Pharmacokinetics of Sirolimus in Thai Healthy Volunteers

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*Sirolimus, a novel immunosuppressive drug, has been used in kidney transplant recipients to minimize calcineurine inhibitor (CNI) and steroid toxicities. Likewise CNI, Sirolimus's pharmacokinetics have both inter and intra-individual pharmacokinetic variations. Due to ethnic differences, the recommended oral loading dose of 6 mg and oral maintenance dose of 2 mg per day for Caucasian patients and oral loading dose of 10 mg and oral maintenance dose of 5 mg per day for African - American patients may not be appropriate for Asian recipients. We, therefore conducted the pharmacokinetic study of sirolimus in Thai population, aimed to delineate the appropriate sirolimus dose for further clinical use. The study was performed in 12 healthy Thai volunteers. After an over night fasting, a single oral dose of 6 mg sirolimus was given. The complete pharmacokinetic study was done by UV high performance liquid chromatography (HPLC-UV) to measure the whole blood sirolimus level at 0.5 hour after the dose (C0.5) and then C1, C1.5, C2, C2.5, C3, C4, C6, C8, C12, and C24 hours. A complete area under the concentration time curve from 0-24 hours ($AUC_{0\text{-}24\ hr}$) was calculated by using the trapezoidal rule. The mean (± SD) time to maximal concentration (T_{max}) was 1.45 ± 0.5 hr (range 1- 3 hrs). The maximal (C_{max}) and minimal plasma concentration (C_{trough}) for sirolimus were 25.3 ± 6.1 ng/ml (range 18.10 – 40 ng/ml) and 4.47 ± 0.57 ng/ml (range 2.90 – 7.20)ng/ml respectively. The $AUC_{0\text{-}24\ hr}$ were 187.9 ± 48.2 ng*hr/ml (range 151.3 – 294.8 ng*hr/ml). Sirolimus level at 4 hr post-dose had the best of correlation with $AUC_{0\text{-}24\ hr}$ (Pearson correlation = 0.76, $p < 0.007$). One volunteer had a very high sirolimus level. This subject's pharmacokinetic data showed $AUC_{0\text{-}24\ hr}$ of 256 ng*hr/ml and C_{max} of 40 ng/ml. In conclusion, the oral loading dose of 6 mg of sirolimus in Thai volunteers did not achieve the recommended therapeutic level (5-10 ng/ml) in most subjects. There are differences in pharmacokinetics of sirolimus between Thais and Caucasians.*

Keywords: *Sirolimus, Pharmacokinetics*

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Sirolimus (rapamycin), a macrolide derived from *Streptomyces hygroscopicus,* was recovered in 1970s in attempt to discover a new antifungal agent[1]. Sirolimus suppresses interleukin-driven T-cell proliferation by blocking post receptor events. This agent has been shown as a potent immunosuppressive drug in a variety of animal experiments and has currently been used as immunosuppressive drug in solid organ transplantation especially in kidney transplantation. A clinical phase II trial of sirolimus in renal transplantation showed that the addition of sirolimus to cyclosporine/corticosteroid regimen markedly reduced the incidence of acute rejection episodes[2,3]. Sirolimus does not appear to have the nephrotoxicity thus the usage of sirolimus allows the minimization or withdrawal of cyclosporine and tacrolimus which renowned for their nephrotoxicities. Dyslipidemia, especially hypertriglyceridemia and thrombocytopenia have been reported as side effects in the clinical study[4]. These toxicities associate with high blood sirolimus concentration (>15

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ng/ml)[5-7]. Sirolimus has a long elimination half-life and has a wide intra and inter-individual pharmacokinetic variations[8]. There was a significant difference in pharmacokinetics between Caucasian and African American people[9]. In renal transplantation, a recommendation has endorsed sirolimus dose of 6 mg orally for the loading dose and 2 mg orally per day as the maintenance dose for Caucasian patients and 10 mg orally for the loading dose and 5 mg orally per day as the maintenance dose for African-American patients. Due to the racial differences of pharmacokinetic, whether this recommendation is appropriate for Thai population is unproved. This study was designed to determine pharmacokinetic parameter of sirolimus in healthy Thai volunteers to determine an appropriate dose of sirolimus for further clinical use.

Material and Method

This study was a prospective observation study and was performed between August 2003 and February 2004 at Chulalongkorn University Hospital. The study has been reviewed and approved by the ethical committee. Informed consent was obtained from each volunteer before the enrollment. The subjects were assigned to receive single oral doses of 6 mg sirolimus solution.

