Pharmacokinetic and pharmacodynamic analysis of a novel leukotriene biosynthesis inhibitor, MK-0591, in healthy volunteers

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- 1 The pharmacokinetic and pharmacodynamic properties of a novel 2-indolealkanoic acid derivative (MK-0591), a potent inhibitor of leukotriene biosynthesis, were investigated in healthy male Japanese volunteers. Single oral doses of 50, 125, 250 and 500 mg and multiple oral doses of 125 mg twice daily for 9.5 days and 250 mg once daily for 10 days were administered.
- 2 After the single-dose administration following overnight fasting, $C_{\max}$ and AUC of MK-0591 in plasma increased in a dose-dependent manner, while elimination half-life remained constant (11.2–13.2 h) irrespective of dose. Food intake decreased $C_{\max}$ and AUC by 71% and 68%, respectively, at a dose of 250 mg. With respect to multiple-dose administration before meals, there were no significant differences in the pharmacokinetic parameters between the first and last days, indicating a lack of significant accumulation of MK-0591 in plasma. Urinary recovery as the unchanged form was negligible throughout the study.
- 3 Ionophore-stimulated production of leukotriene B₄ (LTB₄) in blood *ex vivo* was inhibited significantly from 1 h until 12 to 48 h after single-dose administration as compared with predose value. In parallel, the urinary excretion of endogenous leukotriene E₄ (LTE₄) was significantly decreased from 4 to 8 h until 48 to 72 h after drug administration. Reduction of ionophore-stimulated LTB₄ biosynthesis and urinary excretion of LTE₄ following single administration of MK-0591 was statistically significant as compared with placebo group, and the duration of inhibition of LTB₄ biosynthesis was dose-related. There was no attenuation of pharmacological effect in association with repeated doses of MK-0591.
- 4 At the highest single dose and during the multiple doses, transient, mild to moderate gastrointestinal side effects such as abdominal discomfort or pain and soft stools or diarrhoea that were tolerated without any treatment were encountered.

Keywords MK-0591 5-lipoxygenase inhibitor pharmacokinetics
leukotriene B₄ leukotriene E₄

Introduction

Leukotrienes are a group of arachidonic acid products catalyzed by 5-lipoxygenase in various cell types involved in inflammatory or immunological responses [1]. Leukotriene B₄ (LTB₄) is a potent inducer of chemotaxis and chemokinesis of leukocytes [2], while

the sulphidopeptide leukotrienes, LTC₄, LTD₄ and LTE₄, play a key role in the immediate type of hypersensitivity reaction and collectively account for the activity ascribed to slow-reacting substance of anaphylaxis (SRS-A) [3]. Because of the potentially

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important role of leukotrienes in the pathogenesis of inflammatory and immune responses, considerable effort has been devoted to the development of drugs to control either their production or action. In general, two approaches have been used: the first is to antagonize the action of cysteinyl leukotrienes through the specific LTD₄ receptor [4], and the second is to prevent the production of all leukotrienes by inhibiting the activity of 5-lipoxygenase.

MK-0591, 3-[1-(4-chlorobenzyl)-3-(*t*-butylthio)-5-(quinolin-2-yl-methoxy)-indol-2-yl]-2, 2-dimethyl propanoic acid, was derived from MK-886 and is a potent inhibitor of leukotriene synthesis by an indirect mechanism. Like MK-886, MK-0591 also inhibits the translocation of 5-lipoxygenase from the cytosol to the membrane in neutrophils or phagocytes stimulated by various substances such as calcium ionophore, opsonized zymosan and platelet activating factor [5, 6]. Translocation of 5-lipoxygenase is essential for activation of the enzyme, by binding specifically to a membrane protein called 5-lipoxygenase activating protein (FLAP) [5, 7]. MK-0591 was shown to be a potent inhibitor of leukotriene biosynthesis in intact human and elicited rat polymorphonuclear leukocytes and human, squirrel monkey and rat whole blood [8]. MK-0591 has advantages over MK-886, including increased bioavailability and increased activity, and this increase leads to an approximately six-fold greater inhibition of leukotriene biosynthesis compared with MK-886 in a human whole blood assay [8].

