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Pharmacokinetic Study and Limited Sampling Strategy of Cyclosporine in Japanese Heart Transplant Recipients

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Background The purpose of this study was to characterize the pharmacokinetics of cyclosporine (CsA) in Japanese heart transplant patients, and to optimise the monitoring strategy based on measurements of the area under the curve of plasma concentration absorption phase or 2 h post-dose concentrations (C_2).
Methods and Results At defined time periods during the first year after transplantation, the area under the curve for the CsA serum concentration from 0 to 4 h ($AUC_{0-4\,h}$) was evaluated. Pharmacokinetic parameters and renal function at 1 month and 12 months after transplantation were compared in 7 Japanese patients. The highest coefficient of determination between CsA $AUC_{0-4\,h}$ and a single concentration was observed using C_2 (r^2=0.838). For CsA pharmacokinetics, the mean measurement of whole blood trough levels value at 12 months was significantly lower than at 1 month after transplantation (p=0.026). The mean serum creatinine level at 12 months was significantly higher than at 1 month (1.00 mg/dl vs 0.73 p=0.0194).
Conclusion A single-time-point model that includes C_2 is useful for predicting CsA $AUC_{0-4\,h}$ in Japanese heart transplant patients. Mean C_2 values >1,000 ng/ml were obtained in patients with no rejection at 1 month and 12 months after transplantation; however, renal impairment may occur. (*Circ J* 2006; **70:** 1307 – 1311)

Key Words: C_2 monitoring; Cyclosporine; Heart; Pharmacokinetics; Transplantation

Cyclosporine (CsA) microemulsion (Neoral®) is widely used in solid organ transplantation, but it has side-effects, including hypertension and nephrotoxicity. Therapeutic drug monitoring (TDM) based on the measurement of whole blood trough levels (C_0) has been used to prevent these side-effects, but despite monitoring, the incidence of end-stage renal disease requiring renal replacement therapy after heart transplantation ranges between 1.0 and 8.0%[1] Recently, use of full area under the curve (AUC) analysis was demonstrated to be a precise predictor of acute rejection and graft survival[2] Following oral administration, CsA is rapidly and completely absorbed during the first 4 h. Absorption profiling is needed as a better monitoring strategy[3–7] In renal transplant patients, the AUC during the absorption phase ($AUC_{0-4\,h}$) highly correlates to the full AUC and has been shown to be a better marker for rejection and nephrotoxicity than C_0[4] In addition, the 2 h post-dose concentration (C_2) was shown to be the best single time point to be the most accurate surrogate marker for $AUC_{0-4\,h}$ and C_2 was found to be a better marker for rejection and nephrotoxicity than C_0[3,4] Cantarovich et al demonstrated a clinical benefit in long-term heart transplant patients monitored with C_2 compared to C_0[5,8] and other groups have reported a clinical benefit of C_2 monitoring in heart transplant patients[9,10] Moreover, C_2 has been reported to correlate with the maximal inhibition of calcineurin[11] and the maximal inhibition of interleukin-2 production[12,13]

The pharmacokinetics of CsA in Japanese renal transplant patients has been previously reported[1,14] but not in Japanese heart transplant patients, which was the purpose of this study by compare the monitoring strategies of measuring $AUC_{0-4\,h}$ or C_2.

Methods

Patients and Medications

Seven Japanese patients were enrolled (6 with dilated cardiomyopathy, 1 with dilated phase of hypertrophic cardiomyopathy as the primary disease). They had undergone heart transplantation at the National Cardiovascular Center, Japan between July 2000 and February 2004. All patients received standard triple-drug immunosuppression with CsA, mycophenolate mofetil (MMF) and prednisone. Pharmacokinetics profiles were obtained from the patients during the first 12 months after transplantation. None of the subjects took no concurrent medications that interfered with CsA pharmacokinetics, such as macrolides or calcium-channel blockers. However, fluconazole was administered to all patients during the first 12 months after transplantation. CsA (Neoral®, Novartis Pharma K.K., Tokyo, Japan) was initially administered at a dose of 6 $mg \cdot kg^{-1} \cdot day^{-1}$ in 2 divided doses. Thereafter, the dose was adjusted to achieve trough levels of 350–450 ng/ml during the first month, 250–350 ng/ml at 2–3 months, 200–300 ng/ml at 4–12 months and 100–250 ng/ml at 13 or more months after transplantation. In addition, the dose of CsA was adjusted based on the AUC during hospital admission for periodic biopsy. MMF (Cellcept, Chugai Pharma K.K., Tokyo, Japan) was initially administered at a dose of 1 g in