Volunteer Selection and Safety Assessments

Both male and female subjects were considered eligible to participate the study if they were between 18 and 45 years of age, had body mass index between 18 – 24 and were not taking any medications. Female subjects must have been without childbearing potential. The physical examinations, vital signs, and clinical laboratory tests (CBC, BUN, Cr, electrolyte, LFT, Ca^{+}, PO_4^{2-}, lipid profile, plasma glucose) were performed during the screening period. Subjects will be excluded from the enrollment if they had history or evidence of significant cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, neurological, and respiratory disease or any acute illness, including respiratory tract infection, within 2 weeks before the study. Subjects who used psychoactive drugs, recreational drugs, or prescription drugs within 30 days of the study were excluded from the study. In addition, subjects who had a known hypersensitivity to macrolide compounds such as azithromycin, clarithromycin, and erythromycin will not be recruited. Physical examinations, vital signs, and routine laboratory analysis were performed before the drug administration and after the drug administration at day 7. The adverse events were recorded.

Dose Administration and Pharmacokinetic Sampling

Oral nonaqueous sirolimus solutions containing 1 mg/ml were supplied. After an overnight fasting, sirolimus was stirred more than 1 minute and was administered to the subject with 240 ml of orange juice at room temperature, then follow by pure water from the same glass to wash left drug. The subjects continued to fast for 4 hours after the dose administration. The standard lunch at noon and standard dinner on day 1 consisted of approximately 30% fat. Blood samples were collected onto sodium EDTA for determination of whole blood sirolimus concentration before drug administration and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 6, 8, 12, and 24 hours after sirolimus dosing. All samples were stored at -70^0 C until analyzed.

Pharmacokinetics and statistic analysis

Whole blood sirolimus concentrations were analyzed according to the sequence in the study protocol. Area under the concentration time curve from 0-24 hours ($AUC_{0\text{-}24\ hr}$) was calculated by trapezoidal rule. Half-life was calculated by the equation = 0.693/Ke (Ke = Ln (C12 hr /C24 hr)/12). The volume of distribution (Vd) was also calculated. The correlation between dose and $AUC_{0\text{-}24\ hr}$ were also analyzed. The model fit for prediction of $AUC_{0\text{-}24\ hr}$ from blood sirolimus concentration was calculated by stepwise linear regression analysis.

Results

Study Population (Table 1)

Twelve healthy Thai volunteers were included in the study. The mean age of the subjects was 35.7 years. The mean body weight was 64.73 kg (range 45 – 86 kg), the mean height was 160 cm (range 145 – 170 cm).

Safety and tolerance

There were no complications in all subjects. Laboratory results of pre and 7 days post-dosing were shown in Table 2. There were no significant differences of blood urea nitrogen, creatinine, liver transaminase level, hematocrit, hemoglobin, white blood count, neutrophil, and platelet compared between pre and post-drug dosing.

Pharmacokinetics of sirolimus in Thai healthy volunteers

The average time to maximal concentration (T_{max}) was 1.45 ± 0.5 hr (range 1- 3 hr) (Table 3). The

Table 1. Demographic data of the subjects

	Mean ± SD	Range
Age (years)	35.70±0.34	20-41
Body weight (kg)	64.73±1.39	45-86
Height (cm)	160.00±7.0	145-170
Body mass index (kg/m^2)	25.12±4.64	18.03-32.85
Body surface area (m^2)	1.69±0.16	1.41-2.02
Systolic blood pressure (mmHg)	120.66±11.62	110-150
Diastolic blood pressure (mmHg)	78.0 ± 7.74	70-90

Table 2. Pre and post-sirolimus dosing laboratory results of the subjects

	Pre dosing (mean ± SD)	Post dosing (mean± SD)
BUN (mg/dl)	11.13±2.94	12.13±3.24
Creatinine (mg/dl)	0.80±0.17	0.88±0.12
SGOT	22.37±6.52	21.60±4.89
SGPT	22.33±11.96	21.93±9.80
Hct	39.78±4.95	38.17±3.83
Hb	13.18±1.80	12.85±1.32
Total WBC(x 10^3)	6.95±0.79	7.30±1.27
Neutrophil(%)	55.86±7.18	58.60±6.55
Platelet (x 10 ^{5})	2.54±0.9	2.64±0.95

Table 3. Sirolimus concentration at different time-point after sirolimus oral dose of 6 mg

