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Pharmacokinetics and Safety of Single Oral Doses of Sirolimus (Rapamycin) in Healthy Male Volunteers

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Summary: A phase I study was conducted to determine the pharmacokinetics, safety, and tolerability of sirolimus, a new immunosuppressive drug, in 45 healthy men between 19 and 36 years of age. Nine subjects in each group were randomly assigned to receive single oral doses of either sirolimus (n = 6) or placebo (n = 3) in group I (0.3 mg/m^2), group II (1 mg/m^2), group III (3 mg/m^2), group IV (5 mg/m^2) and group V (8 mg/m^2). No serious adverse events occurred during the study. Twenty-eight of the 45 volunteers (62%) reported an adverse event; 19 of 30 (63%) were in the sirolimus group and 9 of 15 (60%) were in the placebo group (ns). Asthenia was the most common adverse event, occurring in 7 of 30 (23%) in the sirolimus group compared with 6 of 15 (40%) in the placebo group (ns). Absorption occurred within 1 hour in all volunteers. Whole blood peak concentration and area under the concentration–time curve increased proportionally with dose. Mean (± SD) whole blood terminal disposition half-life ($t_{1/2}$), apparent oral dose clearance (Cl/F), and volume of distribution (V_{ss}/F) were 82 ± 12 hours, 278 ± 117 mL/h·kg and 23 ± 10 L/kg, respectively. Distribution of sirolimus into formed blood elements was extensive, with a mean whole blood-to-plasma ratio of 36. Single oral doses of sirolimus (0.3 to 8 mg/m^2) solution were well tolerated in healthy male volunteers. **Key Words:** Sirolimus—Rapamycin—Pharmacokinetics—Safety—Healthy volunteers—Transplantation

Sirolimus (rapamycin, Rapamune) is a macrolide derived from *Streptomyces hygroscopicus.* It suppresses interleukin-driven T-cell proliferation by blocking postreceptor events (1). Sirolimus has shown an immunosuppressive effect in a variety of animal experiments (2–5). It is currently under clinical development for the prevention of acute rejection in recipients of renal, liver, and heart transplants.

A clinical phase II study of sirolimus in renal transplantation showed that the addition of sirolimus to a cyclosporine/corticosteroid regimen markedly reduced the incidence of acute rejection episodes (6). Another pilot study of sirolimus versus cyclosporine in renal transplantation showed no difference between sirolimus and cyclosporine in prevention of acute rejection (7). Sirolimus is of special interest in renal transplantation because it does not appear to have the nephrotoxicity that hampers the use of cyclosporine and tacrolimus.

During previous phase I studies in renal transplant recipients, single and multiple oral doses of sirolimus have been reported to be well tolerated in doses up to 21 mg/m^2 (8–10) and 12 mg/m^2 (11–12), respectively. Those studies showed that sirolimus has a long elimination half-life and that it is distributed extensively into formed blood elements. Patients participating in these studies generally had mild renal impairment and were treated with cyclosporine, prednisolone, and many other

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concomitant medications. Some of these factors could have influenced the pharmacokinetics of sirolimus.

The present study was designed to provide pharmacokinetic data for sirolimus in medically healthy subjects without concomitant medication and to determine the safety and tolerability of sirolimus in healthy volunteers before undertaking studies in this population to evaluate drug interactions and test new formulations. In the current study, single oral doses up to 8 mg/m^2 were evaluated.

METHODS

This study was performed between April 1994 and June 1994 at the Quintiles AB, Phase I Services, Uppsala, Sweden, in collaboration with the Departments of Clinical Pharmacology and Transplantation Surgery, Huddinge Hospital, Huddinge, Sweden. The study protocol was conducted according to the provisions of the Declaration of Helsinki and its amendments. The ethics committee at the Academic Hospital in Uppsala, Sweden reviewed and approved the protocol, and written informed consent was obtained from each volunteer before enrollment.

