Effect of Diltiazem on the Pharmacokinetics of Microemulsion Cyclosporine A in Renal Transplantation

Sakarn Bunnag MD*,
Kriengsak Vareesangthip MD, PhD**, Leena Ong-ajyooth MD, DrMed**

** Renal Division, Department of Medicine, Rajavithi Hospital*
*** Renal Division, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University*

Objective: *Diltiazem might be used as a cyclosporine A (CsA)-sparing agent. There is evidence that CsA (C_2) level is the best single point blood sampling for monitoring the CsA level. The authors, therefore, studied the effect of diltiazem on the pharmacokinetics (PK) of CsA, including C_2, in renal transplant patients.*
Material and Method: *Twenty-five CsA-treated renal transplant patients, with neither diseases nor agents that alter the PK of CsA, were enrolled in the present study. The PK of CsA was studied in all patients before and 2 weeks after taking diltiazem.*
Results: *The area under the concentration-time curve (AUC) of CsA was obtained by 2 methods, AUC_{0-4} and AUC_{0-12}. Before taking diltiazem, the correlation (r) between C_0 with AUC_{0-4} and C_0 with AUC_{0-12} were 0.799 and 0.871, respectively (p = 0.01), r between C_2 with AUC_{0-4} and C_2 with AUC_{0-12} were 0.988 and 0.956, respectively (p = 0.01). Time to maximum concentration (Tmax) of CsA was at 1.5 hr (1.5-4.0 hr) [median (range)]. After two weeks of taking diltiazem, r between C_0 with AUC_{0-4} and C_0 with AUC_{0-12} were 0.577 and 0.784, respectively (p = 0.01), r between C_2 with AUC_{0-4} and C_2 with AUC_{0-12} were 0.988 and 0.896, respectively (p = 0.01). Tmax of CsA was at 1.5 hr (1.5-4.0 hr) [median (range)]. The dosage of CsA could be reduced by 25.8% to maintain the same levels of C_0 and C_2 in the same patients after taking diltiazem.*
Conclusion: *Diltiazem slightly altered the correlation between C_2 with AUC of CsA. This indicates that C_2 is the best single point blood sampling to monitor the therapeutic levels of CsA in renal transplant patients who are taking diltiazem.*

Keywords: *Cyclosporine, Diltiazem, Pharmacokinetics, C2*

J Med Assoc Thai 2006; 89 (Suppl 2): S228-34
Full text. e-Journal: *http://www.medassocthai.org/journal*

Cyclosporine A (CsA) has been widely used as an immunosuppressive agent in renal transplants. This immunosuppressive agent has a narrow range of therapeutic level. Therefore, effective monitoring of drug level is important for both optimizing the immunosuppressive effects and avoiding the drug toxicity, including nephrotoxicity. Area under the concentration-time curve (AUC) of CsA indicates the total drug exposure and has the best correlation with efficacy and toxicity of CsA[1,2], but the AUC monitoring is not practical in the clinical practice because it requires multiple blood sampling, mathematical calculation steps, high cost and work load. Therefore, CsA monitoring by trough level (C_0) has been widely used in renal transplants for efficacy and toxicity of CsA[1]. Recently, there are several studies suggesting that CsA level at the second hour after taking CsA (C_2) is the best single-point blood sampling for CsA monitoring[1,2,3]. There is evidence indicating that C_2 showed the best correlation with AUC, acute rejection and toxicity of CsA. Recently, McDonald et al have demonstrated that renal transplants who were on CsA sparing agent, diltiazem, had a better renal allograft outcome than those who were not on diltiazem[4]. Additionally, diltiazem has been used as a CsA-sparing agent with the purpose to reduce

Correspondence to : Vareesangthip K, Renal Division, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Prannok Rd, Bangkoknoi, Bangkok 10700, Thailand. Phone: 0-2419-8383, Fax: 0-2412-1362, E-mail: sikwn@mahidol.ac.th

the dosage of CsA for financial purposes. Both CsA and diltiazem are predominately metabolized by CYP450 3A4, thus, the combination of CsA and diltiazem can reduce metabolism of CsA by this enzyme. However, the effect of diltiazem on the PK of CsA including correlation between AUC and C_2 has not been studied previously. The authors, therefore studied the effect of diltiazem on the PK of CsA, including C_0, C_2, and AUC.

