นิพนธ์ต้นฉบับ

Determination of abbreviated pharmacokinetic profiles of cyclosporin (Neoral®) by simple linear trapezoidal rule

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Objective : *Compare two methods which are used to calculate abbreviated AUC (i.e.) abbreviated AUC derived by simple linear trapezoidal rule or by stepwise multiple linear regressions.*

Setting : *Division of Nephrology, Department of Medicine, Faculty of Medicine and Department of Pharmacy, Faculty of Pharmaceutical Science Chulalongkorn University*

Design : *Cross-sectional study*

Patients : *10 stable kidney transplantation patients*

Methods : *The complete area under the concentration-blood curve of cyclosporin A (CsA) for the duration of 12 hours, 12-hr AUC, was measured by simple linear trapezoidal rule from 7 concentrations at 0, 1, 2, 4, 6, 8 and 12 hours after administration of a microemulsion formulation (Neoral®) of CsA. No agents having pharmacokinetic effects on CsA had been used in these patients. The abbreviated AUC of CsA was determined either by stepwise multiple linear regression analysis or simple linear trapezoidal rule from a few sampling time points.*

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Results : *By stepwise multiple linear regression analysis, used in calculating abbreviated AUC in all previous reported studies, the model equation that had the highest correlation and the lowest prediction error with the complete AUC was derived by using CsA concentrations at 2 and 8 hours after dosing (12-hr*

$AUC = 4.262C_2 + 8.390C_8 - 669.417$; $r^2 = 0.9808$, *absolute prediction error* $= 3.97 \pm 0.96$*). There were two model equations derived by linear trapezoidal rule that could provide best correlation with the complete AUC : 1) Two-time points selected model equation (12-hr* $AUC = 4C_2 + 5C_8$; $r^2 = 0.9780$, *absolute prediction error* $= 6.41 \pm 1.22$*); 2) Three-time points selected model equation (12-hr* $AUC = 4C_0 + 3C_2 + 5C_6$; $r^2 = 0.9475$, *absolute prediction error* $= 5.00 \pm 1.4$*). When different pharmaco-kinetic data sets were applied to the model equations derived by stepwise multiple linear regression analysis, the values of coefficients and the constant of the regression equation changed from the initial equation. Thus the new model equations will emerge every time the different data is applied. In contradistinction, the value of coefficients in the model equation determined by trapezoidal rule were unaltered when tested by new pharmacokinetic data sets.*

Conclusion : *Abbreviated AUC derived by linear trapezoidal rule would be more simple and superior to that obtained by stepwise multiple linear regression analysis in prediction of the complete AUC.*

Key words : *Cyclosporin, Complete AUC, Abbreviated AUC, Linear trapezoidal rule, Stepwise multiple linear regression analysis.*

ยิ่งยศ อวิหิงสานนท์, ธิติมา กังสัมฤทธิ์, สมชาย เอี่ยมอ่อง, เสาวลักษณ์ ชูศิลป์, เกรียง ตั้งสง่า, ดวงจิต พนมวัน ณ อยุธยา. การหาสมการอย่างย่อโดยวิธีหาพื้นที่สี่เหลี่ยมคางหมู เพื่อทำนายค่า เอยูซีของยาซัยโคลสปอริน-เอ. จุฬาลงกรณ์เวชสาร 2541 พ.ค; 42(5): 353-65

วัตถุประสงค์ : เปรียบเทียบวิธีคำนวณหาสมการ AUC (Area under curve) อย่างย่อ ระหว่างวิธีการวิเคราะห์ถดถอยแบบมีขั้นตอน (Stepwise multiple linear regression) กับการคำนวณพื้นที่โดยใช้สี่เหลี่ยมคางหมู

รูปแบบการวิจัย : การศึกษาแบบ cross-sectional

สถาบันการศึกษา : ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ และภาควิชาเภสัชวิทยา คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