Study Design

This was a randomized, double-blind, placebo-controlled, ascending-dose study. In each of the five treatment groups, the subjects were randomly assigned to receive single oral doses of sirolimus (n = 6) or placebo (n = 3): I (0.3 mg/m^2 sirolimus or placebo), II (1 mg/m^2 or placebo), III (3 mg/m^2 or placebo), IV (5 mg/m^2 or placebo) and V (8 mg/m^2 or placebo). Subjects did not receive higher doses of sirolimus or placebo until all volunteers in the previous group had completed evaluations on day 7 and the investigator had determined that there were no findings that would preclude dose escalation.

Volunteer Selection and Safety Assessments

Medically healthy men within ± 10% of ideal body weight for height and frame were included in the study. Exclusion criteria included: acute illness within 2 weeks of study drug administration; intake of over-the-counter products within 2 weeks of study drug administration or prescription drugs within 1 month; participation in another study or use of an investigational drug within 8 weeks of study start; positive urine drug screen for drugs of abuse; use of tobacco in the last 3 months; and excessive intake of caffeine-containing foods or beverages (>500 mg caffeine/d).

Within 2 weeks of entry into the study, the following assessments were made: weight and vital signs; electrocardiogram (ECG); complete blood count; blood chemistry; serologic test for hepatitis B surface antigen and human immunodeficiency virus (HIV-1) and HIV-2 antibodies; urine drug screen; urinalysis; and coagulation, including prothrombin time, activated partial thromboplastin time, and bleeding time. A chest x-ray film was to be taken within 3 months of dose administration.

Physical examinations, vital signs, ECGs, and routine laboratory analyzes were performed before and during the first 7 days after drug administration. Volunteers were discharged from the center on day 2, after the 24-hour blood sampling, and returned daily each morning from day 3 through day 7 on an outpatient basis. The subjects returned to the study unit on day 14 for a post-study examination and final pharmacokinetic sample.

All adverse event evaluations were made in a totally blinded manner by the principal investigator and subinvestigators. They were spontaneously reported or detected during physical examination and clinical evaluation. In addition, the subject was asked the nonspecific question "How have you been feeling since your last evaluation?"

Dose Administration and Pharmacokinetic Sampling

Oral nonaqueous solutions containing 5 mg/mL sirolimus or placebo were supplied. Before administration, the sirolimus concentrate or placebo was diluted with distilled water by an unblinded third-party dispenser who did not participate in screening, drug administration, or the evaluation of any subject.

On the morning of day 1, after an overnight fast, study drug (sirolimus or placebo) was administered with 240 mL room temperature distilled water. The subjects continued to fast for 4 hours after dose administration. Water was permitted ad libitum except from 1 hour before until 2 hours after dose administration. The standard lunch at noon and standard dinner on day 1 each consisted of approximately 30% fat. Blood samples were collected onto sodium edetate for determination of sirolimus in plasma and whole blood, before administration and at 0.33, 0.66, 1, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 312 hours after administration of sirolimus or placebo. All samples were stored at −70° C until analysis.

Bioanalytical Methodology

Sirolimus in Blood

Blood samples were analyzed by a validated electrospray (ESP)-high-performance liquid chromatography/mass spectrometric (HPLC/MS) method at the Department of Clinical Pharmacology, Huddinge Hospital, Sweden. Acetate buffer (1.0 mL, 0.1 mol, pH 4.7) and the internal standard (32-O-desmethoxy-rapamycin) were added to 1.0 mL blood. Solvent extraction with 5.0 mL butyl chloride/diethyl ether (1:1, v/v) was followed by a solid-phase extraction step (Sep-Pac Vac C-18, Waters; Milford, MA) to provide additional sample clean-up. Chromatography was performed on a Shandon Hypersil BDS column (3 × 100 mm) heated to 70°C. The mobile phase consisted of acetonitrile/methanol/50 μmol sodium acetate (38:34:28, v/v). Electrospray ionization was performed on the API/ESI interface of a Finnigan TSQ 700 mass spectrometer (ThermaQuest; San Jose, CA). Needle potential was 4.5 kV, and the temperature of the heated capillary was held at 210°C. Sirolimus (retention time 8.6 minutes) was monitored at m/z 936.6 and the internal standard (retention time 9.3 minutes) at m/z 906.6.

