, although the extent of absorption is probably a much more important parameter than the rate of absorption for chronic dosing, such as for prophylaxis or treatment of asthma, seasonal and perennial allergic rhinitis. The faster onset of action may be beneficial for prevention of exercise-induced bronchoconstriction in adults. For the 10-mg montelukast film-coated tablet, the T_{\max} is achieved 3 hours after administration in adults in the fasting state, 1-2 hours dosing prior to starting exercise is advised.

The intrasubject CVs obtained from the present study were quite smaller than the previously reported values of 19.8% - 28.4% (Anonymous, 2012), which were assumed in the sample size calculation. The tests, therefore, had 95-99% power to detect bioequivalence. However, such a small intrasubject CV of < 9.4% has been reported recently (Sripalakit *et al.*, 2010).

Montelukast 10-mg film-coated tablet was found to be well tolerated in the present study. This finding was consistent with previous reports where no adverse event was observed in subjects given montelukast (Canovas, Arcabell, Martinez, Canals, & Cabre, 2011; Cheng *et al.*, 1996; Kim *et al.*, 2012; Zhao *et al.*, 1997).

5. Conclusions

This study has demonstrated the bioequivalence of the 10 mg montelukast film-coated tablet formulation manufactured by Unison Laboratories, Co., Ltd., Thailand, and the reference product Singulair[®] manufactured by Merck Sharp & Dohme Ltd., England. It thus can be concluded that the two formulations can be used interchangeably.

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