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Pharmacokinetic and Pharmacodynamic Properties of FK070 (KDI-792), A Novel Thromboxane Receptor Antagonist/Thromboxane Synthetase Inhibitor, After Single and Multiple Oral Administrations to Healthy Volunteers

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Abstract

FK070, a thromboxane A_2 (TXA_2) receptor antagonist/TXA_2 synthetase inhibitor, was given orally to healthy male volunteers in a single- and multiple-dose study.

In the single-dose study (200, 300, 400 mg), the area under the plasma concentration–time curve (AUC) and the maximum plasma concentration (C_{max}) increased non-linearly with dose, while the mean elimination half-life ($t_{1/\beta}$) was essentially unchanged (3·9–7·3 h). Recovery of the unchanged drug in the urine was 12–25%. C_{max} and AUC as determined with 200 mg of drug after a meal decreased by about 60 and 30%, respectively. Ex-vivo platelet aggregation in the plasma by a TXA_2 analogue, U46619, was almost completely inhibited within 1 h, after all doses of drug, with a significant dose-dependent inhibition maintained for 8 h or more, which was much longer than was expected from drug plasma concentration. The aggregation by adenosine diphosphate (ADP) was inhibited to a lesser extent. FK070 also inhibited TXA_2 synthetase as evidenced by decreased production of TXB_2 and reciprocally increased production of 6-keto-prostaglandin $F_{1\alpha}$ in the serum during ex-vivo whole blood coagulation. These effects peaked 1 h after drug and lasted until 4 h with the higher doses.

In the multiple-dose study (300 mg, twice a day, after meals for 6·5 days), drug concentrations in the plasma were well fitted to a three-compartment open model with first-order absorption. FK070 afforded extensive inhibition of platelet aggregation by U46619 throughout the administration period, with a significant inhibition lasting as long as 48 h after conclusion of administration.

No clearly drug-related changes were found in routine laboratory tests, subjective and objective findings, or vital signs.

FK070 was concluded to be well tolerated and to provide long-lasting blockade of TXA_2 receptors, and plasma concentration-dependent inhibition of TXA_2 synthetase in the platelets.

Thromboxane (TX) A_2 is a principal product of the arachidonic acid cascade in the platelets, and a potent inducer of platelet aggregation and vasoconstriction (Moncada & Vane 1979). Other tissues such as the lung, kidney and intestine also liberate TXA_2 to mediate various pathophysiological processes in association with anaphylaxis, circulatory shock, ischaemia, inflammation and bronchial asthma (Ogletree 1987). On the other hand, prostaglandin (PG) I_2 (Moncada et al 1976) produced from arachidonic acid mainly in the vascular endothelial cells, is a potent inhibitor of platelet aggregation and vasodilator.

Recently, agents that selectively inhibit the production of TXA_2 (Nakashima et al 1989; Uematsu et al 1994) or antagonize the action of TXA_2 at its receptor site (Uematsu et al 1991) have been clinically introduced and evaluated for treating ischaemic vascular disorders and bronchial asthma. FK070 (or KDI-792), (5Z)-6-[(2S,4R)-4-(4-chlorophenylsulphonylamino)-1-(3-pyridylmethyl)-2-pyrrolidinyl]-5-hexenoic acid hydrochloride (Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan and identical to KDI-792 of Kissei Pharmaceutical Co., Ltd., Nagano, Japan) is a new class of drug which not only selectively antagonizes the action of TXA_2 at its receptor site but also inhibits TXA_2 synthetase (Fig. 1). The drug inhibits the aggregation of human platelets induced by 9,11-azo-PGH_2, a TXA_2 receptor agonist, with a pA_2 of 7·2, and blocks TXA_2 formation induced by human whole blood clot with an IC50 of $1{\cdot}4 \times 10^{-6}$ M (unpublished data). Moreover, the inhibition of TXA_2 synthesis by FK070, unlike that by aspirin, enhances secondary PGI_2 production. Therefore, the drug may prove to be a useful medication since a pharmacological blockade on TXA_2 synthetase activity combined with blockade of the TXA_2/prostaglandin endoperoxide receptors has been proposed as an improved antithrombotic strategy (Gresele et al 1987).