The method was linear for a concentration range of 0.25–50 ng/mL when 1 mL blood was used. Precision and accuracy were determined by analysis of quality control (QC) samples prepared at three concentrations spanning the calibration range. At each QC sample concentration, the precision was expressed as the percentage coefficient of variation (CV) of QC results. Accuracy was measured as the percent deviation from the theoretical value. The values of CV for QC samples during the study were 32% at 0.314 ng/mL, 8.0% at 5.16 ng/mL, and 12% at 41.3 ng/mL. The percentage errors in accuracy for the QC samples were +13% at 0.314 ng/mL, +10% at 5.16 ng/mL, and −1.0% at 41.3 ng/mL.

Sirolimus in Plasma

Plasma samples were analyzed by a validated HPLC tandem mass spectrometry (HPLC/MS/MS) method in the Drug Metabolism Division, Wyeth-Ayerst Research, Princeton, New Jersey, USA. Sirolimus and the internal standard (32-O-desmethoxy-rapamycin) were extracted from plasma (1.0 mL) with 7.0 mL 1-chlorobutane. A BDS Hypersil C-18 column (2 × 150 mm) with 10 × 2 mm guard column (Keystone Scientific; Bellefonte, PA), heated to 40°C, and mobile phase consisting of methanol/5 mmol ammonium acetate was used for chromatographic separation. The retention times of sirolimus and the internal standard were 3.4 and 3.8 minutes, respectively. Quantitation was effected on a PE Sciex API III+ mass spectrometer (Perkin Ermer; Norwalk, CT). The first quadrupole (Q1) was set to detect the ammonium adduct ions [M + NH_4^+] of sirolimus (m/z 931.6 ± 4) and internal standard (m/z 901.6 ± 4). The third quadrupole (Q3) was set to detect the product ions of sirolimus (m/z 864.5 ± 0.5) and internal standard (m/z 834.5 ± 0.2).

The method was linear throughout a concentration range of 0.1–50 ng/mL when 1 mL plasma was used. Precision and accuracy were determined by analysis of QC samples prepared at three concentrations spanning the calibration range. The values of CV for QC samples during the study were 13.1% at 0.3 ng/mL, 8.0% at 5.0 ng/mL, and 7.9% at 40 ng/mL. The percentage errors in accuracy for the QC samples were +1.4% at 0.3 ng/mL, +3.6% at 5.0 ng/mL, and +2.0% at 40 ng/mL.

Pharmacokinetic and Statistical Analyses

Whole blood and plasma sirolimus concentration-versus-time data for each subject were analyzed using noncompartmental methods (area/moment analysis). The peak concentration (C_{max}) and time to peak concentration (t_{max}) of sirolimus in whole blood and plasma were taken directly from the observed data. For sirolimus in whole blood, the last four to six time points that were judged to be in the terminal phase were used to obtain the terminal disposition slope (λ_z) by log-linear regression.

The area under the first moment curve ($AUMC_t$), truncated at the last observable concentration (C_t) at time

TABLE 1. *Demography*

Treatment group		Age	Weight (kg)	Body surface area (m^2)
Placebo	Mean	22	74.7	1.95
	SD	3	7.4	0.14
	n	15	15	15
0.3 mg/m^2	Mean	24	74.2	1.95
	SD	6	6.1	0.09
	n	6	6	6
1.0 mg/m^2	Mean	30*	82.3	2.06
	SD	5	8.8	0.17
	n	6	6	6
3.0 mg/m^2	Mean	23	74.5	1.94
	SD	4	3.6	0.07
	n	6	6.0	6
5.0 mg/m^2	Mean	27	75.7	1.95
	SD	4	10	0.19
	n	6	6	6
8.0 mg/m^2	Mean	24	74.8	1.98
	SD	4	7.5	0.13
	n	6	6	6
All Subjects	Mean	24	75.8	1.97
	SD	5	7.7	0.13
	Range	19–36	60–100	1.67–2.39
	n	45	45	45

