Pharmacokinetic Studies of Cyclosporin in Thai Kidney Transplantation Patients

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Abstract

Pharmacokinetic studies were performed in 10 Thai patients with kidney transplantation who received microemulsion formulation (Neoral®) of cyclosporin A (CsA) twice daily. No agents having pharmacokinetic effect on CsA had been used in these patients. The mean values of 12-h AUC (area under the concentration-blood curve) were 4603.63 ± 344.61 ng•h/ml. CsA concentrations at 2 hours after dosing had the best value of correlation coefficient with the 12-h AUC. Abbreviated AUC could be calculated by stepwise multiple linear regression analysis and linear trapezoidal rule. The latter is more simple and superior to the former one.

Key word : Neoral, 12-h AUC, Abbreviated AUC, Linear Trapezoidal Rule, Multiple Linear Regression Analysis

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Cyclosporin A (CsA) has become an established immunosuppressant in the management of kidney transplantation. One of the most important issues regarding oral CsA therapy is how to optimize the drug dosage. Because of the convenience for routine clinical practice, trough CsA concentrations have generally been used for drug monitoring purpose[1-3]. Conventional formulation of CsA, Sandimmun, causes marked intra- and interindividual variation in drug pharmacokinetics, resulting in overlap in trough concentrations that could cause rejection or toxicity[4,5]. As such, the area under the blood concentration-time curve, AUC, which precisely indicates total drug exposure, has been determined and shown to be more beneficial in CsA therapy[6-8]. Most pharmacokinetic studies in the

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literature were, however, reported in Western kidney transplantation patients. There are hardly any pharmacokinetic data in Oriental patients[19].

Although the trough levels from the new microemulsion formulation, Neoral, correlate with AUC better than those from Sandimmun, they still can not be used as a reliable substitution for the complete AUC[9-12]. However, the complete AUC, generally calculated by linear trapezoidal rule, requires multiple blood specimens and, thus, is labor-intensive, and expensive. As such, several abbreviated AUC protocols of both sandimmun and neoral have been established in recent years and this involves measurement of only two or three blood samplings to estimate the complete AUC [11-21]. The model equations in calculating AUC in all these protocols are derived by stepwise multiple linear regression analysis. With such a method, however, the regression equation depends totally on the data selected and, thus, can not be applicable to different data[22]. When the new data are added, the value of all coefficients and the constant of the regression equation will inevitably change. Determination of the abbreviated AUC by linear trapezoidal rule from a few sampling time points, the coefficients in the equation of which are constant, appears to be superior, simpler, and thus, more beneficial than the regression analysis-derived one in prediction of the complete AUC. At present, there are no available data regarding the abbreviated AUC of CsA calculated by linear trapezoidal rule.

The objectives of the present study are twofold. First, to perform the pharmacokinetic studies of microemulsion formulation of cyclosporin, Neoral, in Oriental kidney transplantation patients. Second, to determine the abbreviated AUC derived by linear trapezoidal rule and to compare such AUC with the one calculated by stepwise multiple linear regression analysis.

PATIENTS AND METHOD

The study was approved by the Ethics Comittee of the Faculty of Medicine, Chulalongkorn University Hospital, Bangkok, Thailand. Renal transplant patients who consented and fulfilled the following entry criteria were studied: patients with more than 6 months of follow-up at Chulalongkorn hospital, Bangkok, Thailand; patients with the age ranging 20-65 years; patients who had received CsA microemulsion formulation (Sandimmune Neoral®) twice daily. No one was treated with medication known to have pharmacokinetic interactions with CsA. None of the studied patients suffered from any diseases that could alter absorption, metabolism, or excretion of CsA. The renal function in all these patients was stable. There were 10 patients, 6 male and 4 female, participating in the study. The mean (± SE) age of patients was 37.20 ± 1.02 years while the mean (± SE) weight was 62.60 ± 3.98 kg. The patients received 6 cadaveric, and 4 living-related donor kidney transplantations. The time after transplantation was 29.80 ± 7.91 months. Four patients were treated with dual immunosuppressive therapy, CsA and prednisolone. The other six patients were treated with triple drug regimen, CsA, prednisolone, and azathioprine or mycophenolate mofetil. The mean (± SE) value of CsA dose the patients received was 3.74 ± 0.30 mg/kg/12 h.