Material and Method

Twenty-five patients who had a successful renal transplant for at least 3 months were recruited to participate in the present study. The authors included only renal transplants who were on microemulsion CsA (Neoral®) and have had stable renal allograft functions for at least 3 months (the difference of 3 points of serum Cr within 60 days were not more than 0.3 mg/dl). The present study excluded the patients who were on other agents that had the effect on the PK of CsA within 5 half life of these agents, the patients who changed the dosage of CsA within 7 days before enrolling, the patient who had diseases that alter PK of CsA or had contraindication for diltiazem treatment (BP < 100/60 mmHg, HR < 60/min, SA heart block, had a history of diltiazem allergy and pregnancy). The present study was approved by the Ethical Committee on Research Involving Human Subjects, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand. All patients signed an informed consent before participating in the present study. At the beginning of the present study, the data of the patients were collected in the view of age, gender, date renal transplantation, medications, underlying diseases, body weight, blood pressure, BUN, serum creatinine (Cr), liver function test, and ECG. Blood samples for measuring CsA level at C_0, $C_{1.5}$, C_2, C_3, C_4, C_6, C_8, C_{10} were obtained, and then transferred into EDTA contained tube and were assayed within 6 hours by Cloned Enzyme Donor Immunotechnique Assay (CEDIA). AUC 0-4 hours (AUC_{0-4}) and AUC 0-12 hours (AUC_{0-12}) were calculated by linear trapezoid rule.

$$AUC_{0-4} = 0.5 \times \{ (C_0+C_{1.5}) \times 1.5 + (C_{1.5}+C_2) \times 0.5 + (C_2+C_3) + (C_3+C_4) \}$$

$$AUC_{0-12} = 0.5 \times \{ (C_0+C_{1.5}) \times 1.5 + (C_{1.5}+C_2) \times 0.5 + (C_2+C_3) + (C_3+C_4) + (C_4+C_6) \times 2 + (C_6+C_8) \times 2 + (C_8+C_{10}) \times 2 + (C_{10}+C_0) \times 2 \}$$

After the first AUC was performed, all patients received diltiazem (Herbesser R100®) 100 mg oral once daily in the morning. Within 3-5 days after starting diltiazem, the dosage of CsA was adjusted to the optimal range of therapeutic level by C_0 (C_0=150-250 ng/ml for postrenal transplants less than 12 months and C_0=75-150 ng/ml more than 12 months). After two weeks of diltiazem, the second AUC was performed. The PK of CsA were studied before and more than two weeks after taking diltiazem in the view of C_0, C_2, time to Cmax (Tmax), and AUC. All time points before and after taking diltiazem were reported as mean $\pm$ SD and were compared by using paired t-test. Also 95% confidence interval of difference was calculated. Correlation (r) between the time points and CsA with AUC 0-12 before and after was compared. A p-value of less than 0.05 was considered statistically significant.

Results

There were 25 (M:F = 17:8) renal transplant patients with the mean age of 37 $\pm$ 10 years. Their mean BUN and serum creatinine were 23.8 $\pm$ 9.3 mg/dl and 1.46 $\pm$ 0.44 mg/dl respectively. The change in each CsA PK parameter and concentration at each time point pre to post diltiazem were shown in Table 1. The correlations between the concentration of CsA level at any time points and the AUC before and after taking diltiazem are shown in Table 2. Before taking diltiazem, the correlation (r) between C_0 with AUC_{0-4} and with AUC_{0-12} were 0.799 and 0.871 respectively (p = 0.01). The correlation between C_2 with AUC_{0-4} and with AUC_{0-12} were 0.988 and 0.956 respectively (p = 0.01). C_2 had the best correlation with AUC and C_0 had the worst correlation with AUC. After taking diltiazem, the correlation between C_0 with AUC_{0-4} and with AUC_{0-12} were 0.577 and 0.784 respectively (p = 0.01). The correlation between C_2 with AUC_{0-4} and AUC_{0-12} were 0.988 and 0.896 respectively (p = 0.01). All CsA level at any time points after taking diltiazem had less correlation with AUC than the correlation of CsA level before taking diltiazem. Obviously, C_2 still had the best correlation with AUC after 2 weeks of diltiazem. The mean dosage/day and dosage/kg body weight/day of CsA could be reduced by 25.58% and 25.76% respectively after taking diltiazem for maintaining the same C_2 level. After taking diltiazem, mean C_0 level was increased while mean C_2 level, AUC_{0-4}, AUC_{0-12}, and Tmax were decreased. The CsA level at any time points of all 25 patients before and after taking diltiazem are shown in Fig. 1 and 2 respectively while the mean CsA levels of CsA are shown in Fig. 3.