SD, standard deviation.
* Significantly greater than the mean age in the placebo group

TABLE 2. *Adverse events*

Subject no.	Group	Adverse events	Severity	Relationship to drug
1	0.3 mg/m^2	Pharyngitis	Mild	Not related
3	Placebo	Pharyngitis	Mild	Not related
4	0.3 mg/m^2	Pharyngitis	Mild	Not related
6	Placebo	Asthenia	Mild	Possibly related
		Dyspnea, pharyngitis	Mild	Not related
9	0.3 mg/m^2	Asthenia, palpitation, diarrhea, dyspnea	Mild	Not related
10	1.0 mg/m^2	Dry skin	Mild	Not related
11	Placebo	Headache	Mild	Not related
12	1.0 mg/m^2	Otitis media	Mild	Not related
13	1.0 mg/m^2	Asthenia	Moderate	Possibly related
14	Placebo	Headache	Mild	Not related
15	1.0 mg/m^2	Asthenia	Mild	Possibly related
16	Placebo	Asthenia	Mild	Possibly related
17	1.0 mg/m^2	Torticollis	Mild	Not related
19	Placebo	Headache, arthralgia, bursitis, swollen Knee	Mild	Not related
20	3.0 mg/m^2	Asthenia, headache	Mild	Not related
21	Placebo	Asthenia, headache	Mild	Not related
22	3.0 mg/m^2	Asthenia, peripheral edema	Mild	Not related
24	3.0 mg/m^2	Pharyngitis	Mild	Not related
25	Placebo	Rhinitis	Mild	Not related
28	5.0 mg/m^2	Asthenia	Moderate	Not related
		Headache, nausea, pharyngitis	Mild	Not related
31	5.0 mg/m^2	Diarrhea	Mild	Possibly related
33	5.0 mg/m^2	Asthenia	Moderate	Not related
34	5.0 mg/m^2	Pharyngitis	Mild	Not related
38	Placebo	Nausea	Mild	Not related
41	8.0 mg/m^2	Headache	Mild	Not related
43	8.0 mg/m^2	Dyspepsia, dizziness	Mild	Not related
44	8.0 mg/m^2	Furunculosis	Mild	Not related
45	8.0 mg/m^2	Constipation, epistaxis	Mild	Not related

t_{last}, was calculated by applying the linear/log-linear trapezoidal rule. Total area under the concentration-time curve (AUC) and AUMC were estimated as follows: $AUC = AUC_t + C_t/\lambda_z$ and $AUMC = AUMC_t + t_{last} \cdot C_t/\lambda_z + C_t/\lambda_z^2$. Terminal disposition half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. Mean residence time (MRT) was calculated from AUMC/AUC. Apparent oral clearance (CL/F) was calculated and normalized by body weight (BWT) as follows: CL/F = Dose / (AUC · BWT). The apparent oral steady state volume of distribution (V_{ss}/F) uncorrected for absorption was calculated and normalized by body weight as follows: $V_{ss}/F = (CL/F) \cdot MRT/BWT$. AVC_t = area under the curve, trapezoidal segment.

The ratio between concentrations in blood and plasma (B/P) was calculated at individual time points. An overall B/P value in each subject was obtained as the average of available B/P values at individual time-points over the first 24 hours. The overall B/P values were averaged for each dosage group.

