Study of Cyclosporine Level at 2 Hours after Administration in Preoperative Kidney Transplant Recipients for Prediction of Postoperative Optimal Cyclosporine Dose

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Objective: *Absorption profiling of cyclosporine is a current concept of drug monitoring. A single blood concentration measurement 2 hours after cyclosporine administration (C_2) has been shown to be a good predictor of drug exposure and clinical outcome. The recommendation states that achieving the recommended target level of 1700 340 ng/ml within 3-5 days after renal transplantation is associated with a lower rate of acute rejection and nephrotoxicity. The high variation of pharmacokinetic profile and short limited time during early post-transplantation period make it hard to adjust the cyclosporine dose that can reach that target level on time. The present study was designed to be a method to predict the optimal pre-transplant CsA dose.*

Material and Method: *Eleven living-related kidney transplant recipients were recruited to receive cyclosporine and were monitored for C_2 concentration during the 2 weeks before operation by the designed method. The pre-transplant empirical dose of 3.5 mg/kg/dose every 12 hours were assigned to all patients. The first predicted dose was estimated by using C_2 concentration of 1,700 ng/mL. The first predicted dose was prescribed to the patients. The second predicted dose was estimated by using C_2 concentration of the first predicted dose. All patients received the average of the first and the second predicted doses of cyclosporine within 12-24 hrs before transplantation and until the 3rd day after transplantation.*

Results: *Nine out of 11 patients (81.81%) reached the target C_2 level on the 3rd day after transplantation without any serious side effect and complications. The most common side effect was nausea and a flushing sensation that usually abated with a later dose after transplantation.*

Conclusion: *The early postoperative optimal cyclosporine dose can be effectively predicted by pre-transplant C_2 measurement as conducted in the present study.*

Keywords: *Cyclosporine level, Kidney transplantation*

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Cyclosporine (CsA) based immunosuppressive regimen has been used as an effective regimen in renal transplantation. Though CsA inhibits the renal allograft rejection, this agent has been known as a nephrotoxic agent[1]. The toxicity of CsA is blood concentration dependent. The monitoring of CsA concentration is pivotal to minimize the toxicity, yet remain the allograft rejection prevention[2]. The blood CsA concentration can be done by trough level, peak level, and area under the curve (AUC) monitoring. Studies[3,4] have shown that the absorption profiling of cyclospo-rine by AUC at 0-4 hours post-CsA dose (AUC_{0-4hrs}) is a

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current concept of drug monitoring. This has been shown to delineate the intra and inter-patient pharmaco kinetic (PK) variations. $AUC_{0\text{-}4hrs}$ need at least four blood draws and is cumbersome in clinical practice. A single blood concentration measurement 2 hours after cyclosporine administration (C_2) has been shown to have the best correlation with CsA AUC and to be a good predictor of drug exposure and clinical outcome[5]. The recommendation states that achieving the recommended target level of 1700 $\pm$ 340 ng/mL within 3-5 days after renal transplantation is associated with a lower rate of acute rejection and nephrotoxicity[4,6]. This early post-transplantation is a critical step. It is because the immune competent cell of recipient encounters with the renal allograft that harbors the alloantigen. This early encounter triggers the allorecognition and immune response. The initiation of the immune response causes robust amplification of reactive clone of lymphocyte[7]. The early achievement of CsA C_2 concentration thus is important for early inhibition of reactive immune competent cells. The high variation of pharmacokinetic profile and the 3 to 5 days time limit post-transplantation makes it hard to adjust the cyclosporine dose to reach the target level on time. The present study was designed to be a method to predict that optimal CsA dose.

Material and Method

The present study was conducted at Chulalongkorn University Hospital and was approved by the Ethical Committee, Chulalongkorn University. The recruited patients were living-related kidney transplant recipients. The patients' ages were more than 15 years old. The exclusion criteria included liver disease or receiving drugs that interfered with cytochrome P-450 3A4 system such as macrolide antibiotics, azole antifungal agents etc.

