Pharmacokinetics, Bioavailability, and Safety of Montelukast Sodium (MK-0476) in Healthy Males and Females

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Purpose. The safety, tolerability, and pharmacokinetics of intravenous (i.v.) montelukast sodium (Singulair™, MK-0476), and the oral bioavailability of montelukast sodium in healthy males and healthy females were studied.

Methods. This was a two-part study. Part I was a four-period study in males of rising i.v. doses of montelukast sodium (3, 9, and 18 mg) administered as 15-minute constant-rate i.v. infusions (Periods 1–3), followed by a 10-mg oral tablet dose of montelukast sodium (Period 4) under fasting conditions. Part II was a four-period study in females of i.v. montelukast sodium (9 mg) infused over 15 and 5 minutes (Periods 5 and 6, respectively) or injected as a bolus over 2 minutes (Period 7), followed by a 10-mg oral tablet dose of montelukast sodium (Period 8). Plasma samples were collected and analyzed by HPLC.

Results. In males (N = 6), as the i.v. dose of montelukast sodium increased from 3 to 18 mg, the area under the plasma concentration-time curve of montelukast sodium from time 0 to infinity (AUC) increased proportionately. The mean values of plasma clearance (CL), steady-state volume of distribution (V_{ss}), plasma terminal half-life ($t_{1/12}$), and mean residence time in the body ($MRT^{i.v.}$) of montelukast sodium were 45.5 ml/min, 10.5 l, 5.1 hr, and 3.9 hr, respectively, and remained essentially constant over the i.v. dosage range. Following oral administration of a 10-mg tablet of montelukast sodium, the AUC, maximum plasma concentration (C_{max}), time when C_{max} occurred (T_{max}), apparent $t_{1/12}$, mean absorption time (MAT), and bioavailability (F) of montelukast sodium averaged 2441 ng · hr/ml, 385 ng/ml, 3.7 hr, 4.9 hr, 3.4 hr, and 66%, respectively. Following i.v. administration of 9 mg of montelukast sodium to females (N = 6), the values of CL, V_{ss}, $t_{1/2}$, and MRT i.v. averaged 47.6 ml/min, 9.6 l, 4.5 hr, and 3.6 hr, respectively. Following oral administration of a 10-mg tablet to females, the mean AUC, C_{max}, T_{max}, apparent $t_{1/2}$, MAT and F were 2270 ng·hr/ml, 350 ng/ml, 3.3 hr, 4.4 hr, 2.6 hr, and 58%, respectively. These parameter values were similar to or slightly smaller than those in healthy males receiving the same i.v. and oral doses.

Conclusions. The disposition kinetics of montelukast sodium were linear. Gender had little or no effect on the kinetics of montelukast sodium. Safety results from this study indicate that intravenous doses of montelukast sodium from 3 to 18 mg and a 10-mg oral dose are well tolerated.

KEY WORDS: montelukast sodium; Singulair™; MK-0476; pharmacokinetics; bioavailability; gender effect.

INTRODUCTION

Montelukast sodium (Singulair™), also known as MK-0476 [sodium 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)-(E)-ethenyl)-phenyl)(3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)-methyl)-cyclopropane) acetate], is a potent and selective leukotriene D_4 ($cysLT_1$) receptor antagonist (1,2). It is currently being developed for the treatment of chronic asthma.

Preliminary results of clinical studies (3) indicate that: (a) montelukast sodium and its metabolites are excreted mainly in human bile; (b) besides unchanged montelukast sodium, two hydroxylated metabolites are present in human plasma; and (c) montelukast sodium is highly (>99%) bound to plasma protein. Previously, the safety, tolerability, and pharmacokinetic profile of oral montelukast sodium in healthy volunteers have been evaluated (4). Montelukast sodium appears to be well tolerated in man at single oral doses up to 800 mg. In this paper we describe the results of a clinical study of montelukast sodium in healthy males and females that was conducted to: (a) examine the safety, tolerability and pharmacokinetics of montelukast sodium administered intravenously; (b) assess the oral bioavailability of montelukast sodium; and (c) evaluate the effect of gender on the pharmacokinetics of montelukast sodium.