Linearity was assessed by using a nonlinear least-squares fitting of the following function: $P = a \cdot Dose^b$. This equation was applied to sirolimus data for C_{max} and AUC versus dose to obtain estimates of the slope (a) and exponent (b). Linearity was indicated if the 95% confidence interval for the exponent included the value of 1.

A one-way analysis of variance (ANOVA) was performed for the dosage groups. The values that were analyzed were the subject demographic characteristics, whole blood concentration of sirolimus over 144 hours, B/P ratios at individual time points, overall B/P values in each subject, and pharmacokinetic parameters estimated from noncompartmental analysis. The Tukey studentized range test for differences between means was performed when ANOVA showed a significant difference ($\alpha = 0.05$). Statistical tests were performed using the SAS system (SAS Institute, Cary, NC, USA).

RESULTS

Study Population

Forty-five healthy volunteers were included in the study; 30 received sirolimus and 15 received placebo. Overall, volunteers were between 19 and 36 years old (mean 24 years). All volunteers were white men. The characteristics of the different dose groups are listed in Table 1. There were no statistically significant differences in patient characteristics among the dose groups,

TABLE 3. *Blood sirolimus pharmacokinetic parameters*

Group		C_{max} (ng/mL)	t_{max} (hours)	$t_{1/2}$ (hours)	AUC_t (ng · h/mL)	AUC (ng · h/mL)	Cl/F (mL/h · kg)	V_{ss}/F (L/kg)	MRT (hours)
0.3 mg/m^2	Mean	3.52	0.9		34.5				
	SD	2.62	0.1		41.2				
	n	6	6	1	6	1	1	1	1
1.0 mg/m^2	Mean	11.7	0.8	69.7	116	149	251	18.6	76.2
	SD	4.70	0.2	9.9	47	52	109	6.7	14.6
	n	6	6	6	6	6	6	6	6
3.0 mg/m$_2$	Mean	32.2	0.7	86.2	276	335	342	30.2	88.2
	SD	8.89	0.3	10.8	125	136	158	14.5	11.7
	n	6	6	6	6	6	6	6	6
5.0 mg/m^2	Mean	47.6	0.6	80.3	481	565	299	22.4	78.9
	SD	14.2	0.3	19.5	186	204	95	4.6	19.8
	n	6	6	6	6	6	6	6	6
8.0 mg/m^2	Mean	83.60	0.8	86.4	876	924	256	22.5	85.9
	SD	27.13	0.2	16.7	234	231	67	8.1	12.2
	n	6	6	6	6	6	6	6	6
All subjects	Mean	—	0.78	81.5	—	—	278	22.8	14.9
	SD		0.22	15.6			117	10.0	11.6
	Range	0.3–1.0	55.7–113				145–567	6.7–51.3	59.8–109
	n		30	25			25	25	25

C_{max}, peak concentration; t_{max}, time to peak concentration; $t_{1/2}$, disposition half-life; AUC, area under the concentration-time curve; Cl/F, apparent oral dose clearance; V_{ss}/F, volume of distribution; MRT, mean residence time.

except for age. The mean age of volunteers receiving a sirolimus dose of 1.0 mg/m^2 (30 years) was significantly greater than that of volunteers receiving placebo (22 years).