Discussion

Clearly, the present study confirmed the previous studies[3,5] that C_2 has the best correlation with AUC (r = 0.988 with AUC_{0-4} and 0.956 with AUC_{0-12}). C_0

Table 1. The mean ± SD of pharmacokinetics of CsA before and after taking diltiazem (N = 25)

Time point	Before taking diltiazem	After taking diltiazem	p value	95% confidence interval of the difference	
				Lower	Upper
C_0	124.6±74.2	135.0±62.9	<0.001	-32.3	11.4
$C_{1.5}$	939.2±480.6	809.7±417.0	0.003	-43.8	302.7
C_2	774.0±429.5	665.6±310.3	0.001	-28.7	245.5
C_3	534.6±329.8	493.9±227.9	0.002	-71.3	152.7
C_4	374.8±206.7	385.1±179.4	0.011	-90.6	70.1
C_6	222.8±121.0	227.7±112.0	0.004	-50.3	40.5
C_8	161.0±88.8	165.9±82.2	<0.001	-34.0	24.4
C_{10}	136.6±69.6	140.6±65.9	0.002	-29.5	21.5
AUC_{0-4}	2335±1239	2097±935	0.001	-158.7	635.6
AUC_{0-12}	3876±1999	3685±1490	<0.001	-397.2	777.7
Time to Cmax	1.8±0.7	1.7±0.6	0.929	-0.3	0.4

Table 2. The correlation of CsA at any time points with AUC_{0-4} and AUC_{0-12} before and after taking diltiazem (N = 25)

Time point	AUC_{0-4}		AUC_{0-12}	
	r	p value	r	p value
Before taking diltiazem				
C_0	0.799	0.01	0.871	0.01
$C_{1.5}$	0.970	0.01	0.932	0.01
C_2	0.988	0.01	0.956	0.01
C_3	0.967	0.01	0.956	0.01
C_4	0.877	0.01	0.939	0.01
C_6	0.866	0.01	0.941	0.01
C_8	0.869	0.01	0.937	0.01
C_{10}	0.868	0.01	0.929	0.01
After taking diltiazem				
C_0	0.577	0.01	0.784	0.01
$C_{1.5}$	0.952	0.01	0.833	0.01
C_2	0.988	0.01	0.896	0.01
C_3	0.928	0.01	0.893	0.01
C_4	0.774	0.01	0.853	0.01
C_6	0.509	0.01	0.778	0.01
C_8	0.562	0.01	0.813	0.01
C_{10}	0.560	0.01	0.810	0.01

has less correlation with AUC when compared with C_2, but C_0 still had a good correlation with AUC (r = 0.799 with AUC_{0-4} and 0.871 with AUC_{0-12}). This correlation was similar to the results of several previous studies[3,6-9].

After taking diltiazem, the correlation of CsA level with AUC for almost every time point were decreased (r = 0.577 for C_0 and AUC_{0-4} and 0.784 for C_0 and AUC_{0-12}). C_2 still has the best and has very good correlation with AUC (r = 0.988 with AUC_{0-4} and 0.896 with AUC_{0-12}).