METHODS

Subjects

Nine healthy male volunteers between 21 and 37 years of age (mean = 25.9 years old), weighing between 66 and 90 kg (mean = 76.5 kg), and nine healthy female volunteers between 19 and 39 years of age (mean = 26.9 years old), weighing between 55 and 81 kg (mean = 66.1 kg), participated in this two-part study. The study was approved by the local ethical review committee and written informed consent was obtained from each subject before enrollment in the study.

Clinical Study

This was a two-part, double-blind, placebo-controlled, single rising dose study. Part I was a four-period study in males of rising i.v. doses of montelukast sodium (3, 9, and 18 mg) administered as 15-minute constant-rate i.v. infusions (Periods 1–3), followed by a 10-mg oral tablet dose of montelukast sodium (Period 4) under fasting conditions. In Periods 1–4, six males received montelukast sodium, and three received placebo. Subjects who received placebo in Period 1 also received placebo in Periods 2–4. The 10-mg tablet was administered with 150 ml of water in Period 4. The concentration of the i.v. solution of montelukast sodium was 0.12 mg/ml.

Part II was a four-period study in females of i.v. montelukast sodium (9 mg) infused over 15 and 5 minutes (Periods 5 and 6, respectively) or injected as a bolus over 2 minutes (Period 7), followed by a 10-mg oral tablet dose of montelukast sodium

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(Period 8). The concentration of the i.v. solution of montelukast sodium for Periods 5–7 was 0.25 mg/ml. In Periods 5–8, six healthy females received montelukast sodium, and three received placebo under fasting conditions. Subjects who received placebo in Period 5 also received placebo in Periods 6–8. The 10-mg tablet was administered with 150 ml of water in Period 8. Throughout the study, at least 5 days elapsed between the administration of each dose. Each dose was administered at approximately 8–9 A.M. in the morning of each treatment day.

On treatment days, a light snack, lunch and dinner were provided two, four and ten hours post-dose, respectively. Subjects had refrained from alcohol for 24 hours before and after the dose in each period. Subjects had also refrained from using caffeinated products for 8 hours before and 12 hours after each dose. No other medications were to be taken by the subjects for a period of one week prior to the study. However, acetaminophen had been taken by one subject for 3 days in Period 3 for the treatment of a flu-like illness and by a second subject for one day in Period 6 for the treatment of headache. Oral contraception was used by eight of the nine female volunteers throughout the study and at least 14 days following the post study evaluation.

Blood samples (7 ml each) were collected in heparinized tubes prior to dosing and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours after oral dosing. Besides these sampling times, blood samples were also collected at 0.17, 0.25 (end of the infusion), 0.75 and 1.5 hours post i.v. infusion initiation in Periods 1–3 and 5. Because the objective for Periods 6 and 7 was to evaluate the safety of i.v. montelukast sodium infused over 5 minutes or injected as a bolus over 2 minutes, frequent blood sampling was not undertaken and no pharmacokinetic evaluations were performed during these periods. Plasma was obtained from each blood sample and maintained frozen at −70°C until the time of analysis.

Analytical Method

Plasma concentrations of montelukast sodium were determined by a modified HPLC method (5). Briefly, 40 μl of an internal standard (isopropyl analogue of montelukast sodium) solution (5 μg/ml) was added to 200 μl of standards and unknown samples followed by the addition of 400 μl of acetonitrile to precipitate plasma proteins. The mixtures were mixed and centrifuged at 3000 rpm for 10 min. The supernatant was then transferred to an amber glass autosampler vial and 50 μl injected onto an HPLC system (HP1090, Hewlett-Packard, Avondale, PA) with an Apex octadecyl-3-μ column (4.6 mm i.d. × 5 cm, Jones Chromatography, Columbus, OH). The eluent consisted of acetonitrile and 0.05 M ammonium phophate buffer (pH 3.5) (62:38, v/v) and was monitored with a variable wavelength fluorometric detector (model RF-551; Shimadzu Scientific Instruments Inc., Columbia, Maryland). The fluorescence excitation and emission were set at 350 and 400 nm, respectively. The fluorescence output was recorded and analyzed using Turbochrom II software (PE Nelson Systems, Cupertino, CA). A flow rate of 1.5 ml/min was used in the analysis. The retention times of montelukast sodium and the internal standard were 4.0 and 4.9 min., respectively. For each daily analysis, a standard line for montelukast sodium was constructed using a weighted (1/concentration) linear regression of the peak height ratios and the corresponding plasma concentrations of montelukast sodium. The range of concentrations of montelukast sodium (free acid) in the daily standard line was 3.0–964 ng/ml. When a calculated concentration exceeded the standard line range, the sample was diluted with control plasma and reanalyzed. The intra- and inter-day precision values were within 9% relative standard deviation. The intra- and inter-day accuracy values were in the range of 97–104%. The absolute recovery of montelukast sodium was 99%.