The present study was conducted to investigate the safety, pharmacological actions and pharmacokinetic properties of FK070 in healthy human subjects.

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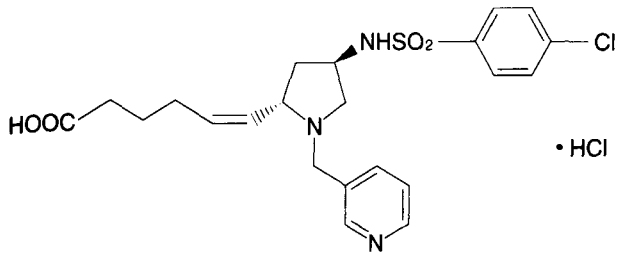

FIG. 1. Chemical structure of FK070.

Methods

Subjects

Twenty-nine healthy male Japanese volunteers, aged 24–50 years and weighing 52·2–78·4 kg, participated in the single- and multiple-dose studies after giving their informed consent. Before the main studies, FK070 was administered to each of two subjects fasted overnight in single increasing doses of 25, 50 and 100 mg to determine the blood-sampling points and to test its pharmacological actions. Then, FK070, 200, 300 and 400 mg were administered to each of 5 or 6 subjects fasted in the same way. The effect of food-intake on the pharmacokinetics of FK070, 200 mg was evaluated after a standard breakfast in the subjects who took 200 mg. The other 6 subjects received 300 mg after meals every 12 h at 0900 h and 2100 h for 6·5 days (total 13 doses).

The study protocol was approved by the local Ethics Committee.

Assessment of safety

In the single-dose study, subjective and objective symptoms, and vital signs including blood pressure, pulse rate and body temperature were checked before administration and periodically up to 24 h after administration. Standard 12-lead electrocardiogram (ECG) was recorded before, and 2 and 24 h after administration. Bleeding time was determined immediately before, and 2 and 24 h after administration with a Simplate I device (Organon Teknika Corporation, Germany); the same analyst performed the determinations on the same subject in all cases to ensure that individual differences in technical skills were kept distinct and constant. Routine laboratory tests including a haematology, blood biochemistry and urinalysis were performed immediately before and 24 h after administration.

In the multiple-dose study the same items as described above were checked before, during and 24 h after the last administration.

Platelet aggregation

Blood samples were anticoagulated with 0·1 vol. 3·13% sodium citrate and centrifuged at room temperature (21°C) for 10 min at 160 *g* to obtain the platelet-rich plasma (PRP). Platelet aggregation in PRP was induced by adding either of two aggregants, a thromboxane mimetic, U46619, and adenosine diphosphate (ADP) and measured by an automatic aggregometer (PAM 8T, Mebanix, Tokyo, Japan). The lowest concentration of U46619 (0·5 to 2 μM; mean 0·9 μM) or ADP (1 to 8 μM; mean 3·4 μM) that induced 80% or more of maximum aggregation was determined in each subject before administration. The platelet aggregations induced both by the above determined concentration (low concentration) for U46619 and ADP, and by that twice the larger one (high concentration) for U46619 were assessed throughout the study. Blood (12 mL) was drawn immediately before, and 1, 4, 8, 24 and 48 h after administration in the main study of the single-dose study. In the multiple-dose study, blood was drawn immediately before the 1st and 3rd administration, 2 h after the 1st, 7th and 13th administration, and 24, 48 and 72 h after the last administration.

U46619 and ADP were purchased from Cayman Chemical Co., Denver, CO and Boehringer Mannheim GmbH., Mannheim, Germany, respectively.

Serum TXB_2 and 6-keto-$PGF_{1\alpha}$ concentrations

To investigate the inhibitory action of FK070 on TX synthetase, the serum concentrations of TXB_2 and 6-keto-$PGF_{1\alpha}$, which are stable degradation products of TXA_2 and PGI_2, respectively, were measured after whole blood coagulation ex-vivo. Blood (15 mL) was collected into a glass tube and immediately placed in warm water (37°C) for 60 min. Then, the serum was separated by centrifugation for 10 min and stored at −20°C until analysed. Concentrations of TXB_2 and 6-keto-$PGF_{1\alpha}$ were measured by radioimmunoassay at Mitsubishiyuka Bio-clinical Laboratories Inc., Japan. Blood sampling was performed before, and 1, 4, 8, 24 and 48 h after administration in the single-dose study. In the multiple-dose study blood was drawn immediately before the 1st and 3rd administration, 2 h after the 1st, 7th and 13th administration, and 24, 48 and 72 h after the last administration.