Among the leukotriene synthesis inhibitors, MK-0591 appears to be the most promising candidate for the development of a novel anti-inflammatory drug because MK-0591 is the most potent inhibitor of leukotriene synthesis *in vitro* reported to date [6] and it has a good safety profile in animal experiments (unpublished data). These observations prompted us to conduct the present study to determine the pharmacokinetic and pharmacodynamic properties of MK-0591 in healthy volunteers. In the pharmacological evaluation, inophore stimulated production of LTB₄ in blood *ex vivo* and urinary excretion of LTE₄ were measured to evaluate the suppression of biosynthesis of leukotrienes by MK-0591.

Methods

Subjects

A total of 30 healthy male Japanese volunteers aged 23–51 (mean: 33.6) years and weighing 52.1–94.8 (65.8) kg participated in this study after giving their informed consent.

In the single-dose study, 16 subjects were allocated to two groups, Group A and B (eight subjects/group). Doses of 50, 125, 250 and 500 mg MK-0591 which were dissolved in PEG400 in soft gelatin capsules, were orally administered in this sequence after confirming the safety of the previous dose: Group A received 50 and 250 mg MK-0591 after overnight fasting and 250 mg after breakfast. The breakfast

consisted of steamed rice, miso-soup, bacon and eggs, a vegetable salad and young sardines boiled down in soy, yielding a total energy of 655.9 kcal, containing 111.3 kcal protein, 249.5 kcal fat and 292.1 kcal carbohydrate. Group B received 125 and 500 mg after overnight fasting. In both groups, each dose was separated by an 8 day interval. At each dose level two of eight subjects were given placebo in a double-blind manner. In each group, placebo was allocated to different subjects over the two or three periods of drug administration.

In the multiple-dose study, six subjects received the capsule formulation which contains 250 mg MK-0591 at 08.00 h (2 h before breakfast) and placebo at 20.00 h (1 h before dinner) for 10 days (total, 10 doses of the active drug and 9 doses of placebo), respectively. Six other subjects received 125 mg MK-0591 twice daily, and the remaining two subjects received placebo twice daily for 9.5 days (total, 19 doses) in a double-blind manner.

The study protocol was approved by the local Ethics Committee.

Determination of drug concentrations in plasma and urine

Blood samples were taken immediately before and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36 and 48 h after drug administration in the single-dose study. Additional samples were taken 72 h after the administration of the 250 and 500 mg doses. In the multiple-dose study, blood was drawn before and 4 h after each morning dose, and 1, 2, 3, 6, 8 and 12 h after the 1st and 19th (last) doses. In addition, blood was drawn 24, 36, 48 and 72 h after the last dose. Urine was collected from 12 h before until 48 or 72 h after administration in the single-dose study, and from 12 h before the first dose until 72 h after the last dose in the multiple-dose study.

The concentration of MK-0591 in plasma and urine was determined according to the method developed by Lin *et al.* [9] using reversed phase high-performance liquid chromatography (h.p.l.c.) with ultraviolet detection at 290 nm. A CPS-Hypersil®-2 column (Keystone Scientific Inc., Bellefonte, PA) was used. The mobile phase was 0.1% trifluoroacetic acid aqueous solution/acetonitrile (45:55). An aliquot (0.5 ml) of the sample was mixed with 2 ml acetonitrile, and the supernatant was applied to a Bakerbond spe (C18) column (J.T. Baker Inc., Phillipsburg, NJ). The column was eluted sequentially with 3 ml methanol/water (1:1) and 2 ml methanol. The methanol eluate was dried and reconstituted for h.p.l.c. analysis. Coefficients of variations of the quality control samples were 18.7% at 0.1 µg ml⁻¹ of MK-0591 and 11.7% at 5 µg ml⁻¹ throughout assays.

The maximum drug concentration in plasma ($C_{\max}$) and the time required to reach maximum concentration ($t_{\max}$) were calculated from the observed drug levels. The plasma concentrations during the elimination phase were analyzed by exponential regression to obtain the elimination half-life. The area under the plasma concentration-time curve (AUC) was calculated according to the trapezoidal rule and extrapolation.

tion to infinity using the obtained time constant of the elimination phase.