Data Analysis

The area under the plasma concentration-time profile from time 0 to time infinity (AUC), plasma clearance (CL), mean residence time in the body (MRT), steady-state volume of distribution (V_{SS}), and apparent plasma terminal half-life ($t_{1/2}$) were calculated with the LAGRAN computer program (6). The mean residence time of montelukast sodium in the body after i.v. bolus administration (MRT^{iv}) was calculated as the difference

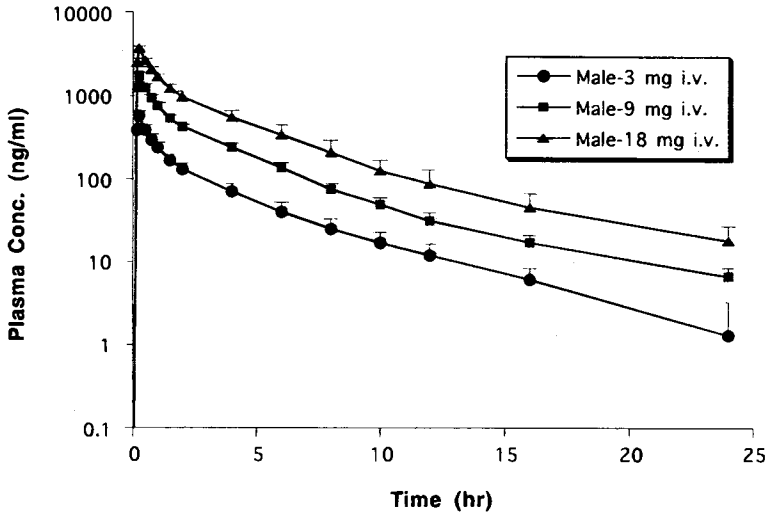

Fig. 1. Mean (± S.D., N = 6) plasma concentration-time profiles of montelukast sodium in healthy males following separate i.v. administration of 3–18 mg.

between the mean residence time of montelukast sodium in the body after i.v. infusion (MRT^{if}) and $\tau/2$, where τ is the intravenous infusion time (7). The mean absorption time of montelukast sodium (MAT) was obtained as the difference between the mean residence time of montelukast sodium after oral administration (MRT^{po}) and MRT^{iv}. The bioavailability of montelukast sodium was calculated as the ratio of the dose-normalized AUC after oral administration of 10 mg of montelukast sodium to that after i.v. administration of 9 mg of montelukast sodium. The pharmacokinetic parameters of montelukast sodium were compared in males and females by the Student's unpaired t test and between the i.v. doses by analysis of variance (ANOVA). Data transformations were used for AUC, C_{max} (logarithmic transform) and $t_{1/2}$ (inverse transform). The decision to use these transforms was jointly based on previous experience with pharmacokinetic data of montelukast sodium, testing of distribution of data using the Shapiro-Wilk test and examination of Q-Q plots. A p value of 0.05 or less was considered to be statistically significant.

RESULTS AND DISCUSSION

Mean plasma concentration-time profiles of montelukast sodium in males receiving single i.v. doses are displayed in Figure 1. There was a linear relation between AUC and the administered dose (AUC = 433.1 × Dose − 450, r = 0.962) over the i.v. dosage range of 3–18 mg (Figure 2). The y-intercept was not significantly (p = 0.242) different from zero. On average, AUC (data not shown) increased 3.23-fold for a three-fold increase in dose (3–9 mg), and 2.30-fold for a two-fold increase in dose (9–18 mg). Thus, as the i.v. dose of montelukast sodium increased from 3 to 18 mg, the AUC of montelukast sodium increased proportionately.