Determination of drug concentrations in plasma and urine

Blood samples were taken immediately before, and 0·25, 0·5, 1, 1·5, 2, 4, 6, 8, 12 and 24 h after administration in the single-dose study. In the multiple-dose study blood was drawn before each morning administration, and 1, 2, 4, 6, 8 and 12 h after the 1st and last administrations. Additionally, blood was drawn 1, 2, 6 and 12 h after the 7th administration, and 24 h after the last administration. Urine was collected as time-block samples until 24 h after administration in the single-dose study and until 24 h after the last dose in the multiple-dose study.

The concentration of FK070 in the plasma and urine was determined by reversed phase HPLC with ultraviolet absorption detection. Briefly, plasma or urine samples were extracted with diethyl ether under acidic condition (pH 5·0). The organic phase was re-extracted with 0·1% phosphoric acid, and the aqueous solution was injected onto a TSK-gel ODS-80TM column (150 mm × 4·6 mm, Tosoh Corporation, Japan). The mobile phase of acetonitrile : 0·02 M acetic acid buffer (pH 5·0) (40 : 60, v/v) was used. The limit of quantitation of the method was 2·5 ng mL^{-1} in the plasma and 50 ng mL^{-1} in the urine. The intra-assay coefficients of variation were 2·6–4·5% for the plasma samples (2·5–250 ng mL^{-1}) and 1·4–2·3% for the urine samples (50–5000 ng mL^{-1}). Calibration curves were prepared between 2·5 and 250 ng mL^{-1} in the plasma ($r = 1·000$), and between 50 and 5000 ng mL^{-1} in the urine ($r = 1·000$).

The maximum drug concentration in the plasma (C_{max}) and the time to reach C_{max} (t_{max}) were obtained from the observed

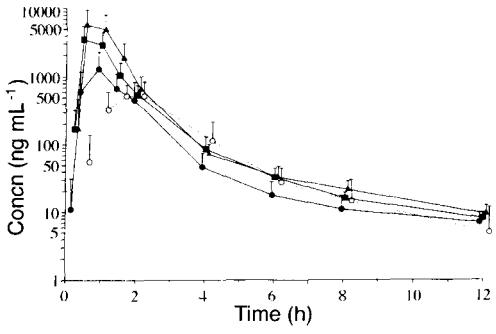

FIG. 2. Plasma concentrations of unchanged drug following single oral administration of 200 (●), 200 (○, after meals), 300 (■) and 400 mg (▲) of FK070. Symbol and bar represent mean ± s.d. (n = 5).

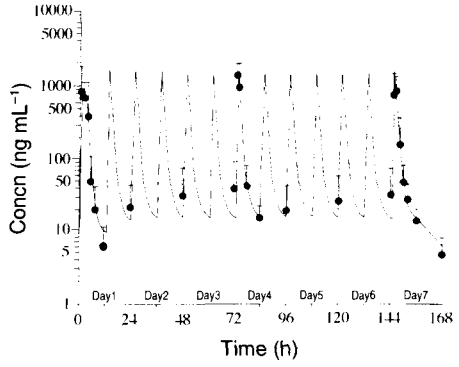

FIG. 3. Plasma concentrations of unchanged drug following multiple oral administration of 300 mg of FK070 after meals every 12 h for 6·5 days. Symbol and bar represent mean ± s.d. (n = 5).

levels. The area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) was calculated by the combination of trapezoidal rule and extrapolation to infinity using the elimination constant. Renal clearance (CL_R) was calculated by dividing the amount excreted in the urine by the AUC. In addition, the plasma concentrations in the multiple-dose study were fitted to a three-compartment open model with first-order absorption using a non-linear least squares program NONLIN (Metzler et al 1974) with a superimposed technique (Elfring & Metzler 1981).