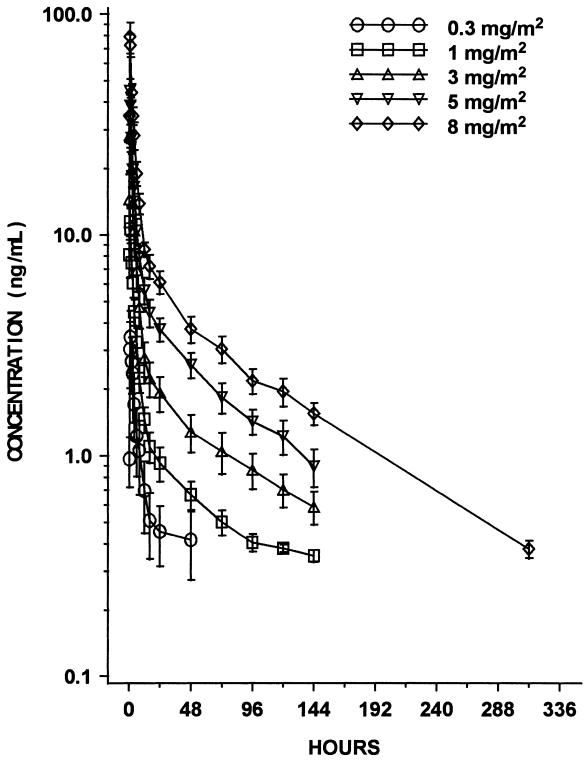

FIG. 1. Mean ± SE sirolimus whole blood concentrations.

Safety and Tolerance

Adverse events were reported for 19 of 30 sirolimus-treated patients: 3 in group I (0.3 mg/m^2), 5 in group II (1 mg/m^2), 3 in group III (3 mg/m^2), 4 in group IV (5 mg/m^2) and 4 in group V (8 mg/m^2), and 9 of 15 placebo-treated patients (Table 2). All events were mild or mod-

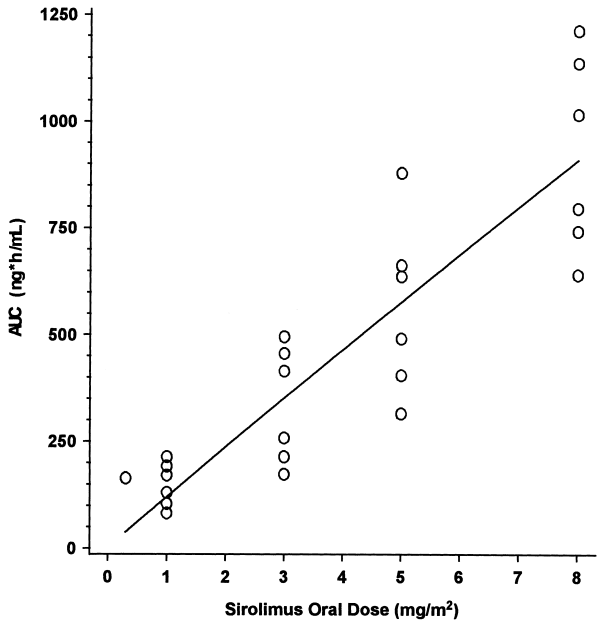

FIG. 2. Whole blood sirolimus area under the curve (AUC) in individual subjects. (Solid line: Y = (Dose)$^{0.97}$, 95% confidence interval for exponent 0.65 to 1.28)

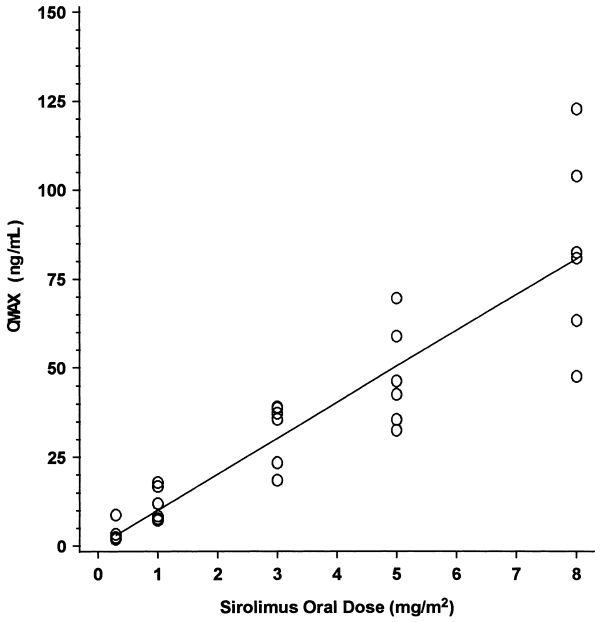

FIG. 3. Whole blood sirolimus peak concentration (C_{max}) in individual subjects. (Solid line: Y = (Dose)$1^{1.00}$, 95% confidence interval for exponent 0.71 to 1.31)

