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Single dose pharmacokinetics, safety and tolerability of MK-0476, a new leukotriene D_4-receptor antagonist, in healthy volunteers

D. F. SCHOORS[1], M. DE SMET[2], T. REISS[3], D. MARGOLSKEE[3], H. CHENG[3], P. LARSON[3], R. AMIN [3] & G. SOMERS[1]

[1]Department of Internal Medicine, Free University of Brussels (VUB), Belgium, [2]Merck Research Laboratories, Brussels, Belgium and [3]Merck Research Laboratories, Rahway, New Jersey and West Point, PA, USA

MK-0476 or sodium 1-(1(R)-(3-(2-(7-chloro-2-quinolinyl)-(E)-ethenyl)phenyl) 3-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cycloproprane) acetate is a novel, potent, and specific LTD_4-receptor antagonist. The safety, tolerability and plasma drug profiles of single oral doses of MK-0476 (capsules) were evaluated in 18 healthy male volunteers assigned to one of the two parallel 9-subject panels. Under fasting conditions, increasing single doses of 20 to 800 mg were administered in a first part of the study and in a second part, 200 mg MK-0476 was given either as a solution, under fasting conditions, or as capsules, after a standard breakfast. All volunteers completed the study. Side effects, reported by the investigator to be related to study drug, were mild and transient. No laboratory abnormalities were noted. In the evaluated dose range of MK-0476 (20 to 800 mg) the median value of t_{max} ranged from 2 to 4 h, while the apparent $t_{1/2}$ value averaged 4 to 5 h. The median t_{max} value of the 200 mg capsule dose was not significantly different from the median t_{max} of the 200 mg oral solution dose indicating that neither disintegration nor dissolution is a rate-limiting step for the absorption of MK-0476 from capsules. There was a statistically significant increase in the AUC (geometric mean ratio of fed/fast was 2.52 with 95% confidence interval of 1.25, 5.06) and in C_{max} (geometric mean ratio of fed/fast was 1.36 with 95% confidence interval of 0.60, 3.04) when MK-0476 was given together with a breakfast, suggesting an increase in bioavailability. We conclude that single oral doses of MK-0476 (range 20 to 800 mg) appear to be well tolerated and both formulations (capsule and solution) achieve similar plasma concentrations.

Keywords MK-0476 LTD_4-receptor antagonist pharmacokinetics

Introduction

Leukotriene (LT) D_4 is one of the biologically active mediators derived from arachidonic acid which, together with LTC_4 and LTE_4, account for the biological activity formerly known as slow-reacting substance of anaphylaxis. Leukotrienes appear to mediate aspects of pathological lung function [1, 2]. Further evidence for the involvement of leukotrienes in human bronchial asthma has been obtained through clinical trials with potent LTD_4-receptor antagonists, such as MK-0571 [3, 4] and MK-0679 [5, 6]. Therefore, the primary clinical target for MK-0476 will be for treatment of chronic asthma.

The objectives of this study were to assess the safety and tolerability of single oral doses of MK-0476 over a dose range of 20 to 800 mg in healthy volunteers and to obtain pharmacokinetic information of MK-0476 administered orally. Additionally, the relative bioavailability of MK-0476 capsules was compared with MK-0476 given as a solution and the effect of food on MK-0476 pharmacokinetics was determined. The dose selection was based upon data obtained with the earlier LTD_4-receptor antagonist, MK-0679, which has already undergone clinical evaluation in asthmatic patients. In preclinical models, MK-0476

Correspondence: Professor Dr G. Somers, Department of Internal Medicine, Free University of Brussels, Laarbeeklaan 101, B-1090, Brussels, Belgium

appears to be at least 10 to 20-fold more potent than MK-0679, which improved asthma symptoms and signs at plasma concentrations of ≥ 4 μg ml^{-1} (Merck Research Laboratories, unpublished observations). If these preclinical extrapolations extend to man, MK-0476 should have significant clinical activity at plasma concentrations of approximately 0.4 μg ml^{-1} or less.

Methods

Subjects

Eighteen young, healthy, non-smoking male volunteers (21–40 years, mean weight 76.7 kg) participated in the study. Medication and alcohol were withheld for 24 h before and after each dose. Subjects fasted from midnight and no caffeine was allowed for 8 h before and after each dose of drug. A light snack, lunch, and dinner were provided for the subjects, 2, 4, and 8 h postdose, respectively. Subjects had to be in good health on the basis of their history, physical examination and routine laboratory tests and have normal spirometry values; i.e. the base-line forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) was at least 90% of the predicted value. The study was performed according to the provisions of the Declaration of Helsinki. Written informed consent was obtained from each participant and the study was approved by the local hospital ethics committee.