ผู้เข้าร่วมการศึกษา : ผู้ป่วยที่รับการปลูกถ่ายไตจำนวน 10 ราย

วิธีการศึกษา : ตรวจหาค่า 12-Hr AUC ด้วยการคำนวณพื้นที่โดยใช้สี่เหลี่ยมคางหมูจาก ความเข้มข้นของยา ณ จุดเวลา 7 จุด ได้แก่ 0, 1, 2, 4, 6, 8 และ 12 ชั่วโมงภายหลังรับประทานซัยโคลสปอริน-เอ (Neoral®) ผู้ป่วยทั้ง หมดไม่ได้รับยาที่มีผลต่อเภสัชจลนศาสตร์ของซัยโคลสปอริน-เอ คำนวณสมการ AUC อย่างย่อโดยวิธีการวิเคราะห์ถดถอยแบบมีขั้น ตอนและวิธีการหาพื้นที่โดยใช้สี่เหลี่ยมคางหมู

ผลการศึกษา : ได้สมการที่สัมพันธ์กับ 12-Hr AUC มากที่สุด 1 สมการ โดยวิธีการ วิเคราะห์ถดถอยแบบมีขั้นตอน (12-Hr AUC = $4.262C_2$ + $8.390C_8$ - 669.417 ; r^2 = 0.9808, absolute prediction error = 3.97±0.96 โดยที่ C_2 และ C_8 หมายถึง ความเข้มข้นของยา ณ จุดเวลา 2 และ 8 ชั่วโมง หลังรับประทานยา) ได้สมการโดยวิธีหาพื้นที่สี่เหลี่ยมคางหมู 2 สมการได้แก่ 1) สมการซึ่งคำนวณจากความเข้มข้นของยา ณ 2 จุดเวลา 12-Hr AUC = $4C_2$ + $5C_8$; r^2 = 0.9780, absolute prediction error = 6.41 ± 1.22 และ 2) สมการซึ่งคำนวณจากความเข้มข้นของยา ณ 3 จุดเวลา 12-Hr AUC = $4C_0$ + $3C_2$ + $5C_6$; r^2 = 0.9475, absolute prediction error = 5.00 ±1.41 การหาสมการ AUC อย่างย่อโดยวิธีการ วิเคราะห์ถดถอยแบบมีขั้นตอนนั้นจะได้ค่าสัมประสิทธิ์และค่าคงที่ เปลี่ยนแปลงไปตามชุดข้อมูลทางเภสัชจลนศาสตร์ ดังนั้นจะมีสมการ ใหม่ทุกครั้งที่เปลี่ยนแปลงชุดของข้อมูล ในทางตรงกันข้าม การคำนวณ โดยวิธีหาพื้นที่สี่เหลี่ยมคางหมูจะได้ค่าสัมประสิทธิ์คงที่ โดยไม่ขึ้นกับ ชุดของข้อมูล

สรุป   :   การคำนวณหาสมการ AUC อย่างย่อโดยวิธีหาพื้นที่สี่เหลี่ยมคางหมูเพื่อ
                                    ทำนายค่า 12-Hr AUC น่าจะเป็นวิธีซึ่งง่ายและดีกว่าการหาสมการโดย
                                    วิธีการวิเคราะห์ถดถอยแบบมีขั้นตอน

One of the most important issues regarding oral CsA therapy in kidney transplantation 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] It appears that there are marked intra- and interindividual variations 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 than the trough concentrations in CsA therapy. [6-12] 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 have been established in recent years and these 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, when the new data sets are determined, the value of all coefficients and the constant of the regression equation will inevitably change. [22-26]

Patients and Method

Renal transplant patients who consented to and fulfilled the following entry criteria were studied: patients with more than 12 months of follow-up at Chulalongkorn Hospital, Bangkok Thailand;

patients with ages ranging between 20-65 years; patients who had received CsA microemulsion formulation (Sandimmune Neoral®) twice dialy. All studied patients did not suffer from any diseases that could alter absorption, metabolism, or excretion of CsA. No one was treated with medication known to have pharmacokinetic interactions with CsA. The renal functions in all these patients were 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 transplant 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 doses the patients received was 3.74 ± 0.30 mg/kg/12 hr.