The pharmacokinetic profiles were determined when the patients were in a steady state, which is normally reached after the third day of administration of the same oral dose of CsA. No dosing adjustment had been made for at least one week before the study. Since the patients had received CsA twice daily, full pharmacokinetic profiles of the complete AUC were, therefore, studied for the duration of twelve hours. Thus, the term "12 h-AUC" will be used interchangeably with the "complete AUC". On the experimental day, blood samples (3 ml) were obtained before their morning dose of CsA and then at 1, 2, 4, 6, 8, and 12 hours after dosing. Each patient was studied once. The samples were collected in tubes containing EDTA as the anticoagulant. All whole blood samples were stored at room temperature for not more than 24 hours before they were assayed by specific-monoclonal antibody Fluorescence Polarization Immunoassay (FPIA, TDx®, Abbott Diagnostics). Although the TDx assay shows extensive cross-reactivity with metabolite 17 (AM_1), the activity of AM_1 is only one-tenth as active as the parent compound. Furthermore, no CsA interacting drugs, which could result in increased relative concentration of AM_1, were used in the patients studied. Thus, the obtained concentrations of CsA in the present study were not overestimated and could represent the CsA parent compound.

The highest measured blood concentration and the corresponding sampling time were defined as C_{max} and t_{max} respectively. Two trough levels were measured, before drug administration (C_{min}, 0 h) and 12-hour after drug dosing (C_{min}, 12 h).

Half-life ($t_{1/2}$), as in previous studies, was determined by the equation: $t_{1/2} = 0.693/ß$, where ß is the terminal slope of the linear least-squares regression line of a semilogarithmic plot of blood concentration versus time. The average steady-state concentration (Cssav) was calculated as AUC/τ where τ is the dosing interval. Non-compartmental analysis was used to compute clearance (Cl/F) and apparent volume of distribution (Vd/F), according to the following equations: Cl/F = Dose/AUC, and Vd/F = Cl/ß, where Cl is clearance and F is a bioavailability factor.

As previously described, the complete AUC for each patient was calculated by linear trapezoidal rule from the seven concentrations in the full profile (0, 1, 2, 4, 6, 8, and 12 hours)[6-8]. As seen in Fig. 1, the complete AUC is the summation of the individual trapezoidal area between each two sampling time points.

Thus, complete AUC

$$= AUC_{0-1} + AUC_{1-2} + AUC_{2-4} + AUC_{4-6} + AUC_{6-8} + AUC_{8-12}$$

$$= \frac{(t_1-t_0)}{2} \bullet (C_0+C_1) + \frac{(t_2-t_1)}{2} \bullet (C_1+C_2) + \ldots\ldots + \frac{(t_8-t_6)}{2} \bullet (C_6+C_8) + \frac{(t_{12}-t_8)}{2} \bullet (C_8+C_{12})$$

where t = time point (hours after dosing)
C = CsA concentration at each time point (ng/ml)

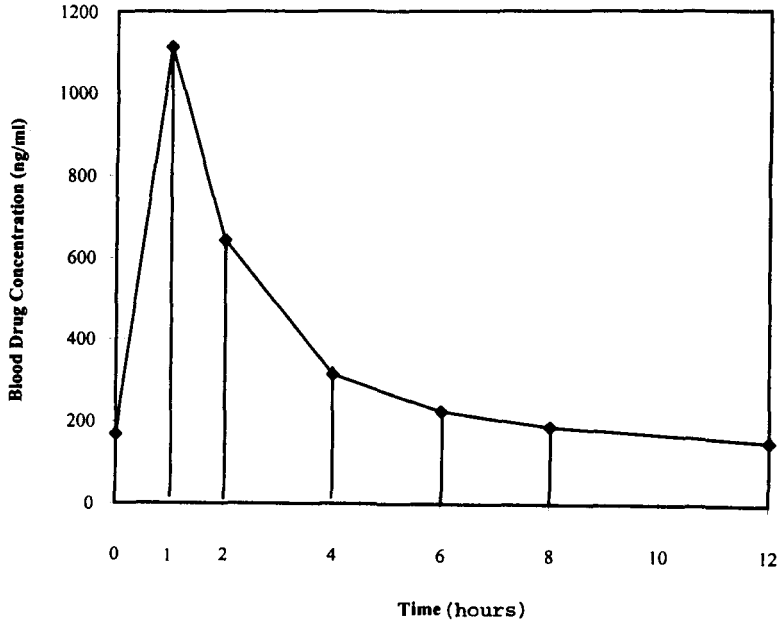

Fig. 1. Method of calculation of complete AUC by "Linear Trapezoidal Rule Analysis".