The mean values of pertinent pharmacokinetic parameters following i.v. administration of montelukast sodium to males are listed in Table I. No significant difference in the parameter values was observed between doses. Mean values for CL, V_{ss}, $t_{1/2}$, and $MRT^{i.v.}$ of montelukast sodium in males were 45.5 ml/min, 10.5 l, 5.0 hr, and 3.9 hr, respectively, and remained essentially constant over the dosage range of 3–18 mg. These constant parameter values and the linear relation between AUC and the administered dose indicate that the disposition kinetics of montelukast sodium are linear over the i.v. dosage range of 3–18 mg.

Table I. Mean (±S.D., N = 6) Values of Pharmacokinetic Parameters for Montelukast Sodium in Healthy Volunteers Receiving Separately Single Intravenous Doses of 3–18 mg

Gender	Dose (mg)	CL (ml/min)	V_{ss} (l)	$t_{1/2}^{a,b}$ (hr)	MRT^{iv} (hr)
Male	3	50.4 ± 12.1	11.3 ± 2.1	4.4 ± 0.9	3.8 ± 0.7
Male	9	46.0 ± 4.2	10.4 ± 1.1	5.4 ± 0.2	3.8 ± 0.4
Male	18	40.2 ± 6.1	9.7 ± 0.6	5.4 ± 0.2	4.1 ± 0.6
Overall Mean		45.5	10.5	5.1	3.9
Female	9	47.6 ± 16.0	9.6 ± 1.3	4.5 ± 0.5	3.6 ± 0.8

[a]Harmonic mean.
[b]Jacknife standard deviation.

Following i.v. administration of 9 mg of montelukast sodium to females, the mean plasma profile of this compound was similar to that in males (Figure 3). Also, the mean parameter values of montelukast sodium in females except for $t_{1/2}$ were not significantly ($p > 0.05$) different from those in males receiving the same i.v. dose (Table I). On average, although the $t_{1/2}$ of montelukast sodium was slightly smaller (p = 0.004) in females than in males, there was no significant (p = 0.488) difference in the $MRT^{i.v.}$ of this compound between both sexes. Thus, gender had little or no effect on the disposition kinetics of montelukast sodium.

Following oral administration of 10 mg of montelukast sodium, the AUC, maximum plasma concentration (C_{max}), time when C_{max} occurred (T_{max}), apparent $t_{1/2}$, mean absorption time (MAT) and bioavailability (F) of montelukast sodium in males averaged 2441 ng·hr/ml, 385 ng/ml, 3.7 hr, 4.9, 3.4 hr and 66%, respectively (Table II). These values and the mean plasma profile (Figure 3) were similar to those in females receiving the same oral dose. Thus, there was little or no gender effect on the absorption kinetics of montelukast sodium.

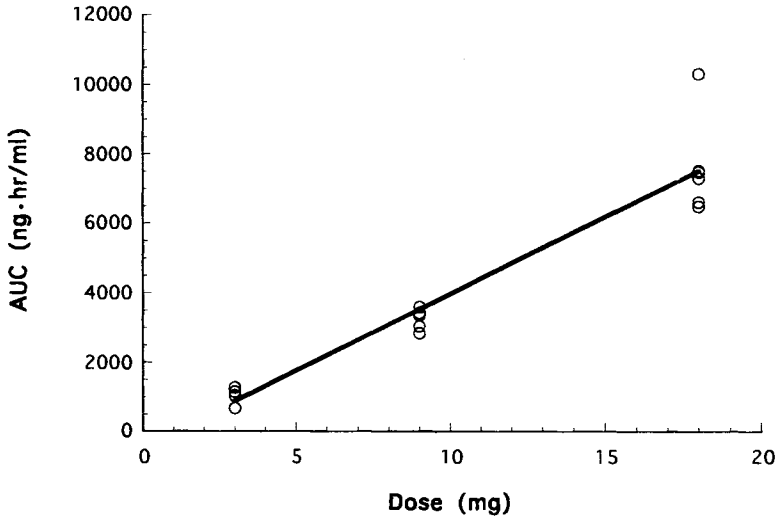

Fig. 2. A plot of AUC versus i.v. dose (3, 9, and 18 mg) of montelukast sodium in males.