erate. Serious adverse events did not occur during the study. Asthenia was the most common adverse event; 7 of 30 patients (23%) in the sirolimus group compared with 6 of 15 patients (40%) in the placebo group (ns). The second most common adverse event was pharyngitis: 5 of 30 patients (17%) in the sirolimus group compared with 2 of 15 patients (13%) in the placebo group (ns).

In the 8 mg/m^2 group, one volunteer was admitted to the hospital 2 months after the study because of chest discomfort. No pathologic results were recorded. These symptoms continued intermittently for a month, after which all symptoms disappeared. Follow-up examinations, including 24-hour ECG monitoring, did not show any signs of cardiologic disease. The original symptoms were judged to be mild and not caused by with the study drug.

Abnormal laboratory results were seen in 23 volunteers. Twenty-one volunteers had elevated creatine kinase (CK) values (> 3.33 μkatals[kat]/L). Fourteen of these volunteers had elevated CK values before dose administration although all were judged to be healthy. The established normal range was therefore considered inappropriate for this population of young men and the elevations were attributed to physical exercise. It was impossible to detect any CK increase causally related to study drug intake. One single elevated value of creatine kinase MB fraction (CK-MB) appeared in connection with a series of high CK values in a subject performing extreme exercise (training and running a marathon) during the study period. The elevated CK-MB value was judged to be related to this extreme physical exercise and not to study drug intake.

Two volunteers in group V (8 mg/m^2 sirolimus) had a slight increase in serum triglyceride values at follow-up 14 days after dose administration (2.13 mmol/L and 2.25 mmol/L, reference value <2.1 mmol/L). These elevations were judged to be not clinically significant.

Pharmacokinetics

Sirolimus pharmacokinetic parameters in whole blood are given in Table 3 and mean concentrations are shown in Figure 1. Blood sirolimus concentration–time profiles for the 0.3 mg/m^2 group were incomplete because of a lack of assay sensitivity, which prevented the estimation of $t_{1/2}$ and other pharmacokinetic parameters in this dose group. The t_{max} of sirolimus was no greater than 1 hour in all subjects (range, 20 minutes to 1 hour). There were no statistical differences in any pharmacokinetic parameters among dose groups. Individual whole blood AUC and C_{max} versus dose are illustrated in Figures 2 and 3, respectively. Both of these values were linear throughout the dose range studied and the 95% confidence interval of the power function included the value of 1.

Plasma sirolimus concentration–time profiles were incomplete, permitting an estimation of only C_{max}, t_{max} and the blood/plasma ratio (B/P) (Table 4). There was a statistically significant difference between groups for the

TABLE 4. *Plasma sirolimus pharmacokinetic parameters*

Group		C_{max} (ng/mL)	t_{max} (hours)	Blood/plasma ratio
0.3 mg/m^2	Mean			
	SD			
	n	1	1	1
1.0 mg/m^2	Mean	0.40	0.67	29.3
	SD	0.11	0.21	4.5
	n	6	6	6
3.0 mg/m^2	Mean	1.15	1.00	28.0
	SD	0.53	0.00	8.0
	n	6	6	6
5.0 mg/m^2	Mean	1.50	0.89	46.9*
	SD	0.96	0.58	14.4
	n	6	6	6
8.0 mg/m^2	Mean	3.00	1.00	38.4
	SD	1.42	0.52	7.5
	n	6	6.00	6
All subjects	Mean	—	0.88	36.1
	SD		0.39	11.6
	Range		0.33–2.00	15–67.1
	n		25	25

C_{max}, peak concentration; t_{max}, time to peak concentration.
* Significantly greater than the value in 1 or 3 mg/m^2 group.