Safety assessment

In the single-dose study, subjective symptoms, objective signs and vital signs including blood pressure, pulse rate and body temperature were checked before and periodically until 48 or 72 h after drug administration. A standard 12-lead electrocardiogram (ECG) was recorded before and 4, 24 and 48 h after administration. Routine laboratory tests including haematology, blood biochemistry and urinalysis were performed immediately before and 24 and 48 h after administration. Additional tests were done 72 h after the administration of the 250 and 500 mg doses. In the multiple-dose study, the above-mentioned parameters were checked before, during and 72 h after the administration period.

Pharmacological effects

Blood and urine samples were collected at the same time as those for drug concentration measurement. To evaluate the pharmacological effects of MK-0591 in healthy volunteers, ionophore-stimulated production of LTB_4 in leukocytes *ex vivo* and the urinary excretion of LTE_4 were determined according to the method of Friedman *et al.* [10] with minor modification.

LTB_4 biosynthesis was stimulated by incubating blood with calcium ionophore (A23187, Sigma, St Louis, MO). The plasma sample separated from the blood was assayed for LTB_4 by radioimmunoassay (r.i.a.) using LTB_4 antisera (LTB_4 sheep #329, Merck Frosst Canada Inc.) and [3H]- LTB_4 (150–250 Ci mmol⁻¹, New England Nuclear). Unbound ligand was separated by dextran coated charcoal. Coefficient of variation of the quality control sample was 7.6% throughout the analysis.

The urine sample was stabilized as previously described by Friedman *et al.* [10] and then spiked with an aliquot of [3H]- LTE_4 (128.5 Ci mmol⁻¹, New England Nuclear) as an internal standard. The sample was purified by Bond Elut C2 column (Analytichem International Inc., Harbor City, CA). The column effluent containing LTE_4 was further purified by h.p.l.c. on a Microsorb 5 μ m C18 column (Rainin, Woburn, MA). Fractions around the LTE_4 peak were collected and assayed. The recovery of LTE_4 was determined by radiometric analysis and the concentration of LTE_4 , by r.i.a. using LTE_4 antisera (monoclonal anti-leukotriene (C_4 , D_4 , E_4) rat culture supernatant, Sigma Chemical Co.) and [3H]- LTE_4 . The concentration of creatinine in the urine was measured using the kinetic Jaffe method. LTE_4 concentrations were expressed as pg LTE_4 mg⁻¹ creatinine.

In the multiple-dose study, the effects of MK-0591 on whole blood coagulation induced by arachidonic acid were evaluated using an impedance aggregometer (C550S, Chrono-Log Corp., Havertown, PA). Heparinized blood was taken from each subject before drug administration. Whole blood coagulation

was induced by arachidonic acid (AA) and the lowest concentration of AA giving a maximal impedance amplitude of more than 20 ohm in 7 min was determined for each subject by changing the concentration of AA from 0.125 to 0.5 μ M by a factor of 2. During the 2nd to 5th administration days, a blood sample was taken only once 2 to 4 h after the morning MK-0591 administration, and whole blood coagulation was examined by using the above-determined and the twice higher concentrations of AA. The degree of whole blood coagulation during MK-0591 administration was compared with that determined before drug administration for each subject.

Statistical analysis

Statistical analysis for pharmacokinetic parameters in the single-dose study were compared between 250 mg fasted and 250 mg fed, and those in the multiple-dose study between day 1 and day 10. The pharmacological effects were compared between before and after dosing or placebo and drug groups in both single and multiple-dose study. Statistical significance was determined with the paired Student's *t*-test (two-tailed).

Results

Adverse effects

At the highest single dose (500 mg), five of six subjects experienced gastrointestinal side effects as follows: abdominal discomfort ($n = 1$) and pain ($n = 1$) and diarrhoea ($n = 3$). These symptoms were of a mild to moderate degree, transient and were tolerated without any treatment. During the multiple-dose study, three of six subjects who received 250 mg once daily and one of six who received 125 mg twice daily complained of transient and mild soft stools and/or diarrhoea, although they needed no treatment. In the other subject who received 125 mg twice daily, eruptions associated with itching appeared on the face, body and upper limbs on the evening of the 9th day. Although his general condition was good, MK-0591 was discontinued in this subject for his safety. He had no abnormal findings on immunological examination including plasma concentrations of immune complex, immunoglobulins and complement, and lymphocyte proliferating reaction to MK-0591. The eruption disappeared spontaneously within 3 days after the cessation of MK-0591. Except for these findings, no abnormality definitely attributable to the test drug was observed in subjective symptoms and objective signs, vital signs, ECG or laboratory tests.