Measurement of CsA C_2 concentration

All the patients received pre-transplant microemulsion CsA dose 3.5 mg/kg/dose orally every 12 hours for four consecutive doses. Before the 4th dose, CsA whole ethylenediaminetetraacetic acid (EDTA) blood concentrations (C_0) were measured by fluorescence polarization immunoassay (FPIA) method. They were also measured at 1 hour (C_1), 2 hours (C_2), and 4 hours (C_4) post CsA. The first predicted CsA dose for C_2 concentration of 1700 ng/ml was estimated by the formula:

First predicted dose = Empirical dose of CsA (3.5 mg/kg/dose) X 1700/C_2 concentration. The "under the curve" of CsA at 0-4 hours ($AUC_{0\text{-}4hrs}$) were estimated by linear trapezoidal rule from the formula:

$$AUC_{0\text{-}4hrs} = AUC_{0\text{-}1} + AUC_{1\text{-}2} + AUC_{2\text{-}4}$$
$$= (C_0 + C_1)X\,(t_1\text{-}t_0)/2 + (C_1 + C_2)X\,(t_2\text{-}t_1)/2 + (C_2 + C_4)X\,(t_4\text{-}t_2)/2$$

t_x = time post-dose (hours)

The first predicted doses were prescribed to the recipients for 4 consecutive doses every 12 hours. The CsA concentrations of the first predicted dose were measured at C_0, C_1, C_2, and C_4. The second predicted doses were calculated by the formula:

Second predicted dose = First predicted dose X 1700/ C_2 concentration

The average dose of the first and the second predicted CsA doses were used for pre-operative CsA dosing. The first CsA dose was given to the patient 12-24 hours before the transplantation. At 3 days post-transplantation, C_0, C_1, C_2 and C_4 were measured.

Immunosuppressions

Besides the CsA, all of the patients received methyprednisolone 1,000 mg intravenously intra-operation, 500 mg intravenously at the first and the second days post-transplantation and oral prednisolone dose at 1 mg/kg/day at day 3. The patients also received azathioprin or mycophenolate mofetil as the protocol for the triple immunosuppressive regimen. A p-value of less than 0.05 was considered significant.

Statistical analysis

The descriptive data were calculated using percentage of patients and mean $\pm$ SD. The Pearson correlation of the variables was analyzed by using bivariate correlation using the Statistical Package for the Social Science version 10.0 (SPSS, Inc, Chicago, Ill, USA).

Results

Patients Demographics (Table 1)

Eleven living-related kidney transplant recipients were included in the present study. They were seven males and four females with the mean age of 42.5 $\pm$ 9.5 years. All patients had chronic hemodialysis before transplantation.

First predicted CsA dose

The empirical doses of CsA (3.5 mg/kd/dose)

Table 1. Demographics of living-related kidney transplantation

	Mean ± SD	Minimum	Maximum
Age (years)	42.5 ± 9.5	30	55
Body weight (kg)	58.6 ± 9.9	46.50	75.00
Height (m)	1.6 ± 0.1	1.41	1.75
Body surface area (m)	1.6 ± 0.2	1.39	1.85
Body mass index	22.8 ± 2.8	19.35	27.55
Hemoglobin (g/dl)	11.3 ± 1.7	8.00	13.00
Hematocrit (%)	34.4 ± 5.7	23.30	41.00
Albumin (g/dl)	4.2 ± 0.3	3.40	4.70
BUN (mg/dl)	54.4 ± 8.2	43.00	67.00
Creatinine (mg/dl)	8.1 ± 2.5	5.10	14.60
Cholesterol (mg/dl)	219.5 ± 36.2	181.00	311.00
Trigleceride (mg/dl)	122.8 ± 43.9	59.00	222.00
HDL (mg/dl)	64.0 ± 21.6	30.00	103.00
Kt/V urea	2.1 ± 0.2	1.95	2.50

Table 2. The CsA C_2 cencentration and $AUC_{0\text{-}4hrs}$ of the empirical doses of 3.5/mg/kg/dose