Study design

The study consisted of two parts. In Part I, safety, tolerability and plasma drug profiles of MK-0476 in a single dose range of 20 to 800 mg were assessed. In Part II, the plasma drug profiles of 200 mg of MK-0476, given as a solution under fasting conditions (Part IIb), and as capsules after a standard meal (Part IIa), were studied. Part I was a double-blind, sequential, placebo controlled three-period, alternating two-panel, single rising dose study, involving two panels of nine healthy volunteers. All medication was given as 10 mg and 50 mg capsules. Under fasting conditions, six subjects in each panel received the active drug and three subjects received placebo by a randomized allocation schedule.

Subjects in panel A received single rising doses of MK-0476 (20, 100 and 400 mg) or placebo and in panel B doses of 50, 200 and 800 mg or placebo. No subject received placebo twice. The investigators were blinded with respect to treatment (placebo *vs* active drug), but not to dose level. At least 48 h elapsed before the alternate panel received the next higher dose for periods 1 and 2 and 72 h for periods 2 and 3. The washout within a panel was at least 5 days.

Part IIb was a double-blind, one-period, placebo-controlled study, in the same nine healthy volunteers from Part I, panel B. In this part, 200 mg MK-0476, administered in a sucrose/water solution was given. Part IIa was an open, one-period study to investigate the effect of food on the plasma concentration profile of MK-0476. The six healthy volunteers from panel B who received the 200 mg dose, received a standard breakfast followed by 200 mg of MK-0476 (4 × 50 mg capsules).

Safety and tolerability were evaluated by performing physical examinations, sitting and orthostatic vital signs (blood pressure, heart rate and respiratory rate), 12-lead ECGs, pulmonary function tests at different time intervals. Local tolerability (taste and throat irritation) was assessed for the oral solution.

Multiple blood samples (predose, 30 min, and 1, 2, 4, 6, 8, 12 and 24 h postdose) were also obtained for the determination of plasma MK-0476 concentrations. Blood and urine samples for laboratory safety studies were also collected from each subject before and 24 h after each dose. The total amount of blood drawn for assays and laboratory safety tests was approximately 277 ml per subject for Part I, 361 ml for Parts I and IIb, and 445 ml for Parts I, IIa and IIb, over a period of 5 weeks.

Measurement of MK-0476 concentrations

Plasma concentrations of MK-0476 were determined by h.p.l.c. [7]. The limit of quantitation was 30 ng ml^{-1}. The intraday precision values (% RSD) were in the range of 0–5.7% and the interday precision values (% RSD) at concentrations of 51 and 2040 ng ml^{-1} were 10% and 3%, respectively.

Analysis of pharmacokinetic data

The total area under the curve (AUC) and the apparent terminal half-life ($t_{1/2,z}$) of MK-0476 were calculated using the LAGRAN computer program [8] which estimates these parameters to infinity using available data to estimate the terminal slope. The maximum concentration (C_{max}) and the time to peak plasma concentration (t_{max}) are the observed values. All data are presented as mean ± s.d. (except t_{max} values which are presented as median values with range).

Statistical comparisons of the pharmacokinetic parameters, AUC, C_{max} and t_{max} determined in part I, IIa and IIb, were performed using paired *t*-tests. A *P* value of less than 0.05 with a two tailed test was considered significant. Additionally, 95% confidence intervals were constructed on the geometric mean ratios from the food *vs* fast and the capsule *vs* solution comparisons for AUC and C_{max}. The confidence intervals were calculated on the difference between treatments and the standard deviation both in natural log units. The upper and lower limits of the resulting intervals were then antilogged to obtain intervals for the geometric mean ratios.

Results

Tolerability

All volunteers completed the study. There were no laboratory abnormalities. A total of 16 adverse experiences, considered by the investigator to be pos-

sibly related to drug were reported in 11 subjects. These included single episodes of headache (six during active treatment and four during placebo), diarrhoea (one during active treatment and one during placebo), facial flushes (one during active treatment), tenderness in the right hypochondrium (one during placebo), abdominal cramps (one during placebo) and abdominal discomfort (one during placebo). Side effects were mild and self-limiting and required no treatment. No side effects occurred that required unblinding of the study drug. In these normal volunteers FEV_1 and FVC did not change significantly after placebo or after MK-0476.

MK-0476 pharmacokinetics

The mean values of AUC, C_{max}, $t_{1/2,z}$ and the median values of t_{max} for the different doses administered under fasting conditions are listed in Table 1. The mean plasma concentration-time profiles of MK-0476 after the different oral doses are shown in Figure 1.

The plasma profile of MK-0476, 200 mg, administered as a sucrose/water solution was similar to the 200 mg dose administered as a capsule (Table 1). There were no statistical differences ($P > 0.2$) between dosage formulation in terms of AUC, C_{max}, and t_{max}. The geometric mean ratio $AUC_{solution}/AUC_{capsule}$ was 1.39 with 95% confidence interval of 0.79, 2.42.

Administration of food immediately prior to dosing with MK-0476 (200 mg) significantly increased the AUC by 143% ($P = 0.016$), increased C_{max} by 31% and increased t_{max} by 135% ($P < 0.05$). The geometric mean ratio AUC_{fed}/AUC_{fast} was 2.52 with 95% confidence interval of 1.25, 5.06.