The pharmacokinetic profiles were determined when the patients were in 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 hr-AUC" will be used interchangeably with the "complete AUC". On the experiment day,

blood samples (3 ml) were obtained before their morning dose of CsA and then again 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 accuracy 98%). All unlabeled blood sample were assayed by single investigator.

The complete AUC for each patient was calculated, as previously described, by linear trapezoidal rule from the seven concentrations in the full profile (0, 1, 2, 4, 6, 8, and 12 hours). [6-8]

where t = time point (hours after dosing)

c = CsA concentration at each time point ng/ml)

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

1. Multiple linear regression analysis, used for calculating the abbreviated AUC in all previous studies, was determined by computer to create a formula for the complete AUC prediction. [11-21] Indeed, multiple linear regression analysis is an extension of the straight-line regression analysis, which involves only one independent variable, to where more than one independent variable are considered. The complete AUC was used as the dependent variable and the blood concentrations.
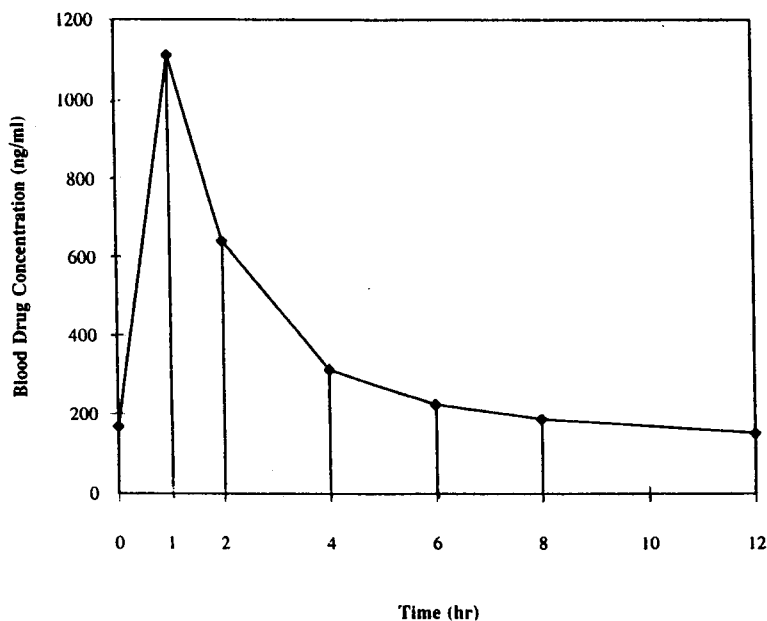

Figure 1. The method of calculation of complete AUC by "Linear Trapezoidal Rule Analysis"

As such, the complete AUC

grouped by time points as the independent variables.

Thus, thecomplete AUC predicted by abbreviated AUC

$$= aC_X + bC_Y + cC_Z + d$$

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

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

a, b, c   = coefficients of each C

d   = constant

2. Linear trapezoidal rule, as used in calculating the complete AUC,was obtained by selecting 2 or 3 time points that could provide the best statistic values for the complete AUC.In our pilot study,and also in the following study,CsA levels at 0,2, and6 hours after dosing, C_0, C_2,and C_6 respectively, could yield the statistically reliable abbreviated AUC which was best correlated with the complete one.