Therefore, C_2 may be the best single-point blood sampling for CsA monitoring in renal transplants for those who have had transplantation for more than 3 months. C_2 can be safely used in renal transplants who received diltiazem. Contrarily, C_0 could only be used in renal transplant patients who were not on diltiazem. There is evidence suggesting that diltiazem might alter

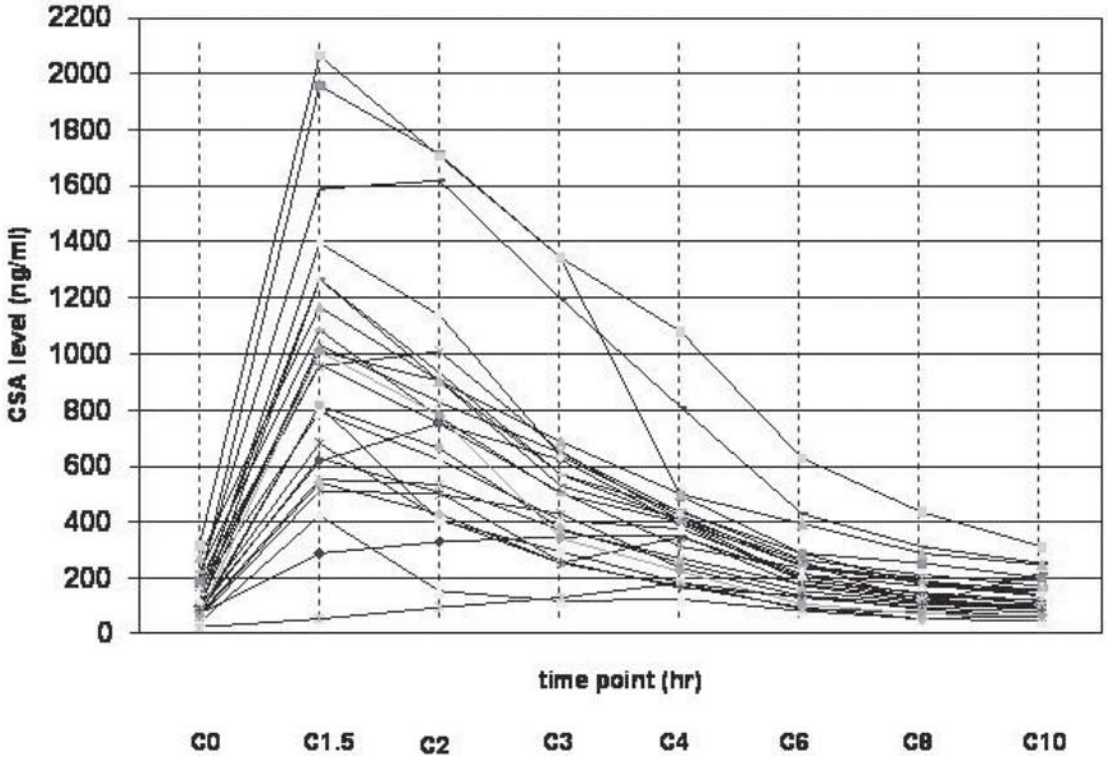

Fig. 1 CsA level at any time points of all 25 patients before taking diltiazem

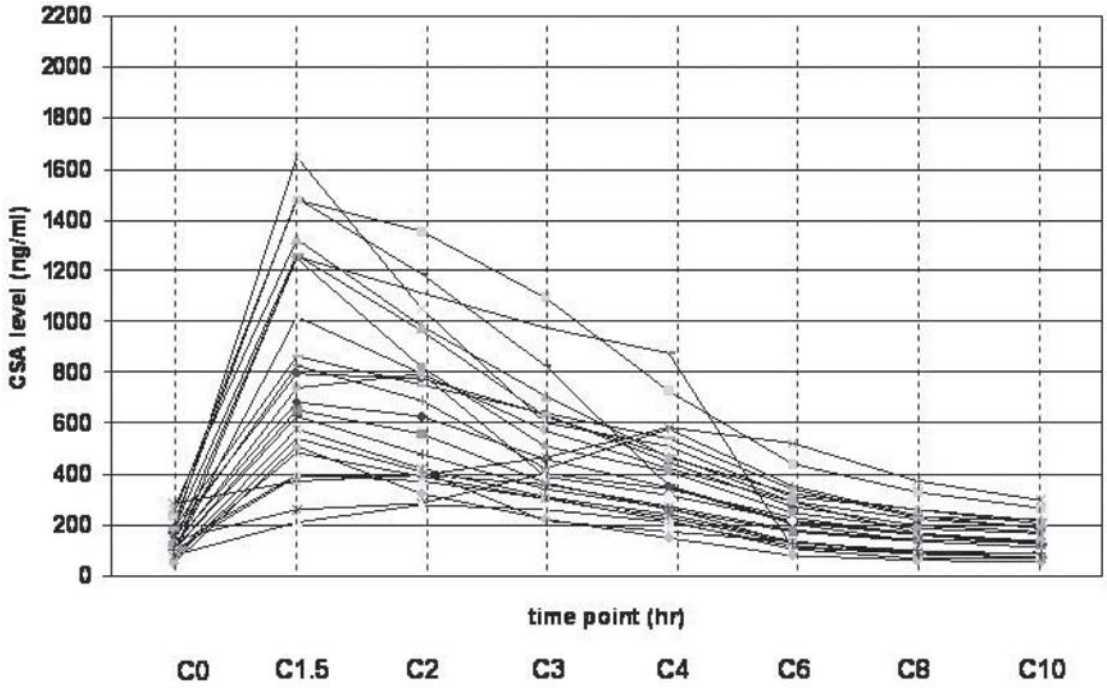

Fig. 2 CsA level at any time points of all 25 patients after taking diltiazem

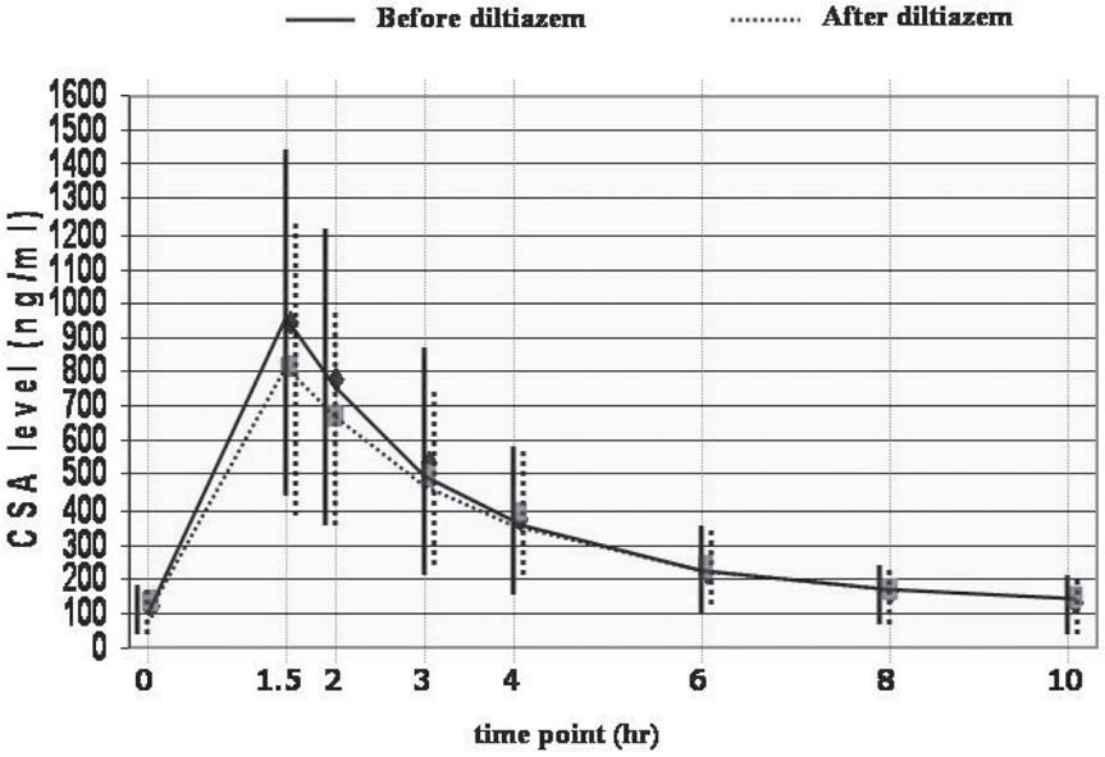

Fig. 3 Mean CsA level ± SD at any time points of all 25 patients before and after diltiazem taking