Discussion

A single dose of the LTD_4 receptor antagonist MK-0476 (up to 800 mg) was well tolerated in healthy volunteers. The incidence of headache was not significantly higher in the placebo-treated subjects (4/21; 19.0%) compared with the MK-0476-treated volunteers (6/48; 12.5%) indicating that headache is probably not a drug-related side effect. Other LTD_4 antagonists (MK-0571, MK-0679) occasionally have produced mild gastrointestinal effects, like loose stools and diarrhoea, at high doses (> 500 mg day^{-1}) [6]. In the present study, diarrhoea occurred in one subject after a 200 mg dose of MK-0476 and in one patient who received placebo.

The pharmacokinetic data with the 200 mg dose as a capsule and the 200 mg as a solution suggest that neither disintegration nor dissolution is a rate-limiting step for the absorption of MK-0476 in capsules. The significant increase in the AUC of MK-0476 when given together with a breakfast, indicates an

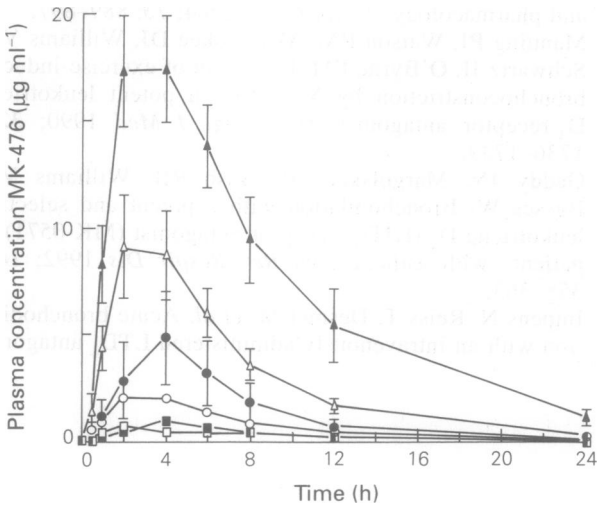

Figure 1 The mean plasma concentrations of MK-0476 in healthy volunteers after single oral doses of 20 (□), 50 (■), 100 (○), 200 (●), 400 (△) and 800 (▲) mg in capsules. Data are summarized as means ± s.d. ($n = 6$). Standard deviations of the three lower doses are not shown for reason of clarity.

Table 1 Pharmacokinetic parameters of MK-0476 in healthy males receiving single oral doses of 20 to 800 mg under fasting conditions. Data summarized are means ± s.d. ($n = 6$), except for t_{max} (median values and range)

Capsule dose (mg)	*AUC (μg ml⁻¹ h)*	C_{max} *(μg ml⁻¹)*	t_{max} *(h)*	$t_{1/2,z}$ *(h)**
Panel A				
20	5.8 ± 1.5	0.84 ± 0.22	2.0 (2.0, 4.0)	4.51 ± 1.70
100	16.0 ± 8.5	2.21 ± 0.98	2.0 (2.0, 4.0)	4.96 ± 1.03
400	68.7 ± 19.1	10.04 ± 3.20	3.0 (2.0, 4.0)	4.94 ± 0.67
Panel B				
50	6.4 ± 3.90	1.02 ± 0.56	4.0 (2.0, 4.0)	4.08 ± 1.65
200	29.3 ± 14.0	4.89 ± 2.18	4.0 (2.0, 4.0)	4.18 ± 0.40
200†	38.0 ± 11.0	5.54 ± 1.31	4.0 (2.0, 4.0)	4.38 ± 0.42
200‡	71.3 ± 27.5	6.38 ± 2.03	8.0 (6.0, 12.0)	3.79 ± 0.57
800	172.8 ± 38.2	19.53 ± 3.13	3.0 (2.0, 4.0)	5.19 ± 0.82

*Harmonic mean, ± Jacknife s.d.
†200 mg administered as oral solution under fasting conditions.
‡200 mg administered as capsules after a standard breakfast.

increase in bioavailability which remains to be clarified. However, the effect of food may be explained by the rate of gastric emptying, since food can delay gastric emptying, thereby increasing the available time for absorption. Food may also increase mesenteric blood flow and enhance absorption; this increased mesenteric blood flow might also cause decreased 'first pass' hepatic clearance by creating functional shunts in the liver [9]. To date, there is no information suggesting that MK-0476 is a 'high clearance' drug susceptible to this effect. Finally, the observed increase in t_{max} after food intake (8 h (range 6.0, 12.0) *vs* 4 h (range 2.0 4.0)) may be explained by the effect of food on decreasing the rate of gastric emptying.

We conclude that both formulations of MK-0476 (capsule and solution) achieve satisfactory plasma profiles and warrant further study in chronic asthma. The apparent increase in bioavailability, after the intake of food, remains to be clarified.

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