Statistical analysis

Pharmacokinetic parameters, and pharmacokinetic and pharmacodynamic time data were analysed respectively by paired *t*-test and by analysis of variance for statistical significances at the level of $P = 0{\cdot}05$ followed by Dunnett's multiple comparison test or Tukey's multiple comparison test when the differences were statistically significant. The results are expressed as the means ± s.d.

Results

Safety

One subject in the multiple-dose study showed a rise of body temperature probably due to a common cold and FK070 was stopped on day 6 of administration afterward. This subject was excluded from the analyses of both pharmacokinetics and pharmacodynamics. No abnormalities attributable to the drug were observed in subjective and objective symptoms, vital signs, ECG, or laboratory tests in either the single- or multiple-dose studies.

Pharmacokinetics

The plasma concentrations and pharmacokinetic parameters of FK070 following oral administration of 200, 300 and 400 mg are shown in Fig. 2 and Table 1. The absorption of FK070 was rapid after fasting, with the mean t_{max} ranging from 0·6 to 1·1 h; drug was eliminated from the plasma with a mean half-life ($t_{1/2}$) of 3·9–7·3 h. On the other hand, C_{max} and $AUC_{0-\infty}$ increased non-linearly with the doses given. The CL_R value of 199–260 mL min^{-1} did not change significantly, while mean ± s.d. urinary recovery increased non-linearly: 12 ± 5, 17 ± 5 and 25 ± 4% of dose as unchanged form at 200, 300 and 400 mg of drug, respectively. The effect of food intake determined for 200 mg of drug, was as follows: t_{max} slightly increased from 1·1 to 1·6 h without statistical significance, and C_{max} and AUC decreased by about 60 and 30%, respectively.

In the multiple-dose study, the overall plasma concentrations were well fitted to a three-compartment open model (Fig. 3), and there was no significant difference between t_{max}, AUC up to 12 h after administration (AUC_{0-12h}), C_{max} or CL_R at the first and the last administrations (Table 2); $t_{1/2}$ after the last administration was 6·2 h. The 24-h urinary recoveries of the unchanged drug were quite constant from the 1st to the 6th day in the range of 11–14%, and showed no abnormal accumulation in the body.

Pharmacological action

In the single-dose study the effect of FK070 on platelet aggregation induced by U46619 was evaluated by using PRP and a conventional aggregometer (Fig. 4). The inhibition of platelet aggregation measured by an aggregometer

Table 1. Pharmacokinetic parameters of FK070 following single oral administration.

Parameter	200 mg (fasted)	300 mg (fasted)	400 mg (fasted)	200 mg (after meal)
C_{max} (ng mL^{-1})	1612 ± 716	3487 ± 1786	7847 ± 2262	664** ± 300
t_{max} (h)	1·1 ± 0·5	0·6 ± 0·2	0·7 ± 0·3	1·6 ± 0·4
$t_{1/2}$ (h)	6·9 ± 3·6	3·9 ± 1·8	7·3 ± 2·7	2·4* ± 1·5
$AUC_{0-\infty}$ (ng h mL^{-1})	2048 ± 856	4384 ± 1925	6658 ± 1959	1464** ± 668
CL_R (mL min^{-1})	206 ± 44	199 ± 34	260 ± 69	232 ± 55

Each value represents the mean ± s.d. *$P < 0{\cdot}05$, **$P < 0{\cdot}01$ vs fasted state (paired *t*-test).

Table 2. Pharmacokinetic parameters of FK070 following multiple oral administrations.