Patient no.	CsA dose (mg/dose)	CsA dose/kg (mg/kg/dose)	CsA C2 Concentration (ng/ml)	$AUC_{0\text{-}4hrs}$ (ng.hr./ml)
1	200	3.5	690.26	2421.22
2	225	3.5	1205.10	3823.81
3	225	3.5	1348.32	3823.29
4	175	3.5	906.12	2567.39
5	250	3.5	1447.10	4408.85
6	150	3.5	1028.46	2994.00
7	200	3.5	875.22	2766.69
8	250	3.5	1549.23	4099.47
9	175	3.5	1333.02	4494.88
10	175	3.5	1181.26	3380.37
11	225	3.5	989.72	2793.85
Mean ± SD	204.55	3.5 ± 0	1139.44 ± 266.54	3415.80 ± 751.85

achieved target CsA C_2 concentration (1700 ± 340 ng/ml) in two patients (18.2%) (Table 2). The mean CsA C_2 concentration of the empirical CsA dose was 1139.44 ± 266.54 ng/ml. The mean $AUC_{0\text{-}4hrs}$ of the first predicted dose was 3415.80 ± 751.85 ng.hr/ml. The mean CsA C_2 concentration of the empirical dose was used to calculate the first predicted dose. The mean first predicted dose was 5.5 ± 1.5 mg/kg/dose (Table 3). The first predicted dose of CsA achieved target CsA C_2 concentration (1700 ± 340 ng/ml) in seven patients (63.6%) (Table 3). The mean CsA C_2 concentration of the first predicted CsA dose was 1908.68 ± 269.43 ng/ml. The mean $AUC_{0\text{-}4hrs}$ of the first predicted dose was 5410.66 ± 739.49 ng.hr/ml. The mean CsA C_2 concentration of the first predicted dose was used to estimate the second predicted dose. The mean second predicted dose was 5.46 ± 1.5 mg/kg/dose (Table 4). The average of the first and the second predicted doses were used as the pre-transplantation CsA dosing. At day 3 post-transplant, the average predicted doses of CsA achieved target CsA C_2 concentration in nine patients (81.8%) (Table 4). The mean CsA C_2 was 1592.20 ± 299.64 ng/ml. The mean $AUC_{0\text{-}4hrs}$ of the pre-transplant dose was 4807.18 ± 1120.95 ng.hr/ml. The most common side effects were nausea and a flushing sensation that usually abated with a later dose after transplantation.

The correlation of CsA concentration and $AUC_{0\text{-}4hrs}$

C_2 CsA concentration had the best correlation with both $AUC_{0\text{-}4hrs}$ for empirical dose, first pre-

Table 3. The CsA C_2 cencentration and $AUC_{0\text{-}4hrs}$ of the first mean predicted dose of 5.5 ± 1.5 mg/kg/dose

Patient no.	CsA dose (mg/dose)	CsA dose/kg (mg/kg/dose)	CsA C2 Concentration (ng/ml)	$AUC_{0\text{-}4hrs}$ (ng.hr./ml)
1	500	8.5	1740.22	5263.33
2	325	4.9	2150.88	6433.20
3	275	4.5	1946.38	5318.12
4	325	6.6	1748.88	5244.34
5	300	4.0	1736.98	5438.06
6	250	5.3	1290.14	3873.86
7	400	7.6	1976.54	6423.52
8	275	3.7	1441.24	4929.52
9	225	4.4	1306.36	5192.24
10	250	5.0	2092.30	6215.01
11	375	5.8	1651.76	5186.05
Mean ± SD	318.18	5.5 ± 1.5	1909.68 ± 269.43	5410.66 ± 739.49

Table 4. The day 3 post-transplant CsA C_2 cencentration and $AUC_{0\text{-}4hrs}$ of the average of the first and the second predicted doses of 5.46 ± 1.5 mg/kg/dose