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Table 1 Characteristics of Study Patients

No. of patients	*7*
Gender (M/F)	*6/1*
*Age at heart transplantation (years)**	*33.1±11.8 (14–46)*
Primary disease (dilated cardiomyopathy/dilated phase of hypertrophic cardiomyopathy)	*6/1*
No. of patients with incidence of ISHLT rejection Grade 3a within 1 year	*1*

*ISHLT, International Society for Heart and Lung Transplantation. *Mean±SD (range).*

Table 2 Correlation of 1-Point, 2-Point, and 3-Point Estimated AUC_{0-4h} With Actual AUC (n=45)

Model	*Sampling times, h*	*Model equation*	r^2	*Prediction error (%)*			
				Mean±SD	*Within±15%*	*<–15%*	*>15%*
1	*0*	$5.95C_0 + 1{,}598.93$	*0.258*	*5.31±24.77*	*24 (53.3)*	*10 (22.2)*	*11 (24.4)*
2	*1*	$1.56C_1 + 1{,}983.71$	*0.808*	*1.51±11.86*	*37 (82.2)*	*3 (6.7)*	*5 (11.1)*
3	*2*	$2.46C_2 + 769.49$	*0.838*	*0.76±10.74*	*41 (91.1)*	*2 (4.4)*	*2 (4.4)*
4	*4*	$-0.77C_4 + 3{,}973.74$	*0.028*	*6.81±27.81*	*18 (40.0)*	*11 (24.4)*	*16 (35.6)*
5	*0, 1*	$2.68C_0 + 1.43C_1 + 1{,}286.64$	*0.854*	*1.20±10.10*	*38 (84.4)*	*3 (6.7)*	*4 (8.9)*
6	*0, 2*	$2.07C_0 + 2.27C_2 + 334.42$	*0.865*	*0.60±9.70*	*40 (88.9)*	*2 (4.4)*	*3 (6.7)*
7	*0, 4*	$6.85C_0 - 1.43C_4 + 2{,}346.00$	*0.349*	*4.50±22.30*	*21 (46.7)*	*10 (22.2)*	*14 (31.1)*
8	*1, 2*	$0.85C_1 + 1.49C_2 + 1{,}027.98$	*0.950*	*0.20±7.00*	*43 (95.6)*	*1 (2.2)*	*1 (2.2)*
9	*1, 4*	$1.72C_1 + 1.08C_4 + 1{,}059.56$	*0.854*	*1.30±11.20*	*39 (86.7)*	*4 (8.9)*	*2 (4.4)*
10	*2, 4*	$2.54C_2 + 0.51C_4 + 309.71$	*0.849*	*0.70±9.60*	*40 (88.9)*	*2 (4.4)*	*3 (6.7)*
11	*0, 1, 2*	$1.72C_0 + 0.83C_1 + 1.37C_2 + 657.43$	*0.968*	*0.10±5.57*	*44 (97.8)*	*1 (2.2)*	*0 (0)*
12	*0, 1, 4*	$1.85C_0 + 1.58C_1 + 0.74C_4 + 862.81$	*0.872*	*1.16±10.09*	*39 (86.7)*	*2 (4.4)*	*4 (8.9)*
13	*0, 2, 4*	$1.82C_0 + 2.33C_2 + 0.23C_4 + 181.18$	*0.866*	*0.62±9.35*	*41 (91.1)*	*2 (4.4)*	*2 (4.4)*
14	*1, 2, 4*	$1.02C_1 + 1.48C_2 + 1.07C_4 + 114.72$	*0.995*	*0.02±2.43*	*45 (100)*	*0 (0)*	*0 (0)*

AUC_{0-4h}, area under the curve (AUC) for the cyclosporine serum concentration from 0 to 4 h; C_0, measurement of whole blood trough levels; C_1, 1 h post-dose concentrations; C_2, 2 h post-dose concentrations; C_4, 4 h post-dose concentrations.