As such, the complete AUC predicted by abbreviated AUC,

$$= AUC_{0-2hr} + AUC_{2-6hr} + AUC_{6-12hr}$$

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

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

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

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

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

As such, the complete AUC

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

$$= 4C_0 + 3C_2 + 5C_6$$

Pearson product-moment correlation coefficients were calculated to evaluate the linear relations between the AUC and the blood concentrations 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:

Absolute prediction error

$$= \frac{(\text{Predicted AUC} - \text{Measured AUC})}{\text{Measured AUC}} \times 100\%$$
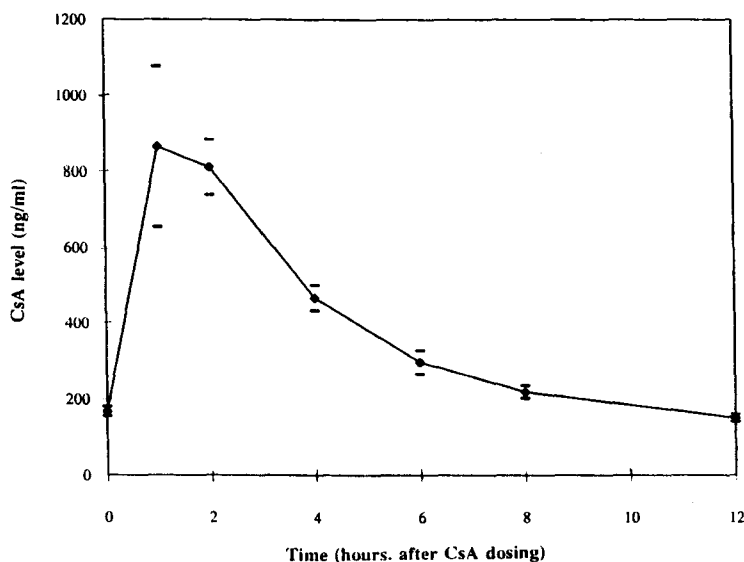
All the data were expressed as mean ± SE.

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

Results

The value of the complete AUC, 12-hr AUC, determined by simple linear trapezoidal rule was 4603.63 ± 344.61 ng•hr/ml. Administration of CsA could reach the maximum concentration within 2 hours in all studied patients.

linear regression analysis, the new regression equation was

$$12\,hr\text{-}AUC = 4.019C_2 + 10.402C_8 - 812.329$$

($r^2 = 0.9927$; absolute prediction error = 2.45±1.10%)

When one compared this new model equation of the six patients with that of the ten

Table 1. 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 (hr after dosing)	Model equations: predicted 12hr-AUC=	r^2	Absolute prediction error (mean ± SE)
1	Stepwise multiple linear regression[2]	2,8	$4.262C_2 + 8.390C_8 - 669.417$	0.9808	3.97 ± 0.96
2	Linear trapezoidal rule[2]	2,8	$4C_2 + 5C_8$	0.9780	6.41 ± 1.22
3	Linear trapezoidal rule[3]	0,2,6	$4C_0 + 3C_2 + 5C_6$	0.9475	5.00 ± 1.41

Table 1 illustrates the model equations of abbreviated AUC obtained by stepwise multiple linear regression analysis and simple linear trapezoidal rule in the present study. By stepwise multiple linear regression analysis, the best model equation, which has the highest correlation coefficient and the least absolute prediction error, was the two time points-selected one 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 equation 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 of all ten patients were determined by stepwise multiple

patients (Table 1, Equation 1), it was obvious that the values of the coefficients and constant in both equations were totally dissimilar.

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

$$12\,hr\text{ - }AUC = 4C_2 + 5C_8$$

(two sampling time points)

($r^2 = 0.9808$; absolute prediction error = 6.70±1.53%)

$$12\,hr\text{ - }AUC = 4C_0 + 3C_2 + 5C_2$$

(three sampling time points)

($r^2 = 0.9893$; absolute prediction error = 4.01±1.31%)

As compared with equations 2 and 3 in the table 1, 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 model.

Previously proposed model equations of 12 hr-AUC, all of which were calculated by stepwise multiple linear regression analysis, are shown in table 2. As compared with the previous studies, the results from the present study shown that both of 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 coefficients with the complete AUC.

from the studies of Lindholm A, et al, Kahan BD, et al, and Serafinowicz A, et al were selected for the test (Table 3). When the pharmacokinetic data of our patients were determined by these equations, the obtained correlation coefficients were apparently different from the original ones (Table 2 and 3).