	Mean	± SD	minimum	maximum
C0.5	10.820	4.694	6.00	24.20
C1	21.650	5.813	11.80	30.90
C1.5	22.220	6.733	15.70	40.00
C2	19.620	6.968	13.30	38.50
C2.5	18.200	7.746	12.00	36.00
C3	17.420	7.280	10.00	36.00
C4	12.720	7.730	7.30	23.40
C6	8.540	5.508	5.40	15.90
C8	6.840	3.132	4.80	12.70
C12	5.760	2.283	4.30	10.10
C24	4.470	0.570	2.90	7.20
C_{max}	25.340	6.190	18.00	40.00
T_{max} (hr)	1.450	0.500	1.00	3.00
$T_{1/2}$ (hr)	46.050	39.280	18.63	142.71
Vd(L/Kg)	35.500	0.750	21.67	49.36
$AUC_{0-24\ hr}$	187.940	48.260	151.30	294.85

maximal (C_{max}) and minimal concentration (C_{trough}) of sirolimus were 25.3 ± 6.1 ng/ml (range 18.10 – 40 ng/ml) and 4.47 ± 0.57 ng/ml (range 2.90 – 7.20 ng/ml) respectively. The mean $AUC_{0-24\ hr}$ were 187.9 ± 48.2 ng$_*$hr/ml (range 151.3 – 294.8 ng$_*$hr/ml). The half-life and volume

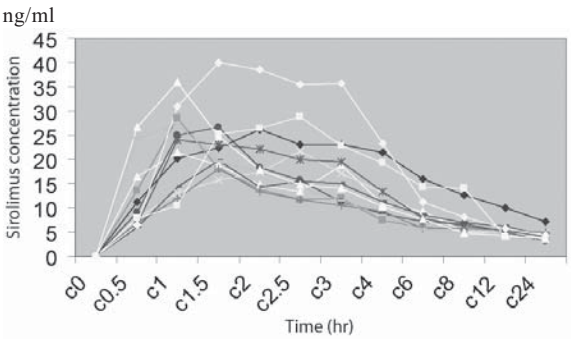

Fig. 1 Concentration – time curve of each of 12 subjects

distribution of the drug were 46.05 ± 39.28 hours and 35.50 ± 0.75 liters respectively. One subject had high peak sirolimus concentration as C_{max} of 40 ng/ml (Fig. 1). This subject had $AUC_{0-24\ hr}$ of 256 ng$_*$hr/ml. However, the trough sirolimus concentration which has been advocated for the therapeutic drug monitoring of sirolimus of this subject was within the therapeutic range.

Sirolimus concentration at 4 hrs post-dose had the best correlation with $AUC_{0-24\ hr}$. However the correlation of this single time point of correlation (r^2) was only 0.76 by Pearson correlation ($p<0.007$) ($AUC_{0-24\ hr}$ = 5.841C4 + 107.005). The model fit from stepwise linear regression analysis showed a significant correlation when a single C24 or C24 and C1 were added (r^2 = 0.75 and 0.72 respectively: $P < 0.005$) ($AUC_{0-24\ hr}$ = 4.099C4 + 19.360C24 + 48.082 and $AUC_{0-24\ hr}$ = 4.196C4 + 23.479C24 + 2.597C1 - 23.895). However this correlation level was not better than the single correlation with C4 concentration. There were no significant correlation between the pre-dose laboratory results and $AUC_{0-24\ hr}$ (Table 4).

Table 4. The Pearson correlation between before pre-dose laboratory parameter and $AUC_{0-24\ hr}$

	Correlation	P value
Cholesterol	0.160	0.65
triglyceride	0.005	0.99
HDL	0.170	0.37
BUN (mg/dl)	0.210	0.56
Creatinine (mg/dl)	0.100	0.77
SGOT	0.027	0.94
SGPT	0.140	0.70
Hct	0.380	0.26
Hb	0.310	0.37
Total WBC	0.130	0.70
Neutrophil	0.420	0.22
Platelet	0.210	0.55

Table 5. Comparison of pharmacokinetic parameter betweem studies in Thais and Caucasians