2 divided doses, and finally 2–3 g for maintenance in accordance with the leukocyte count. Subsequent doses of MMF were adjusted based on the AUC of mycophenolic acid during the admission for scheduled biopsy. A standard prednisone taper was carried out in all patients in accordance with the protocol of the National Cardiovascular Center.[15]

The surveillance protocol of the National Cardiovascular Center following heart transplantation consists of an endomyocardial biopsy once weekly for the first 3 weeks, then 5th, 7th, 11th, and 18th weeks. After 6 months, biopsies are performed every 6 months during the first year. After the first year, biopsies are performed every 6 months for the next 5 years, and then at 12 month intervals thereafter. In this study Grade 3a rejection or above according to the criteria of the International Society for Heart and Lung Transplantation (ISHLT) was considered as rejection. All research procedures were conducted according to the institute's clinical research guidelines and all patients gave written informed consent for disclosure of their clinical data.

TDM and Pharmacokinetic Profiles

Pharmacokinetic profiles were obtained from the 7 patients during periodic hospital admissions for biopsy within the 12 months after transplantation. The plasma concentration of CsA was measured by fluorescence polarization immunoassay (TDx, Abbott Japan Co, Ltd). We collected a blood sample from the patients before taking CsA and 1, 2, 4, 6, and 12 h after dosing. Approximately 1 ml of venous blood was collected each time into a disposable syringe and transferred to a vacuum blood collection tube. The samples were centrifuged, and harvested serum was frozen at –30°C until analysis.

Limited Sampling Strategy (LSS) Development

We searched for predictive models of CsA AUC_{0-4h} using multiple regression analysis. The CsA AUC_{0-4h} values were calculated by trapezoidal approximation. These analyses produced equations of the form, $AUC = a_1C_1 ... + a_nC_n + b$, where a_n and b are coefficients and n is the number of samples ($n \leq 3$). Data were analyzed using Statcel 2 (Excel, Visual Basic for Applications for Windows.

Statistical Analysis of Pharmacokinetic Data and Renal Function

Pharmacokinetic parameters at 1 month (34–49 days) and 12 months (358–377 days) after transplantation were calculated in the 7 patients. One patient had 2 pharmacokinetic profiles calculated at 12 months after transplantation because of rejection. Rejection data was excluded and a total of 14 profiles without rejection were used for the analyses. The time to maximum concentration (t_{max}), C_0 and C_2 were derived directly from the measured values. Data are expressed as mean±SD. The mean±SD for Dose, AUC_{0-4h}, AUC_{0-4h}/Dose, C_0, C_2, t_{max} and renal function were compared using Student's t-test. Statistical significance was defined if the null hypothesis could be rejected at the $p<0.05$ level.

Results

Patient Characteristics (Table 1)

A total of 7 patients were evaluated (6 males, 1 female; mean age±SD, 33.1±11.8 years, range 14–46 years) (Table 1). One of them experienced ISHLT Grade 3a rejection at 6 and 12 months after transplantation.