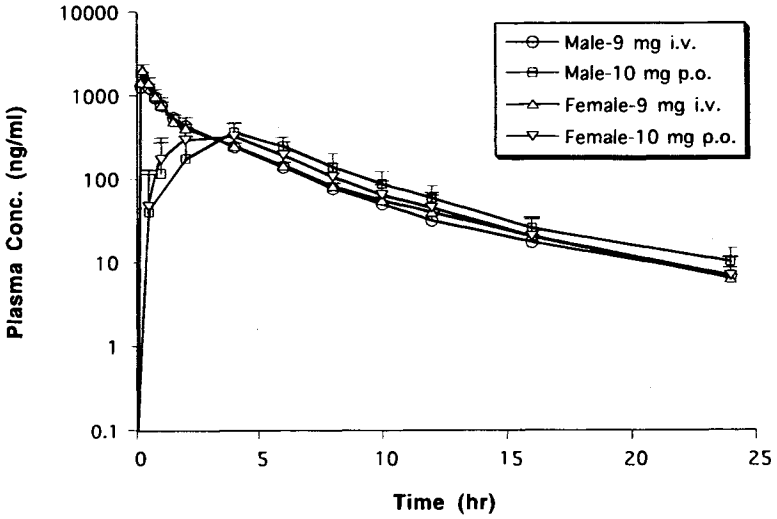

Fig. 3. Mean (± S.D.) plasma concentration-time profiles of montelukast sodium in healthy males (N = 6) and females (N = 6) following separate i.v. (9 mg) and oral administration (10 mg).

Table II. Mean (±S.D., N = 6) Values of Pharmacokinetic Parameters for Montelukast Sodium in Healthy Volunteers Receiving Separately a Single Oral 10-mg Tablet Dose

Gender	AUC (ng·hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	$t_{1/2}^{a,b}$ (hr)	MRT^{po} (hr)	MAT (hr)	F[c] (%)
Male	2441 ± 441	385 ± 85	3.7 ± 0.8	4.9 ± 0.4	7.3 ± 1.3	3.4 ± 1.0	66 ± 13
Female	2270 ± 919	350 ± 161	3.3 ± 1.0	4.4 ± 0.7	6.2 ± 1.0	2.6 ± 0.7	58 ± 15

[a]Harmonic mean.
[b]Jacknife standard deviation.
[c]Geometric mean.

Intravenous doses of montelukast sodium from 3 to 18 mg and a 10-mg oral dose were well tolerated. There were a total of 16 clinical adverse experiences in 8 of the 18 subjects. While the study was still blinded, five of these (3 on placebo, 2 on montelukast sodium) were considered by the investigator to be possibly related to study medication. The other 11 adverse experiences were thought to be probably not, or definitely not related to study medication. The five possibly drug-related adverse experiences included fatigue and sleepiness (in subjects given montelukast sodium) as well as headache (two episodes) and decreased blood pressure (in subjects given placebo). All adverse experiences were rated as mild (9 out of 16) or moderate (7 out of 16). Headache was the most frequently reported adverse experience (10 out of 16). No treatment effect or dose effect was apparent in the adverse experience profile. Also, all infusion rates in females were well tolerated. There were no laboratory adverse experiences in the study.

In conclusion, the results of this study indicate that: (a) the disposition kinetics of montelukast sodium are linear over the dosage range of 3–18 mg of i.v. montelukast sodium in healthy males; (b) there is little or no effect of gender on the kinetics of MK-0476; (c) the bioavailability of MK-0476 in the 10-mg tablet is approximately 60–70%; and (d) single intravenous doses of montelukast sodium from 3 to 18 mg and the 10-mg oral dose are well tolerated.

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