	Normal Caucasian healthy volunteer[16] (sirolimus dose 3 mg/m^2)	Stable post kidney transplantation Caucasian[19] (sirolimus dose 2.7 mg/m^2)	Thai healthy volunteer (sirolimus dose 3.6mg/m^2)
C_{max} (ng/ml)	32 ± 8.89	25 ± 14	25.3 ± 6.19
T_{max} (hr)	0.7 ± 0.3	2.5 ± 1.4	1.45 ± 0.5
$AUC_{0\text{-}24\ hr}$ (ng*hr/ml)	276 ± 125	317 ± 149	187.9 ± 48.26
$T_{1/2}$ (hr)	86.2 ± 10.8	NA	46.05 ± 39.28
Vd(L/Kg)	30.2 ± 14.5	NA	35.50 ± 0.75

NA= not available, Cmax = maximum concentration, Tmax = time to maximal concentration, AUCt = area under concentration time curve by trapezoidal rule, Vd = volume of distribution

Discussion

Pharmacokinetic data of immunosuppressive drug are a major focus in therapeutic drug monitoring of immunosuppressive agents in renal transplantation. The pharmacokinetic variations and inappropriate immunosuppressive drug dosing result both renal allograft dysfunction and unavoidable drug toxicities[10-12]. Cytochrome P450 3A4 enzymes in the liver[13] and P-glycoprotein in the intestine[14] are responsible for biotransformation of sirolimus. The individual cytochrome P450 3A4 and P-glycoprotein function cause inter-subject pharmacokinetic variation. The concomitant administration of agents that interact with sirolimus interferes with the pharmacokinetic and cause intra-subject pharmacokinetic variation. In previous studies, the adverse effects of sirolimus namely thrombocytopenia, leukopenia, hypercholesterolemia, and hypertriglyceridemia associated with drug concentration[15].

In this study, a single oral doses of sirolimus 6 mg were well tolerated and safe in healthy Thai volunteers. After single oral sirolimus doses of 6 mg, absorption was rapid. Time to peak blood sirolimus concentrations (T_{max}) was 1.45 ± 0.5 hours. Comparison of pharmacokinetic of sirolimus with previous study performed in Caucasian, T_{max} of sirolimus in Caucasian was faster (0.7 ± 0.3 hour)[16] than our population (Table 5). However the half-life of sirolimus of our population was shorter (46.05 ± 39.28 hrs in Thai vs. 86.2 ± 10.8 hrs in Caucasian) when the same dose of sirolimus was given. When compared with the data [17] in African-American, the African-American population had more prolonged T_{max} (2.03 ± 1.73 hrs). The different of pharmacokinetic among ethics can be from the variation of drug absorption which determined by P-glycoprotein and from variation of hepatic drug metabolism which determined by cytochrome P450 3A4 enzymes. The differences of genetic background results variation of P-glycoprotein and cytochrome P450 3A4 enzymes functions. The data in this study confirmed this postulation as our population had lower absorption rate, but more rapid clearance, and lower $AUC_{0\text{-}24\ hr}$ compared with the Caucasian.

Thus, the 6 mg oral loading dose (mean 3.6 mg/m^2) may not achieve the recommended therapeutic sirolimus C_{trough} concentration (5-10 ng/ml). As our population had half-life more close to African-American, we may need a loading dose of between 6 – 10 mg as in the middle range between the dose recommended for Caucasian and African-American patients. In a study, the data showed that African-American population had 45% higher clearance of sirolimus more than Caucasian[18]. This study was performed in healthy Thai volunteers, the appropriate dose for post-transplantation need to be confirmed in further study. Previous study in Caucasian showed that there were differences of pharmacokinetic of sirolimus among healthy and post-transplant subjects (Table 6)[19]. The drug interactions with sirolimus post-transplantation such as cyclosporine, steroid and diltiazam caused the more complicated pharmacokinetic variation.

In conclusion, the oral loading dose of 6 mg sirolimus in Thai volunteers did not achieved the recommended therapeutic level (5-10 ng/ml) in most subjects. There are differences in pharmacokinetics of sirolimus between Thai and Caucasian.

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เภสัชจลนศาสตร์ของยาไซโรลิมุสของอาสาสมัครสุขภาพดีในคนไทย

อัษฎาศ์ ลีฬหวนิชกุล, ณัฏฐดา อารีเปี่ยม, สมฤทัย วัชราวิวัฒน์, เกื้อเกียรติ ประดิษฐ์พรศิลป์, ยิ่งยศ อวิหิงสานนท์, เถลิงศักดิ์ กาญจนบุศย์, สมชาย เอี่ยมอ่อง, เกรียง ตั้งสง่า