To obtain abbreviated AUC, we used two methods to select the optimum sampling times for calculating the model equation.

(1) Multiple linear regression analysis, used for determining the abbreviated AUC in all previous reports, was performed by computer to create a formula for the complete AUC prediction [9-12]. Multiple linear regression analysis can be determined as an extension of straight-line regression analysis, which involves only one independent variable, to the circumstance where there are more than one independent variable to be considered. By such analysis, the complete AUC was used as the dependent variables and the blood concentrations grouped by time points as the independent variables.

Thus, complete AUC (predicted by regression analysis)

$= a C_X + b C_Y + c C_Z + d$

Where, C = CsA concentration at each time point (ng/ml)

X, Y, Z = time points (hours after dosing)

a, b, c = coefficients of each C

d = constant

By multiple linear regression analysis, it appears that when new data are added, the initial equation will be changed[26]. This means that the selected time points might not be X, Y, or Z. The values of the coefficients, a, b, and c, and the constant d would also be changed. Although the selected time points are unaltered, the new values of the coefficients and the constant of the regression equation will inevitably occur (see detailed data in the "Result" part).

(2) Linear trapezoidal rule, as used in calculating the complete AUC, was obtained by selecting 2 or 3 time points that had yielded the best predictive value for the complete AUC. In our preliminary and following study, CsA levels at 0, 2, and 6 hours after dosing, C_0, C_2, and C_6 respectively, could provide the statistically reliable abbreviated AUC which had the best correlation with the complete AUC (see detailed data in the "Result" part).

To calculate the abbreviated AUC by linear trapezoidal rule, thus,

Complete AUC (predicted by abbreviated AUC)

$= AUC_{0\text{-}2\ h} + AUC_{2\text{-}6\ h} + AUC_{6\text{-}12\ h}$

$= \frac{(t_2-t_0)}{2} \bullet (C_0+C_2) + \frac{(t_6-t_2)}{2} \bullet (C_2+C_6) + \frac{(t_{12}-t_6)}{2} \bullet (C_6+C_{12})$

$= \frac{2}{2} \bullet (C_0+C_2) + \frac{4}{2} \bullet (C_2+C_6) + \frac{6}{2} \bullet (C_6+C_{12})$

$= C_0 + C_2 + 2C_2 + 2C_6 + 3C_6 + 3C_{12}$

$= C_0 + 3C_2 + 5C_6 + 3C_{12}$

Theoretically, at a steady state, the value of C_{12} would not be significantly different from that of C_0. Thus, C_{12} in the above equation could be substituted by C_0.

As such, complete AUC (predicted by abbreviated AUC)

$= C_0 + 3C_2 + 5C_6 + 3C_0$

$= 4C_0 + 3C_2 + 5C_6$

It should be noted that if C_0, C_2, and C_6 are the selected time points when the new data are added, all the coefficients, the figure number 4, 3, and 5, in the equation will not change. This is totally opposite to that observed in the case of multiple linear regression analysis.

Pearson product-moment correlation coefficients were calculated to evaluate the linear relations between the AUC and the blood concentration at a given time. The correlation between the predicted and measured AUC was evaluated by correlation coefficient and the absolute prediction error calculated as follows:

$$\text{Absolute prediction error} = \frac{(\text{Predicted AUC} - \text{Measured AUC})}{\text{Measured AUC}} \times 100\%$$

All the data were expressed as mean ± SE.