the PK of CsA in renal transplant patients. Firstly, diltiazem could decrease intestinal absorption of CsA because both diltiazem and CsA are good substrates for P-glycoprotein, which is an important molecule for CsA absorption[10,11]. Therefore, both C_2 and AUC have a tendency to decrease after taking diltiazem. Secondly, the action of diltiazem may not cover through 24 hours, thus, a nighttime AUC would not be similar to a daytime AUC. Therefore, C_0 may only relate to a nighttime AUC because the blood for measuring C_0 was taken in the morning. However, if this hypothesis is true, a daytime AUC should be more than a nighttime AUC. In this present study, the authors adjusted the dose of CsA usage by measuring C_0, therefore AUC of renal transplants should be increased after taking diltiazem. Finally, a nighttime AUC may naturally not be similar to a day-time AUC because of intra-patient variations. There is evidence showing that C_0 might be similar to C_{12}[3]. Unfortunately, in this present study, the authors did not measure C_{12} and a nighttime AUC. Therefore, the authors could not explain the mechanism of alterations of the PK of CsA by diltiazem through the discrepancy of a daytime AUC and a nighttime AUC.

Interestingly, in this present study, a combination of diltiazem with CsA can reduced the dosage of CsA by approximately 26% without the significant change in C_0, C_2, or AUC. No serious side effects were detected in all study patients. The benefits of CsA dose reduction by diltiazem are therapeutic cost reduction and may lead to less nephrotoxicity caused by CsA[4].

In conclusion, the authors demonstrated that C_2 has the best correlation with the AUC of CsA in renal transplants. This correlation was not different in patients with or without CsA sparing agent, diltiazem. This indicates that C_2 might be the best single-point blood sampling for CsA monitoring in renal transplant patients.

References

1. Mahalati K, Belitsky P, Sketris I, West K, Panek R. Neoral monitoring by simplified sparse sampling area under the concentration-time curve: its relationship to acute rejection and cyclosporine nephrotoxicity early after kidney transplantation. Transplantation 1999; 68: 55-62.
2. Filler G, Mai I, Filler S, Ehrich JH. Abbreviated

cyclosporine AUCs on Neoral-the search continues!. Pediatr Nephrol 1999; 13: 98-102.
3. Kungsamrith T, Eiam-Ong S, Tungsanga K, Chusil S. Pharmacokinetics of cyclosporine A in oriental kidney transplantation patients. Nephrology 2001; 6: 236-42.
4. McDonald SP, Russ GR. Associations between use of cyclosporine-sparing agents and outcome in kidney transplant recipients. Kidney Int 2002; 61: 2259-65.
5. Canadian Neoral Renal Transplantation Study Group. Absorption profiling of cyclosporine microemulsion (Neoral) during the first 2 weeks after renal transplantation. Transplantation 2001; 72: 1024-32.
6. Keown P, Landsberg D, Halloran P, Shoker A, Rush D, Jeffery J, et al. A randomized, prospective multicenter pharmacoepidemiologic study of cyclosporine microemulsion in stable renal graft recipients. Transplantation 1996; 62: 1744-52.
7. Kahan BD, Dunn J, Fitts C, Van Buren D, Wombolt D, Pollak R, et al. The Neoral formulation: improved correlation between cyclosporine trough levels and exposure in stable renal transplant recipients. Transplant Proc 1994; 26: 2940-3.
8. Mueller EA, Kovarik JM, van Bree JB, Lison AE, Kutz K. Pharmacokinetics and tolerability of a microemulsion formulation of cyclosporine in renal allograft recipients-a concentration-controlled comparison with the commercial formulation. Transplantation1994; 57: 1178-82.
9. Hoppu K, Jalanko H, Laine J, Holmberg C. Comparison of conventional oral cyclosporine and cyclosporine microemulsion formulations in children with a liver transplant. Transplantation 1996; 62: 66-71.
10. Hsing S, Gatmaitan Z, Arias IM. The function of Gp170, the multidrug-resistance gene product, in the brush border of rat intestinal mucosa. Gastroenterology 1992; 102: 879-85.
11. Emi Y, Tsunashima D, Ogawara K, Higaki K, Kimura T. Role of P-glycoprotein as a secretory mechanism in quinidine absorption from rat small intestine. J Pharm Sci 1998; 87: 295-9.