LSS

Forty-five pharmacokinetic profiles were obtained from

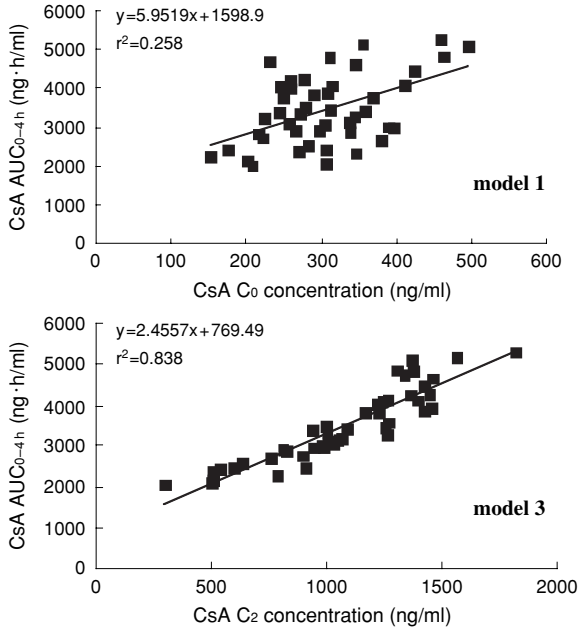

Fig 1. Correlation analysis graphs for C_0 and C_2 with $AUC_{0-4\,h}$. CsA, cyclosporine; $AUC_{0-4\,h}$, area under the curve during the absorption phase; C_0, measurement of whole blood trough levels; C_2, 2 h post-dose concentration.

the 7 patients during the first 12 months after transplantation. The correlations between CsA concentrations at the time points and CsA $AUC_{0-4\,h}$ values and prediction errors for the abbreviated $AUC_{0-4\,h}$ profiles are summarized in Table 2. Fourteen models were developed and analyzed for their ability to estimate the CsA AUC_{0-4h}. The best model for predicting the CsA $AUC_{0-4\,h}$ was a 3-time-point model (model 14: C_1, C_2, C_4; r^2=0.995) with a mean prediction error of 0.02±2.43%. The estimated prediction errors fell within ±15% in 100% of the profiles (45/45) using this model. The 2-sample model that gave the best r^2 value (0.95) was model 8 (C_1, C_2) with a mean prediction error of 0.20±7.00%. Using this model, 95.6% profiles (43/45) had an estimated prediction error within ±15%. The highest coefficient of determination between the CsA $AUC_{0-4\,h}$ and a single concentration was observed with C_2 (r^2=0.838) with a mean prediction error of 0.76±10.7%. Using this model, 91.1% profiles (41/45) had an estimated prediction error within ±15%. C_0 poorly correlated with CsA $AUC_{0-4\,h}$ values with an r^2 value of 0.258 (Fig 1). Using this method, the mean prediction error was 5.31±24.77% and the estimated prediction error fell within ±15% in only 53.3% of the profiles (24/45).

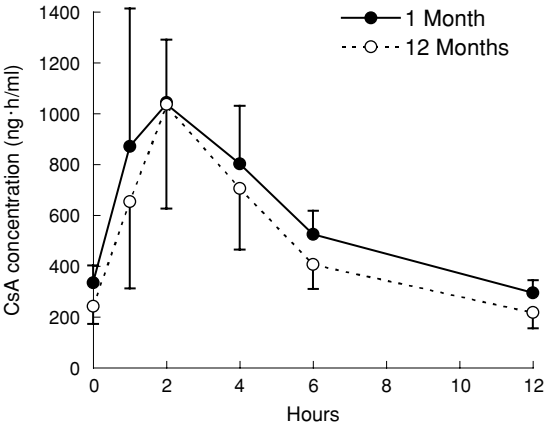

Fig 2. Concentration–time profiles of cyclosporine (CsA) at 1 month (●) and 12 months (○) after transplantation. Each circle represents the mean (±SD) of independent data (1 month; n=7, 12 months; 0–4 h' post dose n=7, 6–12 h post dose n=6).

CsA Pharmacokinetics

The pharmacokinetic profiles are shown in Fig 2. CsA absorption varied more widely between patients during the first 4 h post dose. The pharmacokinetic parameters of CsA at 1 month and 12 months after transplantation are presented in Table 3. The mean dose at 1 month and 12 months was 3.83 and 4.95 $mg \cdot kg^{-1} \cdot day^{-1}$, respectively. The mean $AUC_{0-4\,h}$ value was 3,399.46 and 3,027.39 $ng \cdot h/ml$, respectively, and the mean $AUC_{0-4\,h}$/Dose was 447.80 and 328.12 $ng \cdot h^{-1} \cdot ml^{-1} \cdot mg^{-1} \cdot kg^{-1} \cdot day^{-1}$, respectively. The mean C_0 was 336.20 and 242.60 ng/ml, respectively and the mean C_2 was 1,036.86 and 1,029.97 ng/ml, respectively. There was no significant difference in the mean doses of CsA, mean $AUC_{0-4\,h}$ values, mean $AUC_{0-4\,h}$/Dose values, C_2 values and t_{max} values between about 1 month and 12 months after transplantation. However, the mean C_0 value at about 12 months was significantly lower than at 1 month after transplantation (p=0.026). The mean serum creatinine (Scr) level at 12 months was significantly higher than at 1 month (1.00 mg/dl vs 0.73 p=0.0194) (Fig 3). One patient developed rejection with lower C_2 values (607.2 ng/ml) and lower $AUC_{0-4\,h}$ values (2,407.9 $ng \cdot h/ml$) at 12 months after transplantation. The pharmacokinetic profiles in the patients with rejection at 6 months after transplantation were not measured.