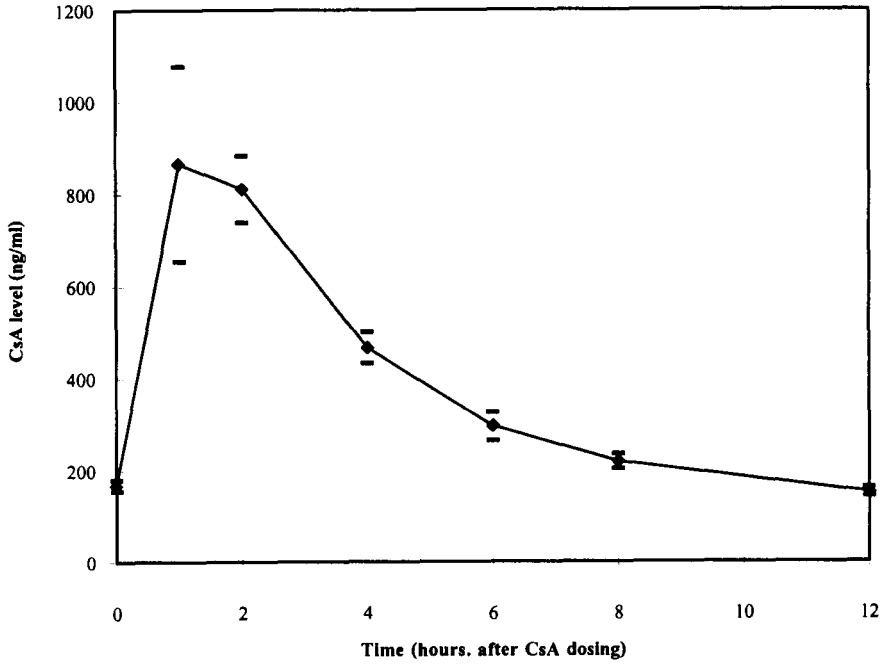

Fig. 2. The mean concentration of CsA at different time points in 10 Thai kidney transplantation patients. (Data were expressed as mean ± SE).

Table 1. CsA pharmacokinetics in kidney transplantation.

Authors	Pharmacokinetic parameters				
	Dose	t_{max} (h)	C_{min} (C_0) (ng/ml)	C_{max} (ng/ml)	12 h AUC (ng•h/ml)
Kovarik et al, 1994	124 ± 36 mg/12 h	1.2 ± 0.3	94 ± 33	901 ± 317	3202 ± 1002
Poradori et al, 1995	1.16 ± 0.36 mg/kg/12 h	1.2 ± 0.2	NA	822 ± 215	2770 ± 424
Masri et al, 1996	2.96 ± 1.39 mg/kg/12 h	1.57 ± 0.49	102.6 ± 28.1	671.5 ± 216.3	NA
Rial et al, 1997	3.72 mg/kg/24 h	1.73	NA	963.42	4577.88 ± 1404.76
Kungsamrith et al (The present study)	3.74 ± 0.30 mg/kg/12 h	1.70 ± 0.15	167.61 ± 12.46	963.27 ± 142.65	4603.63 ± 344.61

NA = no available data
All data were expressed as mean ± SE

RESULTS

Fig. 2 depicts the mean CsA concentrations at different time points. CsA administration could reach the maximum concentration within 2 hours in all studied patients.

The pharmacokinetic parameters of CsA in our patients and in those of previous studies are comparatively shown in Table 1. The data in the present study not shown in Table 1 includes: $t_{1/2}$ = 6.26 ± 0.42 h, Cssav = 383.64 ± 28.72 ng/ml, Vd/F = 228.35 ± 24.11 L, Cl/F = 25.46 ± 1.96 L/h.

Table 2 details the correlation coefficients among CsA levels, 12 h-AUC, and CsA dose. The

Table 2. Correlation coefficients between CsA level, AUC, and dose[a].

	12-h AUC (ng•h/ml)	CsA dose (mg)
C_0	0.6937 (P<0.05)	0.4485 (P=0.194)
C_1	0.6712 (P=0.068)	0.3392 (P=0.411)
C_2	0.9322 (P<0.05)	0.5646 (P=0.089)
C_4	0.5388 (P=0.108)	0.3653 (P=0.299)
C_6	0.4705 (P = 0.201)	0.4571 (P=0.216)
C_8	0.6090 (P= 0.062)	0.3280 (P=0.355)
C_{12}	0.7307 (P<0.05)	0.4128 (P=0.236)

[a] Pearson product-moment correlation coefficients (P value)

Table 3. The model equations derived from stepwise multiple linear regression and linear trapezoidal rule.