Parameter	Day 1	Day 7
C_{max} (ng mL^{-1})	1335 ± 776	1233 ± 332
t_{max} (h)	1·8 ± 1·3	1·6 ± 0·5
$t_{1/\beta}$ (h)	—	6·2 ± 1·6
AUC_{0-12} (ng h mL^{-1})	2720 ± 1441	2473 ± 771
CL_R (mL min^{-1})	264 ± 36	324 ± 64

Each value represents the mean ± s.d.

showed a dose-dependence within the range of 25–100 mg of FK070. As shown in Fig. 4, inhibition was almost complete 1 h after the administration of drug at any dose of 200, 300 and 400 mg. Significant inhibition tended to last dose-dependently from 8 to 48 h after administration. The aggregation of platelets induced by ADP was also inhibited but only in the secondary component and to a lesser extent (30 to 60% aggregation) than the aggregation induced by U46619. The production of TXB_2 in the serum during whole blood coagulation ex-vivo was decreased 1 h after the administration of drug at any dose, and was associated with a reciprocal increase of 6-keto-$PGF_{1\alpha}$

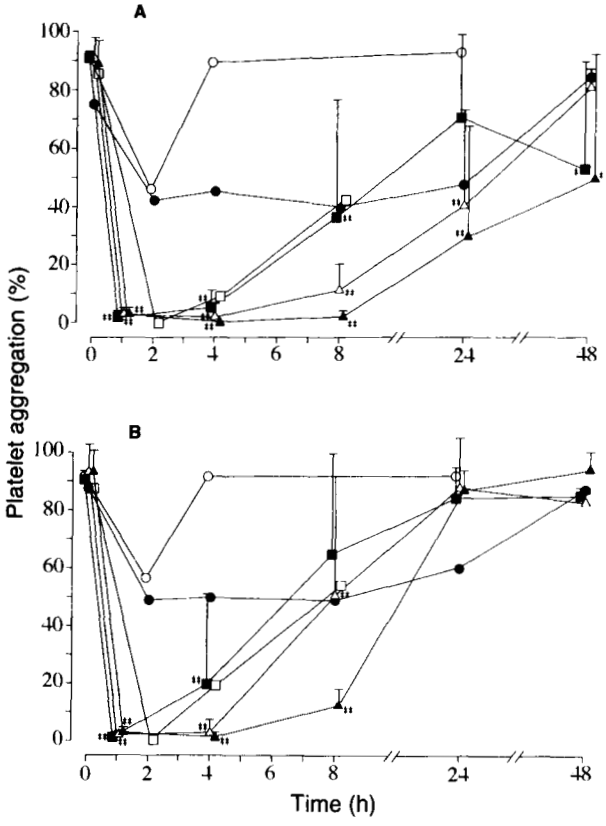

FIG. 4. Maximum platelet aggregation in plasma induced by U46619 at low concentration (A) and high concentration (B), following single oral administration of 25 (○), 50 (●), 100 (□), 200 (■), 300 (△) and 400 mg (▲) of FK070 after fasting overnight. Symbol for 25, 50 and 100 mg represent mean (n = 2), and symbol and bar for 200, 300 and 400 mg represent mean ± s.d. (n = 5 or 6). $*P < 0.05$, $**P < 0.01$ vs predrug value (Dunnett's multiple comparison test).

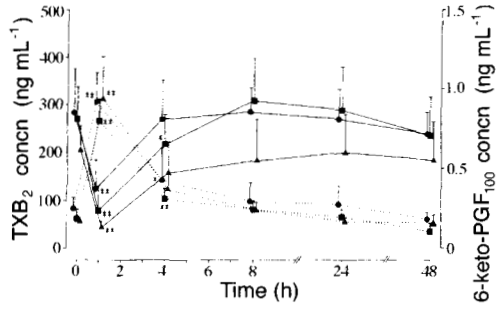

FIG. 5. Serum TXB_2 and 6-keto-$PGF_{1\alpha}$ concentrations produced during whole blood coagulation following 200 (●), 300 (■) and 400 mg (▲) of FK070. Symbol and bar represent mean ± s.d. (n = 5 or 6). $*P < 0.05$, $**P < 0.01$ vs predrug value (Dunnett's multiple comparison test).

production (Fig. 5). With the higher doses of drug, significant changes in these productions were observed until 4 h after administration.

In the multiple-dose study, almost complete inhibition of platelet aggregation induced by U46619 was repeatedly attained 2 h after each administration throughout the administration period, and significant inhibition induced by low concentrations of U46619 was observed until 2 days after the conclusion of administration (Fig. 6). Decreased production of TXB_2 and reciprocally increased production of 6-keto-$PGF_{1\alpha}$ were observed after each administration (Fig. 7).