ไซโรลิมุส (sirolimus) เป็นยากดภูมิคุ้มกันที่ออกฤทธิ์แตกต่างจากไซโคลสปอริน (cyclosporin) และทาโครลิมุส (tacrolimus) ซึ่งมีหลักฐานว่าสามารถใช้ร่วมกับยากดภูมิคุ้มกันชนิดอื่นๆ เพื่อลดขนาดยา CsA และ steroid ลงได้ และจากกลไกการออกฤทธิ์ของยาน่าจะไม่ขัดขวางการเกิด tolerance ในระยะยาวต่างจากยากลุ่มอื่น ๆ ในต่างประเทศมีการใช้ยาขนาดเริ่มต้น 6 มิลลิกรัม แล้วตามด้วย 2 มิลลิกรัมต่อวัน ในชาวยุโรป-อเมริกัน แต่ใช้ยาขนาด 10 มิลลิกรัมตามด้วย 5 มิลลิกรัมต่อวัน ในชาวอัฟริกัน-อเมริกัน และยังไม่มีการศึกษาเภสัชจลนศาสตร์ของยาในคนเอเชียอย่างชัดเจนมาก่อน ดังนั้นจึงใช้ยาในขนาดของชาวยุโรปมาทำการศึกษาในคนไทย เพื่อประโยชน์ในการปรับใช้ยาต่อไป ผู้ป่วยที่เข้าการศึกษาครั้งนี้เป็นอาสาสมัครสุขภาพปกติทั้งสิ้น 12 ราย ได้ศึกษาเภสัชจลนศาสตร์โดยการเก็บตัวอย่างเลือดก่อนและหลังรับประทานยาไซโรลิมุส ขนาด 6 มิลลิกรัม ที่เวลา 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, 12 และ 24 ชั่วโมง แล้วนำไปตรวจทางห้องปฏิบัติการ ด้วยวิธี high performance liquid chromatographyUV พื้นที่ภายใต้เส้นระดับยาที่จุดเวลาต่าง ๆ ภายหลังการให้ยาในช่วงเวลา 24 ชั่วโมง ($AUC_{0-24\ h}$) อาศัยการคิดพื้นที่สี่เหลี่ยมคางหมู พบว่าพื้นที่ภายใต้เส้นระดับยาที่จุดเวลาต่าง ๆ ภายหลังการให้ยาในช่วงเวลา 24 ชั่วโมง ($AUC_{0-24\ h}$) มีค่าเฉลี่ย 187.9 $\pm$ 48.2 (151.3 -294.8) นาโนกรัม ชั่วโมงต่อมิลลิลิตร ระดับยาสูงสุดเฉลี่ย 25.3 $\pm$ 6.1 (18.10 - 40) นาโนกรัม ต่อมิลลิลิตร ระยะเวลาที่ระดับยาสูงสุดเฉลี่ย 1.45 $\pm$ 0.5 (1- 3) ชั่วโมง ระดับยาต่ำสุดเฉลี่ย 4.47$\pm$0.57 (2.90 - 7.20) ระดับยาในเลือดที่เวลา 4 ชั่วโมง ภายหลังการรับประทานยามีความสัมพันธ์ทางสถิติสูงสุดกับค่า ($AUC_{0-24\ h}$) (pearson correlation = 0.76,p <0.007)ระดับยาในเลือดที่เวลา24 ชั่วโมง ภายหลังการรับประทาน ยามีความสัมพันธ์ทางสถิติกับค่า ($AUC_{0-24\ h}$)รองลงมา (pearson correlation value of 0.72, p <0.011) มีอาสาสมัคร 1 รายที่มีการตอบสนองต่อยามากกว่าปกติโดยมีค่าระดับยาในเลือด40นาโนกรัม ต่อมิลลิลิตรและมีค่า$AUC_{0-24\ h}$ เป็น 256 นาโนกรัม ชั่วโมงต่อมิลลิลิตรแต่มีระดับยาในเลือดที่เวลา24 ชั่วโมงอยู่ในค่าเฉลี่ย ผลการวิจัยพบว่า การใช้ยา 6 มิลลิกรัม ไม่สามารถเพิ่มระดับยาให้ขึ้นถึงระดับที่ใช้ในการรักษาได้ (5-10 นาโนกรัมต่อเดซิลิตร) ในผู้ป่วยส่วนใหญ่ ดังนั้นน่าจะมีความแตกต่างทางเภสัชจลนศาสตร์ของยา ไซโรลิมุสระหว่างคนไทยและชาวต่างประเทศ การนำผล การศึกษาจากต่างประเทศมาใช้จึงควรมีความระมัดระวัง