No. of equation	Method (No. of sampling time points included in equation)		Time points (h after dosing)	Model equations : predicted 12 h-AUC =	r^2	Absolute prediction error (%)	
						mean ± SE	range
1	Stepwise multiple linear regression	(2)	2,8	$4.262C_2 + 8.390C_8 - 669.417$	0.9808	3.97 ± 0.96	0.96-10.24
2	Linear trapezoidal rule	(2)	2,8	4C2 + 5C8	0.9780	6.41 ± 1.22	0.31-11.43
3	Linear trapezoidal rule	(3)	0,2,6	$4C_0 + 3C_2 + 5C_6$	0.9475	5.00 ± 1.41	0.04-14.01

Table 4. Previously reported stepwise multiple linear regression analysis-derived model equations for abbreviated AUC of CsA (Neoral).

Authors	Model equations	r^2	Absolute prediction error (%)	
			mean ± SE	range
Foradori et al, 1995	12-h AUC = $0.681C_1 + 1.859C_{2.5} + 3.411C_5 + 791.74$	0.9100	NA	NA
Kahan et al, 1995	12-h AUC = $2.4C_2 + 7.7C_6 + 195.8$	0.9380	NA	+0.02 to +30.7
Tsang et al, 1996	12-h AUC = $1.89C_{1.5} + 17.5C_{12} + 452.4$	0.9380	0.36	NA
Serafinowicz et al, 1996	12-h AUC = $9.131C_0 + 0.784C_1 + 2.617C_2 + 193.561$	0.9540	8.8	-14 to +17

Abbreviations : NA, no available data

Table 5. Statistical correlations derived by testing the previous model equations with the pharmacokinetic data in the present study.

Authors	Proposed model equations: Predicted 12 h-AUC =	r^2	Absolute prediction error (%)	
			Mean ± SE	Range
Kahan et al., 1995	$2.4C_2 + 7.7C_6 + 195.8$	0.8537	7.65 ± 2.33	+0.37 to +19.66
Serafinowicz et al., 1996	$9.131C_0 + 0.784C_1 + 2.617C_2 + 193.561$	0.9603	5.86 ± 1.14	+2.29 to +11.28

C_2 concentration, not the trough concentration, C_0, had the best correlation with the complete AUC (r^2 = 0.9322 *vs* 0.6937 respectively). For each time point, there also was a poor correlation between the dose of CsA and the contemporaneously obtained CsA concentration (Table 2). Furthermore, the 12 h-AUC also was poorly correlated with CsA dose; the correlation coefficients of which was only 0.5911 ($P > 0.05$).

In order to confirm whether there was statistically significant difference between C_0 and C_{12}, paired-samples T test was performed between all pairs of both trough levels. It was shown that both C_0 and C_{12} were similar ($p = 0.001$) with the mean paired difference (± SE) was 15.85 (± 6.24). As such, in calculating abbreviated AUC by linear trapezoidal rule analysis, C_{12} could be substituted by C_0 (see details of calculation in the "Patients and Method" part).

Table 3 illustrates the model equations of abbreviated AUC obtained by stepwise multiple linear regression analysis and linear trapezoidal rule in the present study. By stepwise multiple linear regression analysis the best model equation was the two time points-selected one which was derived from C_2 and C_8 (equation 1). There were two model equations derived by linear trapezoidal rule that could provide the best statistical values : two and three time points selected ones which were obtained by C_2 and C_8, and C_0, C_2 and C_6 respectively (equation 2 and 3).

When pharmacokinetic data of only six from all the ten patients were determined by stepwise multiple linear regression analysis, the new regression equation was

12 h-AUC = $4.019C_2 + 10.402C_8 - 812.329$ (r^2 = 0.9927; absolute prediction error = 2.45 ± 1.10%)

When one compared this new model equation of the six patients with that of the ten (Table 3, Equation 1), it was obviously seen that the values of the coefficients and constant in both equations were totally different.

The model equations of such 6 patients calculated by the linear trapezoidal rule derived model equation were,

12 h-AUC = $4C_2 + 5C_8$ (two sampling time points) (r^2 = 0.9808; absolute prediction error = 6.70 ± 1.53%)

12 h-AUC = $4C_0 + 3C_2 + 5C_6$ (three sampling time points) (r^2 = 0.9893; absolute prediction error = 4.01 ± 1.31%)

As compared with equation 2 and 3 in Table 3, which represented pharmacokinetic data of 10 patients, it was clear that both equations had the same values of coefficients, 4 and 5 in the two-time points selected model and 4, 3, and 5 for the three-time points selected one.