Pharmacokinetics

As shown in Figure 1 and Table 1, the plasma concentration of MK-0591 following single oral administration of 50, 125, 250 and 500 mg on an empty stomach reached C_{max} at 3.0 to 3.3 h, and the C_{max}

and AUC values increased proportionally to the doses given. Food intake slightly prolonged the time to reach C_{max} from 3.2 to 3.7 h, while C_{max} and AUC values significantly decreased ($P < 0.05$ vs 250 mg fasted) by 71% and 68%, respectively (Figure 1 and Table 1). Urinary recovery as the unchanged form was negligible.

In the light of these findings, the multiple-dose administration of MK-0591 was performed before meals. No abnormal accumulation was observed irrespective of once daily or twice daily regimen (Figure 2a,b). There were no significant differences in the values of t_{max} , AUC, C_{max} or $t_{1/2}$ between the first and the last doses (Table 1). Urinary recovery as the unchanged form was also negligible.

Pharmacological effects

Ionophore stimulated LTB₄ biosynthesis in blood *ex vivo* following single administration was measured and expressed as plasma concentration of LTB₄. The mean predose value $\pm$ s.d. of the LTB₄ levels in group of placebo and 50, 125, 250 (fasted), 500 and 250 mg (fed) were 192.8 ± 32.8 , 196.7 ± 58.7 , 231.3 ± 117.0 , 239.6 ± 48.6 , 235.5 ± 85.7 and 256.8 ± 47.3 ng ml⁻¹, respectively. The predose LTB₄ level after ionophore stimulation ranged from 106.8 to 403.5 ng ml⁻¹. A significant decrease in LTB₄ production was observed as compared with the predose value from 1 until 12 to 48 h after administration. LTB₄ levels in the placebo group fluctuated with time. LTB₄ levels after

Figure 1 Plasma concentration of MK-0591 following single oral administration of 50 (●), 125 (○), 250 (■), 500 mg (□) of MK-0591 after fasting and 250 mg (▲) after food intake. Each symbol and bar represents mean $\pm$ s.d. ($n = 6$).

Table 1 Pharmacokinetic parameters of MK-0591 after single and multiple oral administration of MK-0591

Dose (mg)	Food	Day	Pharmacokinetic parameter			
			C _{max} (μg ml ⁻¹)	t _{max} (h)	t _{1/2} (h)	AUC (μg ml ⁻¹ h)
Single dose						
50	fasted		1.49 ± 0.68	3.3 ± 1.5	12.3 ± 3.2	14.7 ± 6.0
125	fasted		4.91 ± 1.12	3.3 ± 1.0	11.2 ± 2.4	49.4 ± 8.7
250	fasted		7.74 ± 3.47	3.2 ± 1.0	13.2 ± 3.9	80.0 ± 35.8
500	fasted		15.81 ± 4.48	3.0 ± 0.9	12.2 ± 2.9	170 ± 57.0
250	fed		2.27 ± 1.42*	3.7 ± 0.5	13.4 ± 4.8	25.7 ± 14.6*
Multiple dose						
250 once daily	fasted	1	10.1 ± 3.39	2.7 ± 0.8	8.5 ± 1.2 ^a	103 ± 34
	fasted	10	8.10 ± 2.27	2.7 ± 0.5	9.2 ± 1.7 ^a	86.3 ± 25.0
125 twice daily	fasted	1	5.90 ± 2.10	2.4 ± 0.5	9.2 ± 3.1 ^b	52.3 ± 14.9
	fasted	10	5.93 ± 2.06	2.4 ± 0.5	8.3 ± 2.9 ^b	65.9 ± 22.8

Each value represents mean $\pm$ s.d. of six subjects (125 mg twice daily, $n = 5$).

* Significantly different from 250 mg fasted group ($P < 0.05$).