Discussion

The present study of Japanese heart transplant patients demonstrated that a single-time-point model including C_2

Table 3 Pharmakocinetic Parameters for CsA in Heart Transplant Patients Without Rejection (n=7)

Parameters	*After transplantation day*		*p value*
	1 month (34–49 days) Mean	*12 months (358–377 days)* Mean	
Dose ($mg \cdot kg^{-1} \cdot day^{-1}$)	*3.83±0.63*	*4.95±1.96*	*0.12*
$AUC_{0-4\,h}$ ($ng \cdot h/ml$)	*3,399.46±818.48*	*3,027.39±875.72*	*0.43*
$AUC_{0-4\,h}$/Dose ($ng \cdot h^{-1} \cdot ml^{-1} \cdot kg^{-1} \cdot day^{-1}$)	*447.80±107.64*	*328.12±100.24*	*0.052*
C_0 (ng/ml)	*336.20±67.41*	*242.60±70.06*	*0.026*
C_2 (ng/ml)	*1,036.86±256.15*	*1,029.97±401.81*	*0.97*
T_{max} (h)	*2.29±1.25*	*2.29±0.76*	*0.5*

CsA, cyclosporine; T_{max}, time to maximum concentration. Other abbreviations see in Table 2. Values are expresssed as mean±SD.

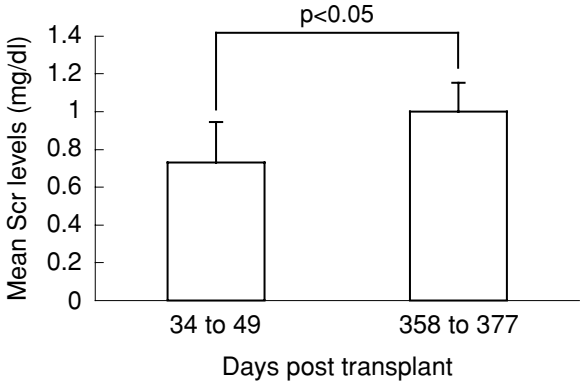

Fig 3. Mean serum creatinine (Scr) levels at 1 month (34–49 days) and 12 months (358–377 days) after transplantation.

was useful for predicting the full CsA AUC_{0-4h} in patients treated with MMF and prednisone concomitantly. Several pharmacokinetic studies of CsA in heart transplant patients have been reported,[1,5,7–10,13,16] but not in Japanese patients. It has been reported that the AUC_{0-4h} of CsA is significantly associated with post transplant clinical events, but the measurement of CsA AUC_{0-4h} using a full set of samples requires considerable personnel time, laboratory resources and quantities of the patient's blood. To support TDM of CsA in clinical practice, LSS should be developed. In the present study, the highest coefficient of determination observed was between CsA AUC_{0-4h} and C_2. Using this model, 91.1% of profiles had an estimated prediction error within ±15%. Cantarovich et al demonstrated that a single-time-point model that included C_2 is the best model for predicting the CsA AUC_{0-4h} in stable post-heart transplant patients at 1 year or more.[8] Arizon del Prado et al reported that a single-time-point model that included C_2 is the best model for predicting the CsA AUC_{0-4h} in post-heart transplant patients during the first month or after 1 month.[17] The present study also demonstrated that a single-time-point model including C_2 is the best model for predicting the CsA AUC_{0-4h} in the early stage of post-heart transplantation.