Previously proposed model equations of 12 h-AUC of microemulsion CsA (Neoral are shown in Table 4. Of note, all these equations were calculated by stepwise multiple linear regression analysis. Furthermore, some of these reports showed only correlation coefficients but not the percentage of absolute prediction error in AUC prediction. Indeed, the former statistical parameter measures only the strength, whereas, the latter determines the agreement of a relationship between two variables. As compared with the previous studies, the results from the present study have shown that both the two time points-selected model equations derived by stepwise multiple linear regression analysis, and the two and three time points-selected model equations determined by linear trapezoidal rule had comparable values of correlation coefficient with the complete AUC.

By using the pharmacokinetic data of our patients, we tested the model equations proposed by previous studies to determine whether such previous model equations could predict the complete AUC obtained in our patients. On the basis of the available data in the present study that could be used in the calculation, the model equations from the works of Kahan et al, and Serafinowiez et al were selected for the test (Table 5). When the pharmacokinetic data of our patients were determined by these equations, the obtained correlation coefficients were apparently different from the original ones (Table 4 and 5).

DISCUSSION

The results in the present study have shown that 1) CsA concentrations at two hours after dosing or C_2, instead of the trough concentrations, have the best correlation coefficient with the complete AUC. 2) Abbreviated AUC derived by either stepwise multiple linear regression analysis or by linear trapezoidal rule analysis could be used as a reliable substitution for the complete AUC. 3) Abbreviated AUC determined by linear trapezoidal rule is superior to stepwise multiple linear regression analysis-derived one.

Heretofore, there were scarce data regarding the pharmacokinetic studies of CsA in the oriental kidney transplantation patients. The results obtained in the present study which are comparable to those in the Western literature, thus, would establish that it is feasible to apply pharmacokinetic strategy in monitoring CsA therapy in Oriental kidney transplantation patients. There are, however, certain discrepancies in various pharmacokinetic parameters among these studies (Table 1). Such disparities might be caused by the differences in CsA dose, drug absorption, and bioavailability of the drug.

In therapeutic drug monitoring of cyclosporin, two general approaches have been recommended: trough concentrations and complete pharmacokinetic profiles (complete AUC). Accumulating evidence has shown that the trough concentrations of CsA are less informative and less useful for diagnosis or prediction of adverse events[4,5]. In particular, they have limited value for assessing adequate immunosuppression or determining renal toxicity. Monitoring trough concentrations of CsA, however, may be beneficial in recognition of the unusual and extreme cases of patients who have rapid drug metabolism or poor gastrointestinal absorption. Although it has recently been demonstrated that the trough levels of the microemulsion formulation of CsA, Neoral, shows an improved correlation with AUC (r^2 = 0.823 *versus* 0.620 with a conventional formulation)[11], the results from most studies have obviously shown the limited value of the trough concentrations in such circumstances[9-12]. In concurrence with these previous studies, the present work has reconfirmed that it is not sufficient to use the trough CsA concentrations as a single indicator of total drug exposure. Indeed, the best correlation in the present study is obtained from C_2 (r^2 = 0.9322). This is in agreement with several previous observations[20]. However, the optimally therapeutic range of CsA concentrations at C_2 is still unestablished, leading to limited use of C_2 as the parameter in CsA monitoring.

Single CsA concentrations at three, five, or six hours after dosing have been previously reported as an appropiate alternative indicator of total drug exposure as they have a better correlation with AUC values than trough levels[23-25]. Such observations, however, could not be confirmed by others[9-12]. Available data of CsA concentrations at six hours after dosing, C_6, in the present study showed a correlation coefficient value of only 0.4705 (Table 2).

Because of several limitations of trough CsA concentrations, AUC has been determined and demonstrated as a better index of drug exposure. In this regard, monitoring of AUC at clinical steady state has been shown to be more effective than trough levels in CsA dosage adjustment. Complete AUC is generally calculated by linear trapezoidal rule. Although the complete AUC could provide more precise information, it requires several blood samplings. The method is, thus, expensive, time consuming, and thus is difficult for routine clinical purposes. As such, a number of abbreviated AUC profiles involving two or three time points of blood samplings have been reported and shown as a reliable alternative to accurately predict the complete AUC[11-21]. The model equations of abbreviated AUC in all these studies were calculated by stepwise multiple linear regression analysis. In agreement with previous works, the results in the present study have shown that the two time points abbreviated AUC determined by regression analysis has an excellent value of correlation coefficient with the complete AUC. (Table 3, equation 1, r^2 = 0.9808)

For stepwise multiple linear regression analysis, the regression equations would vary with the data set[26]. When new pharmacokinetic data are added, we will inevitably find a new regression equation. The essential basis of this variation is that the values of coefficients and constant in the new equation will inevitably change every time the equation is recalculated. Such considerations were obviously observed in the present study. The values of coefficients and constant of the regression analysis-derived model equation of all the 10 patients are totally different from those of the six (see the "Results" part and Table 3). Indeed, the limited value of abbreviated AUC derived by stepwise multiple linear regression analysis has been previously reported in pharmacokinetic studies of the conventional CsA[22].