Patient no.	CsA dose (mg/dose)	CsA dose/kg (mg/kg/dose)	CsA C2 Concentration (ng/ml)	$AUC_{0\text{-}4hrs}$ (ng.hr./ml)
1	500	8.59	1980.12	6432.895
2	275	4.19	1800.54	4542.045
3	250	4.16	1176.26	3051.68
4	325	6.63	1538.48	4860.535
5	300	4	1784.42	5470.51
6	300	6.45	1774.48	5371.24
7	350	6.73	1542.19	4967.075
8	300	4.05	1468.11	4616.34
9	250	4.9	1961.06	6363.395
10	225	4.5	1420.10	4157.87
11	375	5.85	1068.44	3045.385
Mean ± SD	313.63	5.46 ± 1.5	1592.20 ± 299.64	4807.18 ± 1120.95

dicted dose, and average of the first and the second predicted doses (Table 5). The correlation improved as shown by the Pearson correlation for empirical dose, first predicted dose, and average of the first and the second predicted doses (Pearson correlation = 0.877, 0.879, and 0.940 respectively.

Discussion

Cyclosporine has been used as a major immunosuppressive agent in renal transplant recipients. The PK variation, both inter-patient and intra-patient, of CsA causes morbidities to the patient. The overdose of CsA results in allograft rejection. A study[8] has shown that patients who had a high magnitude of CsA intra-patient PK variation as shown by high percentage of Coefficient Variation (% CV) had a high incidence of chronic allograft nephropathy. Chronic allograft nephropathy may be caused by both CsA nephrotoxicity and allograft rejection. The CsA blood concentration monitoring using 2 hours post-dose (C_2) by mathematical rules has been used to tailor the CsA dose and minimizing the morbidities caused by this agent[9]. Patients who had high percentage of % CV will benefit from frequent CsA blood concentration monitoring. This will prevent the over immunosuppression or under immunosuppression. Studies[4,10] have shown that achievement of the target CsA C_2 concentration within 3 days post-transplantation at 1,700 ng/

Table 5. The Pearson Correlation of AUC_{0-4}hrs (P value) and C0, C1, C2 and C4 CsA concentration

	Pearson Correlation (p value)			
	C0	C1	C2	C4
AUC_{0-4hrs} for empirical CsA dose	.313 (.349)	.854* (.001)	.877* (.000)	.375 (.255)
AUC_{0-4hrs} forFirst predicted dose	.659* (.027)	.424 (.193)	.896* (.001)	.352 (.288)
AUC_{0-4hrs} for Average of first and second predicted doses	.761* (.006)	.923* (.000)	.940* (.000)	.751* (.008)

* Correlation is significant at the 0.05 level (2-tailed)

ml may be the optimum concentration and minimize the risk of allograft rejection and nephrotoxicity since the intra-patient PK variation causes unpredictable CsA level. The empirical dose or fixed dose of CsA in every patient will not achieve the target C_2 concentration at day 3 post-transplantation. The present study has shown the benefit of pre-operation renal transplantation C_2 concentration study of the empirical CsA dose for prediction of post-operation optimal CsA dose.

The data in the present study demonstrated that CsA C_2 concentration had the best correlation with AUC_{0-4hrs} and concurs with a previous study[11]. This data confirmed CsA C_2 concentration as a surrogate marker for $AUC_{0-4hrs.}$ By the pre-operative renal transplant CsA C_2 concentration measurement, the prediction dose for achievement CsA C_2 concentration of 1,700 ng/ml by 81.81% at day 3 post-transplantation. The most common side effects were nausea and a flushing sensation that usually abated with a later dose after transplantation.

In conclusion, the early postoperative optimal cyclosporine dose can be effectively predicted by pre-transplant C_2 measurement as conducted in the present study.