Bleeding time was slightly prolonged from 7·1 ± 1·9 min of pre-dose value to 9·9 ± 3·3 min, 2 h after the administration of 300 mg ($P < 0.05$) in the single-dose study, and from 7·6 ± 1·3 min of pre-study value to 12·1 ± 2·6 min ($P < 0.05$), 2 h after the morning administration on the 4th day of the multiple-dose study.

Discussion

This study demonstrated that FK070 produces specific and long-lasting TXA_2 receptor blockade as well as plasma concentration-dependent inhibition of TXA_2 synthetase after single and multiple oral administration. Throughout the entire study period, no clearly drug-related abnormality

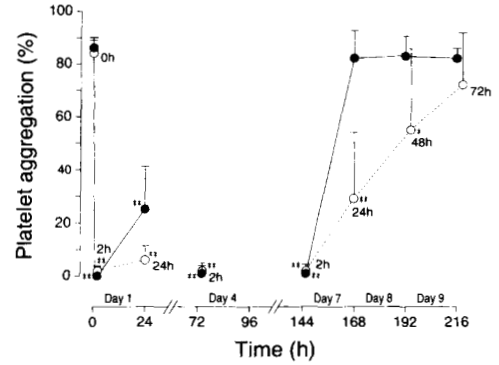

FIG. 6. Maximum platelet aggregation in plasma induced by U46619 at high (●) and low (○) concentrations following 300 mg of FK070 every 12 h for 6·5 days. Symbol and bar represent mean ± s.d. (n = 5). $*P < 0.05$, $**P < 0.01$ vs predrug value (Dunnett's multiple comparison test).

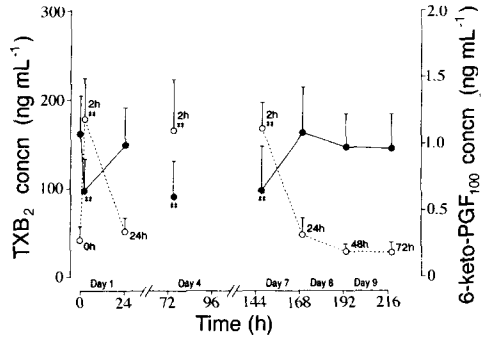

FIG. 7. Serum TXB_2 (●) and 6-keto-PGF_α (○) concentrations produced during whole blood coagulation ex-vivo following 300 mg of FK070 every 12 h for 6·5 days. Symbol and bar represent mean ± s.d. (n = 5). $^*P < 0{\cdot}05$, $^{**}P < 0{\cdot}01$ vs predrug value (Dunnett's multiple comparison test).

was found in subjective and objective symptoms, vital signs, or routine laboratory tests, indicating that FK070 was well tolerated by healthy subjects.

The pharmacokinetic data demonstrated that oral FK070 after a single administration was rapidly absorbed in the fasting state and eliminated from the plasma triexponentially. The $t_{1/\beta}$ generally was constant, whereas the C_{max} and $AUC_{0-\infty}$ increased non-linearly with the doses given. Drug recovery in the urine in the unchanged form in the first 24 h also increased non-linearly with dose. Plasma concentrations during multiple administration, on the other hand, were well described by a linear three-compartment open model and the estimated $t_{1/\beta}$ was in the range of those after a single administration. In addition, urinary recoveries were constant throughout the administration period. These findings suggest that, although the pharmacokinetics of FK070 were non-linear, no abnormal accumulation in the body due to non-linearity would occur with long-term administration.