Discussion

There are two strategies in therapeutic drug monitoring of CsA: trough concentrations and complete pharmacokinetic profiles (complete AUC). [1-3,6-12] Previous studies have shown that the trough concentrations of CsA provide less information in

Table 2. Previously proposed model equations.

Model Equations (Authors) 12-hr AUC =	r^2
$4.3C_{3.5} + 5.5C_8 + 3.1C_{10} - 333$ [13]	0.9898
$4.44C_0 + 2.42C_2 + 5.91C_6 + 83$ [16]	0.96
$2.11C_2 + 3.23C_4 + 5.69C_9 + 250$ [17]	0.9619
$0.681C_1 + 1.859C_{2.5} + 3.411C_5 + 791.74$ [18]	0.91
$2.4C_2 + 7.7C_6 + 195.8$ [11]	0.938
$1.89C_{1.5} + 17.5C_{12} + 452.4$ [19]	0.938
$9.131C_0 + 0.784C_1 + 2.617C_2 + 193.561$ [20]	0.954

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. Thus, the model equations

diagnosis or prediction of adverse events. [4,5] Specifically, they have limited value in differentiating between adequate immuno-suppression and renal toxicity. As such, AUC has been determined and shown to be an abviously more

Table 3. The correlation between the measured AUC and the predicted AUC computed by previously proposed models.

Previously Proposed Model Equations: Predicted 12 hr-AUC =	r^2	Absolute prediction error (%) Mean $\pm$ SE
$4.44C_0 + 2.42C_2 + 5.91C_6 + 83$ [16]	0.9030 (0.96)	7.03 $\pm$ 1.74
$2.4C_2 + 7.7C_6 + 195.8$ [11]	0.8537 (0.938)	7.65 $\pm$ 2.33
$9.131C_0 + 0.784C_1 + 2.617C_2 + 193.561$ [20]	0.9603 (0.954)	5.86 $\pm$ 1.14

The number in the parasenthesis indicates the value of r^2 from the original work.

reliable index of drug exposure. [6-12] At clinical steady state, monitoring of AUC has been demonstrated to be more effective than trough levels in CsA dosage adjustment. Complete AUC is generally calculated by linear trapezoidal rule. The complete AUC, which requires several blood samplings, is expensive and 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 those studies were determined by stepwise multiple linear regression analysis. In agreement with previous work, the results of our 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 1, equation 1, $r^2 = 0.9808$).

For stepwise multiple linear regression analysis, it appears that the regression equation would vary with the data set [26] This means that the selected time points and, consequently, the coefficients and the constant in the new model equation could be totally different from those in the initial equation. Despite the selected time points being unchanged, the new values of the coefficients and the constant of the new equation will inevitably emerge. Such circumstances were observed in the present study. The values of coefficients and the constant of the regression analysis-derived model equation of the whole set of ten patients are totally different from those of the six patients. Indeed, the variation in model equations derived by stepwise multiple linear regression analysis observed in our work had also been reported in a previous study on conventional formulation of CsA (Sandimmun). [22]

Furthermore, when the pharmacokinetic data of our patients were tested by the model equations of Lindholm A, et al, Kahan BD, et al, and Serafinowicz A, et al, the correlation coefficients were 0.9030, 0.8537, and 0.9603 respectively, as compared with 0.96, 0.938, and 0.954 respectively, in the original studies.

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 the coefficients of each time point concentration in the model equation are unchanged despite new pharmacokinetic data being added. Our work demonstrated this. Therefore, the abbreviated AUC derived by trapezoidal rule is more simple in calculation and are more applicable to different data than that derived by stepwise multiple linear regression analysis. To our knowledge, this is the first study regarding an abbreviated AUC obtained by simple linear trapezoidal rule.

In conclusion, abbreviated AUC calculated by simple linear trapezoidal rule is superior to that derived by multiple linear regression analysis and is a reliable alternative in the prediction of complete AUC.

Acknowledgements

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