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การศึกษาระดับยาซัยโคลสปอรินที่ 2 ชั่วโมงหลังรับประทานยาในผู้ป่วยก่อนการผ่าตัดปลูกถ่ายไต เพื่อใช้คาดคะเนขนาดยาซัยโคลสปอรินที่เหมาะสมหลังการผ่าตัดปลูกถ่ายไต

นรินทร์ สุขะวัชรินทร์, เกื้อเกียรติ ประดิษฐ์พรศิลป์, ยิ่งยศ อวิหิงสานนท์, ภาวิณี คุปตะวินทุ, รัชนี โอเจริญ, เถลิงศักดิ์ กาญจนบุษย์, เกรียง ตั้งสง่า, สมชาย เอี่ยมอ่อง

วัตถุประสงค์: *ระดับยาซัยโคลสปอริน ในช่วงที่ร่างกายมีการดูดซึมยา (absorption profiling) เป็นแนวความคิดใหม่ในการติดตามระดับยาเพื่อการรักษา ระดับยาที่ 2 ชั่วโมงหลังรับประทานยา (C_2) ซึ่งอนุมานว่า ตรงกับระดับยาสูงที่สุดในเลือดเป็นระดับยาที่ได้รับการพิสูจน์แล้วว่าเป็นตัวชี้ที่ดีต่อทั้งปริมาณที่ได้รับและผลทางคลินิก มีข้อแนะนำกล่าวว่าการมีระดับยา C_2 เท่ากับ 1700 $\pm$ 340 นาโนกรัมต่อมิลลิลิตร ภายใน 3-5 วันหลังการผ่าตัดจะสัมพันธ์กับอัตราการเกิดปฏิเสธไตและพิษต่อไตต่ำที่สุด ด้วยความแปรปรวนทางเภสัชจลนศาสตร์ของยา และระยะเวลาอันจำกัดทำให้เป็นการยากที่จะปรับขนาดยาให้ได้ระดับ C_2 ที่ต้องการตรงตามเวลา การศึกษานี้มีวัตถุประสงค์เพื่อหาขนาดยาที่เหมาะสมดังกล่าว*

วัสดุและวิธีการ: *ผู้ป่วยซึ่งรอเข้ารับการผ่าตัดปลูกถ่ายไตที่ได้รับบริจาคจากญาติ ในช่วงก่อนการผ่าตัดไม่เกิน 2 สัปดาห์ จำนวน 11 ราย จะได้รับยาซัยโคลสปอรินและตรวจวัดระดับ C_2 ระดับ C_2 ที่ได้ก่อนการผ่าตัดจะถูกนำมาคำนวณหาขนาดยาที่เหมาะสม ผู้ป่วยทุกคนจะได้รับยาในขนาดที่คาดคะเนไว้ในช่วงเวลาก่อนการผ่าตัด 12-24 ชั่วโมง จนถึงวันที่ 3 หลังการผ่าตัด*

ผลการศึกษา: *ด้วยวิธีคาดคะเนขนาดยาดังกล่าว ผู้ป่วย 9 ใน 11 ราย (ร้อยละ 81.81) จะมีระดับ C_2 ตามเป้าหมายที่ต้องการ ในวันที่ 3 หลังการผ่าตัด โดยที่ไม่พบอาการข้างเคียงที่รุนแรง อาการข้างเคียงที่พบได้บ่อยที่สุดคือ อาการร้อนวูบวาบตามตัวและอาการคลื่นไส้อาเจียน พบได้เท่ากันร้อยละ 81.81 ซึ่งจะดีขึ้นและหายไปในที่สุดหลังการผ่าตัด และจากการวิเคราะห์ทางสถิติพบว่า ไม่มีความสัมพันธ์ระหว่างขนาดยาที่เหมาะสม หรือ ระดับยาที่เหมาะสมกับ อายุ เพศ น้ำหนัก หรือค่าทางเคมีอื่น ๆ ของผู้ป่วย เช่น ความเข้มข้นของเลือด อัลบูมิน ยูเรียไนโตรเจน และ ครีอะตินีน ทั้งก่อนและหลังการผ่าตัด*

สรุป: *ขนาดยาที่เหมาะสมในช่วง 3 วันแรกหลังการผ่าตัดสามารถ คาดคะเนได้โดยการตรวจวัดระดับ C_2 ก่อนการผ่าตัด ดังที่ใช้ในการศึกษานี้ ได้อย่างมีประสิทธิภาพ*