B/P ratio. The mean B/P for the 5 mg/m^2 dose group was significantly greater (approximately 40%) than that for the 1 and 3 mg/m^2 dose groups.

DISCUSSION

Healthy volunteers are seldom used in clinical trials with immunosuppressive drugs because of the potential risks. This trial, however, showed that single oral doses of sirolimus up to 8 mg/m^2 were well tolerated and safe in healthy volunteers. Furthermore, pharmacokinetic data of immunosuppressive drugs in healthy volunteers are of special interest and importance because renal transplant recipients receive many concomitant medications and have renal impairment (6–12). Cytochrome P450 3A4 enzymes in the liver (13) and intestine (14) are responsible for biotransformation of sirolimus. Interaction with other similarly metabolized drugs, such as cyclosporine, is therefore likely to complicate pharmacokinetic studies in patients.

In a phase II trial, sirolimus had efficacy similar to that of cyclosporine in preventing rejection (7). However, it has not shown nephrotoxic, neurotoxic, or hypertensive effects during phase II trials (6,7,15). Clinical adverse effects of sirolimus include thrombocytopenia, leukopenia, hypercholesterolemia, and hypertriglyceridemia (6, 7,8,15). We found slightly increased serum triglyceride levels in two healthy volunteers at follow-up 14 days after sirolimus 8 mg/m^2. In our previous single-dose study in stable renal transplant recipients, thrombocytopenia was detected in the high-dose group (15 mg/m^2). This complication was not seen in healthy volunteers given a maximum dose of 8 mg/m^2.

We found elevated CK values in several healthy volunteers. This finding was attributed to physical exercise, indicating that the normal range of CK was inappropriate in this population of healthy, physically active young men. Asthenia and pharyngitis were the most commonly reported adverse events, but they were equally distributed in the placebo group and the sirolimus groups and, therefore, were not judged to be related to sirolimus.

After single oral sirolimus doses of 0.3 to 8 mg/m^2, absorption was rapid and peak blood sirolimus concentrations occurred within 1 hour in all volunteers. These findings are in accordance with our previous results in stable renal transplant recipients (8). The concentrations of sirolimus in whole blood decreased slowly, with a mean $t_{1/2}$ of 82 hours. The $t_{1/2}$ was somewhat longer in healthy volunteers than in stable renal transplant recipients, in whom the mean $t_{1/2}$ has variously been reported as 57 hours (8), 59 hours (9), and 62 hours (11). In a population analysis of renal transplant recipients from three different studies, a $t_{1/2}$ of 63 hours was reported (10). The population analyses also showed that the mean CL/F was 127 mL/h · kg, which is approximately 54% lower than for the healthy subjects in the current study (CL/F = 278 mL/h · kg). A lower sirolimus oral-dose clearance in renal transplant recipients receiving concomitant cyclosporine is probably largely the result of intestinal and hepatic metabolic inhibition of sirolimus by cyclosporine, although other factors could also contribute. Because of the long $t_{1/2}$ sirolimus can be given once daily, and a loading dose is recommended to reach steady state concentrations quickly.

Extensive distribution contributes to the large apparent volume of distribution (V/F) of sirolimus, which averaged 22.8 L/kg in the present trial. Indeed, distribution into formed blood elements, as measured by the entire mean B/P ratio of 36 in healthy volunteers, was similar to that found in renal transplant recipients (mean B/P ratios 31 to 49, (8,9–11)) after a single oral dose. A rapid gastrointestinal absorption, a long $t_{1/2}$, and extensive partitioning between whole blood and plasma were also found in stable renal transplant recipients after multiple oral doses of 0.5 to 6.5 mg/m^2 sirolimus, given twice daily (11).

This phase I study showed that single doses of sirolimus up to 8 mg/m^2 are well tolerated and safe in healthy volunteers. Volunteers are an alternative to patients for pharmacokinetic studies with sirolimus when drug exposure is limited.

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