The present study confirmed that FK070 markedly inhibited the platelet aggregation induced by a TXA_2 analogue and inhibited ADP-induced secondary aggregation as well, though to a lesser degree. Moreover, significant inhibition by U46619 was observed for more than 8 h after administration. Since the mean plasma concentrations of FK070 8 h after administration of 200, 300 and 400 mg were in the narrow range of 10 to 20 ng mL^{-1}, and the concentrations were as low as 1/150–1/350 compared with the maximum concentrations, the duration of inhibition seemed to be longer than would be expected from the plasma concentration. The production of TXB_2 in the serum during whole blood coagulation ex-vivo was also suppressed with a reciprocal enhancement of production of 6-keto-$PGF_{1\alpha}$. The enhancement of 6-keto-$PGF_{1\alpha}$ production is thought to result from conversion of PGH_2/G_2 accumulated in the platelets due to inhibition of TXA_2 production, and from the increase of PGI_2 production in the leucocytes, the so-called PGH_2-steal phenomenon (Defreyn et al 1982). The time profiles of these phenomena tended to parallel that of the plasma concentration. The difference in the duration of the actions of FK070 suggests a much slower dissociation of the drug from the TXA_2 receptor sites than from TXA_2 synthetase.

The duration of inhibitory action of FK070 on platelet TXA_2 receptor was much longer than those of TXA_2-receptor antagonists such as BM13.117 (Patscheke et al 1986; Staiger et al 1986) and SQ28,688 (Friedhoff et al 1986), and was shorter than that of vapiprost (Uematsu et al 1991). No active metabolite of FK070 has so far been found and the inhibitory action of FK070 on TXA_2 synthetase was in parallel with the plasma concentration. Therefore, the progressive and sustained inhibition of TXA_2 receptor was possibly achieved through a slow dissociation from the receptor in the same manner as with vapiprost (Armstrong et al 1989). This suggests a clinical relevance of FK070 for the prevention or treatment of thrombotic disorders and bronchial asthma. In addition, the finding that its action lasted more than 24 h after a single oral administration should also be a merit in its clinical application.

As an index of TXA_2-synthetase activity in-vivo, the production of TXB_2 during whole blood coagulation ex-vivo has been widely used and was adopted in the present study, because the plasma concentration of circulating TXB_2 is readily influenced by the ex-vivo activation of platelets due in the course of blood-sampling procedures. An alternative strategy is to measure the enzymatic products of TXB_2 in the plasma or urine (Catella et al 1986; Minuz et al 1991). In fact, we have measured the changes in plasma 11-dehydro-TXB_2 in healthy subjects who took sodium 2-(imidazoylmethyl)-4,5-dihydrobenzo[b]thiophene-6-carboxylate, a specific TXA_2-synthetase inhibitor (Uematsu et al 1993). When the changes in plasma 11-dehydro-TXB_2 were compared with those in TXB_2 production ex-vivo (Uematsu et al 1994), the time-course of the former was almost the same as that of the latter, although the concentration of TXB_2 in the circulating blood itself was much higher (about 50 000-fold) than 11-dehydro-TXB_2. Therefore, the extent and duration of suppression of ex-vivo production of TXB_2 and 6-keto-$PGF_{1\alpha}$ could be a measure of TXA_2-synthetase inhibition by FK070. However, the inhibition of platelet TXB_2 production by multiple dosing with 300 mg FK070 was approximately 50%. Whether the single action of FK070 to cause such a partial inhibition of the biosynthetic capacity of platelets would be of benefit in antiaggregatory treatment may be questionable.

Although the single pharmacological inhibition of TXA_2 synthetase activity eliminates the production of the platelet-aggregating TXA_2 and enhances the production of anti-aggregatory prostanoids such as PGD_2 and PGI_2, this procedure also produces an accumulation of prostaglandin endoperoxides acting on the TXA_2/prostaglandin endoperoxide receptors. Therefore, a pharmacological blockade of TXA_2-synthetase activity combined with that of the TXA_2-receptor sites has been proposed as an improved strategy. In fact, the combination of a TXA_2-synthetase inhibitor (UK 38485) and a TXA_2-receptor antagonist (ICI 185282) was reported to provide a better protection against arrhythmias than with either agent alone (Kanzik et al 1991). Along with this, such drugs as ridogrel (R 68070) and (E)-7-phenyl-7-(3-pyridyl)-6-heptenoic acid which exert effects upon both TXA_2 synthetase and receptor have been developed and tested in man (Imura et al 1988; De Clerck et al 1989). However, the ratio of the TXA_2-synthetase-inhibiting

potency to TXA_2-receptor blocking is variable among these agents and the most desirable potency should be clarified in further clinical studies.

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