It is well known that there are many medications that interfere with CsA pharmacokinetics, such as macrolides, calcium-channel blockers, and azole antifungal drugs. In the present study, all patients were co-administered fluconazole during the study period. It has been reported that C_2 significantly correlates with AUC_{0-5h} when ketoconazole is co-administered,[16] so would be expected that the use of fluconazole should not affect the correlation between AUC_{0-4h} and C_2.

In the present study, the mean dose at 12 months after transplantation tended to be higher than at 1 month; however, no significant differences were observed in the mean AUC_{0-4h} values between 1 month and 12 months post transplantation. As a result, the mean AUC_{0-4h}/Dose tended to decrease at 12 months after transplantation, which suggests that clearance of CsA increases with time. It is well known that patients with severe heart failure have the potential for general decreased total body clearance, including hepatic clearance as well as renal clearance.[18,19] It has been reported that heart function affects pharmacokinetic parameters for some drugs.[20,21] The patients in this study had severe heart failure prior to transplantation, thus in the early stages post-heart transplantation patients may potentially have decreased total body clearance, but which subsequently increases with time. Further studies are needed to investigate this issue.

Cantarovich et al studied the impact of C_2 monitoring on de novo adult heart transplant patients receiving thymoglobulin (antithymocyte globulin)! The C_2 target levels of their study were: 0–3 months, 600–800 ng/ml; 4–6 months, 500–700 ng/ml; >6 months, 400–600 ng/ml. They reported that the mean C_2 at 1 month and 12 months was 809±160 and 616±221 ng/ml, respectively. Delgado et al reported that high C_2 values are associated with fewer episodes of acute cellular rejection in post-heart transplant patients.[9] The mean C_2 values of their study with no rejection were: 3–6 months post-heart transplantation 1,403±285 ng/ml, and 6–12 months post-heart transplantation 1,175±215 ng/ml. The C_2 values in their study were higher than those reported by other heart transplant groups. It was reported that acute cellular rejection should be suspected when the C_2 value is below 600 ng/ml.[5,10] In the present study, although the mean C_0 values significantly decreased, no significant differences were observed in the mean C_2 values between 1 month and 12 months after transplantation. Mean C_2 values >1,000 ng/ml were obtained in patients with no rejection at 1 month and 12 months after transplantation. In the case of rejection developing at 12 months after transplantation, a lower C_2 value (607.2 ng/ml) was observed, which suggests that a lower C_2 value is associated with an increased risk of rejection.

Cantarovich et al reported that renal function could be improved by the use of long-term C_2 monitoring[1] and Delgado et al reported that monitoring with C_2 is feasible in terms of preservation of renal function.[9] In the present study, a high level of C_2 was offered by our protocol based on C_0 and as a result, the Scr level significantly increased at 12 months after transplantation. Mean C_2 values >1,000 ng/ml at 12 months might not be needed. In terms of preservation of renal function, prudent reduction of the C_2 values by dose reduction is recommended. In the present study the number of patients with rejections was too small to decide a target range of C_2 for CsA to reduce the risk of acute rejection or renal dysfunction.

The development of a LSS for estimation of CsA AUC_{0-4h} in Japanese heart transplant patients is highly important. We demonstrated that a single-time-point model that included C_2 was useful for predicting the full CsA AUC_{0-4h} in patients treated with MMF and prednisone concomitantly. Although our study is based on a limited number of patients, it is the first to characterize the pharmacokinetic parameters of CsA in Japanese heart transplant recipients. A more detailed study is necessary to verify the assumption that a single-time-point model that includes C_2 is valuable for Japanese heart transplant patients treated with CsA. The study could not present a target range of C_2 or AUC_{0-4h} for CsA to reduce the risk of acute rejection or renal dysfunction. Further studies should be conducted to investigate the relationship between CsA C_2 or AUC_{0-4h} and the risk of rejection and renal dysfunction in Japanese heart transplant patients. Furthermore, the optimal therapeutic C_2 range for long-term therapy in Japanese heart transplant patients should be investigated.

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