Certain limitations have emerged when one uses multiple linear regression analysis for statistical work[26]. First, it is more difficult to choose the best model, since there are sometimes several reasonable candidates. Second, it is more difficult to visualize what the fitted model looks like, particularly if there are more than two independent variables. This is because it is not possible to plot

directly in more than three dimensions either the data or the fitted model. The use of more than two time point concentrations to calculate the model equation in most studies of abbreviated AUC, thus, creates more than two independent variables. Lastly, it is sometimes more difficult to interpret what the best-fitting model means in real-life terms. Taken together, the model equation derived by stepwise multiple linear regression analysis has limited value and would not be generally applicable to different pharmacokinetic data or when the new data are added. The results in the present studies, thus, have reconfirmed such observations (Table 3 and 5). When pharmacokinetic data of our patients were tested by the model equations of Kahan et al, and Serafinowicz et al, the correlation coefficients were much different from the original ones.

Abbreviated AUC derived by trapezoidal rule, primarily used in determining complete AUC, appears to be superior to that obtained by regression analysis. The value of coefficients of each time-point concentration in the model equation is unchanged despite the new pharmacokinetic data being added. Results from the present work have demonstrated such a conclusion and have shown that the two time points-selected AUC derived by trapezoidal rule is the best model equation in prediction the complete AUC ($r^2 = 0.9780$). As such, the abbreviated AUC obtained by trapezoidal rule is simpler in calculation and is more applicable to different data than that derived by stepwise multiple linear regression analysis. To our knowledge, this is the first study regarding the abbreviated AUC obtained by trapezoidal rule.

In conclusion, pharmacokinetic characteristics of CsA in Oriental kidney transplantation patients are comparable to those of the Western ones. Abbreviated AUC calculated by linear trapezoidal rule is superior to that derived by multiple linear regression analysis as a reliable alternative in prediction of the complete AUC. This would lead to better drug monitoring and, possibly, better renal allograft survival. We encourage other kidney transplantation nephrologists to test our model equation with the pharmacokinetic data of their patients.

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Pharmacokinetic Studies of Cyclosporin in Thai Kidney Transplantation Patients

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ได้ทำการศึกษาเภสัชจลนศาสตร์ในผู้ป่วยปลูกถ่ายไตชาวไทย 10 ราย ซึ่งได้รับยา cyclosporin A (CsA) ชนิดไมโครอีมัลชัน (Neoral®) วันละ 2 เวลา ผู้ป่วยไม่ได้รับยาที่มีผลต่อเภสัชจลนศาสตร์ของ CsA พื้นที่ภายใต้เส้นแสดงระดับยาที่จุดเวลาต่าง ๆ ภายหลังการให้ยาในช่วงเวลา 12 ชั่วโมง (12-h AUC) มีค่าเฉลี่ย 4603.63 ± 344.61 นาโนกรัม • ชั่วโมง ต่อมิลลิลิตร พบว่าระดับยา CsA ในเลือดที่เวลา 2 ชั่วโมงภายหลังการให้ยามีความสัมพันธ์ทางสถิติสูงสุดกับค่า 12-h AUC สามารถคำนวณหาค่า 12-h AUC แบบย่อ (Abbreviated AUC) โดยวิธีวิเคราะห์สมการถดถอยและโดยวิธีกฎเกณฑ์สี่เหลี่ยมคางหมู พบว่าวิธีกฎเกณฑ์สี่เหลี่ยมคางหมูมีความง่ายกว่าและมีประโยชน์เหนือกว่าวิธีวิเคราะห์สมการถดถอย

คำสำคัญ : Neoral, 12-h AUC, Abbreviated AUC, Linear Trapezoidal Rule, Multiple Linear Regression Analysis

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