Pharmacokinetic parameters on day 10 were not significantly different from those on day 1 ($P < 0.05$).^a $t_{1/2}(12-24$ h), ^b $t_{1/2}(8-12$ h).

Values of 95% confidence intervals on the difference of pharmacokinetic parameters between 250 mg fasted and fed conditions were $(-9.16, -1.78)$ for C_{max} and $(-90.3, -18.4)$ for AUC.

administration were expressed as % of the predose value in each subject to evaluate dose dependency of the inhibition of LTB₄ production by MK-0591 because there was large inter-subject variation in the predose value. LTB₄ biosynthesis was inhibited significantly after administration of MK-0591 as compared with placebo group. Almost complete inhibition of LTB₄ biosynthesis was observed at doses of 125, 250 and 500 mg from 2 h until 8 or 12 h after administration, and the duration of subsequent significant suppression was dose-related.

Concentrations of LTE₄ in urine (expressed as pg mg⁻¹ creatinine) were measured. The mean predose value $\pm$ s.d. of the LTE₄ levels in groups of placebo and 50, 125, 250 (fasted), 500 and 250 mg (fed) were 30.8 ± 24.1 , 48.7 ± 28.4 , 162.7 ± 220.9 , 63.3 ± 31.4 , 104.2 ± 130.5 and 69.6 ± 32.8 pg mg⁻¹ creatinine, respectively. A significant decrease in LTE₄ concentration was observed when comparing predose values with those obtained from 0 to 4 h until 36 to 48 or 72 h in the groups receiving 50 and 250 mg MK-0591. The urinary excretion of LTE₄ was also decreased in groups receiving 125 and 500 mg MK-0591, although these differences were not statistically significant, probably because the predose values of

LTE₄ levels were scattered. Urinary concentrations of LTE₄ expressed as % of the predose value are shown in Figure 3. In parallel with the suppression of ionophore stimulated LTB₄ biosynthesis in blood, the urinary excretion of LTE₄ was reduced significantly with MK-0591 administration as compared with the placebo group. This significant decrease persisted until 48 to 72 h after drug administration.

In the multiple-dose study, significant suppression of ionophore stimulated LTB₄ biosynthesis and LTE₄ excretion in urine was observed as compared with the predose value throughout the administration period. LTB₄ biosynthesis expressed as % of the predose value was reduced significantly with MK-0591 administration as compared with the placebo group as shown in Figure 4. These data indicate a lack of attenuation of pharmacological effect in association with repeated doses. During MK-0591 administration, the capacity of LTB₄ biosynthesis in leukocytes was decreased to less than 10% of that before dosing, irrespective of once daily or twice daily regimen.

Multiple doses of MK-0591 did not affect platelet aggregation in whole blood evoked by adding arachidonic acid.

Figure 2 Plasma concentration of MK-0591 following multiple oral administration of a) 250 mg once daily of MK-0591 before breakfast for 10 days ($n = 6$) and b) 125 mg twice daily before meals every 12 h for 9.5 days ($n = 5$). Each symbol and bar represents mean $\pm$ s.d.

Figure 3 Time-profiles of ionophore-stimulated leukotriene B₄ (LTB₄) biosynthesis in whole blood *ex vivo* and urinary excretion of leukotriene E₄ (LTE₄) following single oral administration of 50 (●), 125 (○), 250 (■) and 500 mg (□) of MK-0591 after fasting and 250 mg (▲) after food intake and placebo (△). Levels of LTB₄ and LTE₄ are expressed as % of predose value. Each symbol and bar represents mean + s.d. (*n* = 6 for MK-0591, *n* = 10 for placebo, ¹*n* = 6). *: *P* < 0.05, #: complete inhibition.

Discussion

The present study has clearly demonstrated that oral MK-0591 suppresses the biosynthesis of leukotrienes *in vivo* and that its duration of action is long, as shown by the apparent and persistent decrease in urinary excretion of LTE₄. Similar pharmacokinetic and pharmacodynamic characteristics of MK-0591 were observed in Caucasians (45/48), Hispanics (2/48) and Indians (1/48) (personal communication). In addition, the capability of leukocytes to synthesize leukotrienes was shown to be completely negated at a dose of 125 mg or more.