ผลของยา diltiazem ต่อการเปลี่ยนแปลงเภสัชจลนศาสตร์ของยา cyclosporine

สกานต์ บุนนาค, เกรียงศักดิ์ วารีแสงทิพย์, ลีนา องอาจยุทธ

คำนำ: *ยา cyclosporine (CSA) เป็นยาที่ยังใช้กันอย่างแพร่หลายในผู้ป่วยที่ได้รับการปลูกถ่ายไต จากการศึกษาที่ผ่านมาพบว่า การวัดระดับยาที่ 2 ชั่วโมง หลังรับประทานยา (C_2) ดีกว่าก่อนรับประทานยาทันที (C_0) และ C_2 เป็นวิธีที่ดีที่สุดในการตรวจติดตามและปรับขนาดยา และพบว่ายา diltiazem สามารถเปลี่ยนแปลงเภสัชจลนศาสตร์ (PK) ของยา CSA ทำให้ระดับยาในเลือดสูงขึ้น จึงถูกนำมาใช้ลดปริมาณการใช้ยา CSA*

วัตถุประสงค์: *เพื่อศึกษาผลของยา diltiazem ต่อ PK ของยา CSA และหาเวลาที่เหมาะสมที่สุดในการวัดระดับยา CSA ในผู้ป่วยที่รับประทานยา CSA ร่วมกับยา diltiazem*

วัสดุและวิธีการ: *ทำการศึกษาในผู้ป่วยที่ได้รับการปลูกถ่ายไต 25 ราย ที่ได้รับยา CSA และไม่มีโรคหรือได้รับยาใดที่มีผลต่อ PK ของยา CSA ผู้ป่วยจะได้รับการตรวจวัดระดับยา CSA ที่ระยะเวลาต่าง ๆ หลังรับประทานยา และนำมาคำนวณหา พื้นที่ใต้กราฟระหว่างระดับยากับเวลา (AUC) ทั้งแบบ 0-4 ชั่วโมง (AUC_{0-4}) และแบบ 0-12 ชั่วโมง (AUC_{0-12}) และหาความสัมพันธ์ (r) ระหว่างระดับยา ณ เวลาต่าง ๆ กับ AUC และนำมาเปรียบเทียบกันระหว่างก่อน และหลังได้รับยา diltiazem*

ผลการศึกษา: *ก่อนรับประทานยา diltiazem r ระหว่าง C_0 กับ AUC_{0-4} และ AUC_{0-12} = 0.799 และ 0.871 ตามลำดับ r ระหว่าง C_2 กับ AUC_{0-4} และ AUC_{0-12} = 0.988 และ 0.956 ตามลำดับ และหลังจากได้รับยา diltiazem r ระหว่าง C_0 กับ AUC_{0-4} และ AUC_{0-12} = 0.577 และ 0.784 ตามลำดับ r ระหว่าง C_2 กับ AUC_{0-4} และ AUC_{0-12} = 0.988 และ 0.896 ตาม ลำดับ (p = 0.01) และพบว่าสามารถลดขนาดยา CSA ลงได้ 25.8% โดยระดับ C_0 และ C_2 ไม่เปลี่ยนแปลง*

สรุป: *ยา diltiazem มีผลเปลี่ยนแปลงความสัมพันธ์ระหว่าง C_2 และ AUC เพียงเล็กน้อย และ C_2 เป็นวิธีที่ดีที่สุดในการตรวจติดตามและปรับขนาดยา CSA ในผู้ป่วยที่ได้รับยา CSA ร่วมกับยา diltiazem*