The results of the present study showed that urinary excretion of LTE₄ decreased significantly after oral administration of MK-0591. It was reported that urinary LTE₄ may be a useful measure of whole body production of the cysteinyl leukotrienes [11]. This suggests that MK-0591 is active in inhibiting the biosynthesis of sulphidopeptide leukotrienes in healthy volunteers. It is expected that MK-0591 is also potent in patients in inflammatory disease if the

function of FLAP is preserved in the disease state. However, it is difficult to predict the extent of the pharmacological effect in asthmatic patients from the data in healthy subjects, because the amount of cysteinyl leukotrienes in the body in an inflammatory state is much higher than that normally seen. Figure 5 shows the relationship between the plasma concentration of MK-0591 and the ionophore stimulated production of LTB₄ in blood expressed as % of predose value. As the drug levels were increased, LTB₄ production tended to be decreased. More than 90% suppression of LTB₄ biosynthesis was observed when plasma levels of the drug were above 1 µg ml⁻¹. This result seems to offer the possibility of estimating the effective drug concentrations if the respiratory parameters such as FEV₁ correlate with ionophore stimulated LTB₄ production in blood.

As was reported for the related compound, MK-886 [12], MK-0591 does not inhibit leukotriene biosynthesis through a direct action on 5-lipoxyge-

Figure 4 Time-profiles of ionophore-stimulated leukotriene B₄ (LTB₄) biosynthesis in whole blood *ex vivo* following multiple oral administration of 250 mg once daily of MK-0591 before breakfast for 10 days (○: *n* = 6), 125 mg twice daily before meals every 12 h for 9.5 days (●: *n* = 5) and placebo (△: *n* = 2). Ionophore-stimulated production of LTB₄ in whole blood is expressed as % of pre-dose value. Each symbol and bar represent mean + s.d. *: *P* < 0.05, #: complete inhibition.

Figure 5 Correlation between plasma concentration of MK-0591 and ionophore-stimulated leukotriene B₄ (LTB₄) biosynthesis in whole blood *ex vivo* following single oral administration of 50 (●), 125 (○), 250 (■), 500 mg (□) after fasting and 250 mg (▲) after food intake. Each point represents individual data.

nase. MK-0591 has been shown to bind selectively to FLAP with high affinity [8]. The binding of MK-0591 to FLAP may prevent the activation and association of 5-lipoxygenase with FLAP and hence prevent leukotriene biosynthesis [5]. Therefore, the long-lasting inhibition of leukotriene biosynthesis by MK-0591 may be explained by either its slow disso-

ciation from FLAP or its irreversible binding to FLAP leading to destruction of bound FLAP and subsequent *de novo* synthesis of the protein, although this should be clarified by further study.

Several orally active agents that are selective 5-lipoxygenase inhibitors have recently been described, including Wy-50,295 [13], A-64,077 [14] and Sch

40120 [15]. Leukotrienes are considered to be involved in the initiation and the maintenance of a variety of inflammatory diseases such as ulcerative colitis, Crohn's disease, bronchial asthma, rheumatoid arthritis and anaphylactic shock [14]. In ulcerative colitis, for example, LTB₄ has been detected in rectal dialysis fluid in the active state and is normally absent during remission, indicating a positive correlation between LTB₄ generation and disease activity [16]. Therefore, leukotriene synthesis inhibitors are expected to be clinically efficacious in preventing or treating these diseases. In fact, A-64,077 a selective 5-lipoxygenase inhibitor, has been suggested to be effective in ulcerative colitis [17].

Only at the highest single dose and during the multiple-dose study, mild and transient abdominal dis-

comfort or pain and diarrhoea occurred. No such symptoms were observed at a single dose of 250 mg or less of MK-0591, although sufficient suppression of LTB₄ biosynthesis was observed. In addition, only one of six subjects complained of transient diarrhoea with the twice daily regimen, and again almost complete suppression was observed throughout the administration period. Therefore, a daily dose of MK-0591 up to 250 mg twice daily should be well tolerated.

In conclusion, oral MK-0591 showed linear pharmacokinetics and demonstrated potent and long-lasting inhibition of leukotriene biosynthesis in healthy volunteers. Within the optimal range of doses, oral MK-0591 was also well tolerated.

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