Co-administration of Diltiazem and Cyclosporine for Kidney Transplant Recipients : A Four Year Follow-Up Study

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***Background**: Diltiazem and cyclosporin A (CsA) share a similar metabolism and degradation via the hepatic cytochrome p 450 subfamily 3A4. Co-administration of diltiazem with CsA may lead to CsA dosage reduction, blood pressure control and renal protection.*
***Objectives**: To study the four year outcome of kidney transplant recipients who received diltiazem administration with CsA. This was compared to the outcomes of patients who received CsA without diltiazem and were matched for blood pressure control and other baseline characteristics.*
***Material and Method:** Forty eight patients were included in the diltiazem group and seventy patients in the non-diltiazem group. CsA monitoring was done by using trough level (monoclonal fluorescent polarization immunoassay).*
***Results:** The results showed that both groups has similar 4-year graft survival (92 and 95 %) with a similar mean final serum creatinine (1.3 mg/dl). Mean dose of CsA during the first month was 30 % lower in the diltiazem than non-diltiazem group. At one year, CsA dose was 11% lower in the diltiazem than non-diltiazem group. However, the diltiazem group was associated with significantly higher probability to have chronic allograft nephropathy than the non-diltiazem group (31% VS 19%) (RR 2.93; p = 0.03; Multivariate Cox regression).*
***Conclusion:** Co administration of diltiazem with trough level adjusted CsA is associated with benefits in terms of CsA dose reduction and good graft survival and function. However, there appeared to be no protective effect of diltiazem on the progression to chronic allograft nephropathy.*

***Keywords**: Cyclosporine, Diltiazem, Kidney transplantation, Chronic allograft nephropathy*

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The introduction of cyclosporine A (CsA) has led to significant improvement in the outcome of kidney transplantation especially in the first year[1]. Since CsA is metabolized via the hepatic microsomal cytochrome P-450 subfamily 3A4, circulating cyclosporine levels are influenced by drugs that affect hepatic microsomal enzymes[2]. Diltiazem is a calcium channel blocker that shares the same metabolized pathway with CsA and can be used as CsA sparing agent. The use of diltiazem in renal transplant patients is therapeutically desirable because of the antihypertensive and antiatherogenic property[3]. In addition, diltiazem may improve glomerular filtration rate by minimizing the vasoconstriction and thus improve long-term graft function. Foradori et al demonstrated that co-administration of diltiazem led to significant reduction (25%) in the average dose of Neoral^{R}, an increase in trough level and a 57% increase of AUC (1-8hr) without changing the time to peak concentration[4]. Data concerning the clinical outcome of this co-administration are few and limited to pharmacological aspect of the oil-based formulation of CyA with a short-term transplant outcome. Also, no study has addressed the effect of this co-treatment on the long-term outcome. The authors, therefore, conducted the present study to determine

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the efficacy and safety of diltiazem administration in kidney transplant recipients who were being treated concurrently with micro-emulsion formulation of CsA.

Material and Method

The present study included adult patients who had undergone primary or repeated renal transplantation in a single center, University based hospital, and had their last follow up during a four year observation period. Recipients who died or had graft failure within 6 months after kidney transplantation were excluded. Patients who received intermittent administration of diltiazem or received other CsA sparing agents were also excluded. Studied patients were classified as the diltiazem group (received diltiazem throughout the study period) and the non-diltiazem group (never received diltiazem in the follow-up time). Patients received maintenance immunosuppression with standard double (CsA, prednisolone), triple (CsA, azathioprine, prednisolone) or triple MMF (CsA, prednisolone, MMF) therapy. Due to the metabolism by hepatic microsomal cytochrome P-450 IIIA pathway, patients who received sirolimus (combined with CsA) were excluded. CsA blood levels were measured in whole blood by monoclonal FPIA fluorescence polarization immunoassay. Target trough CsA level was 250-300 ng/dl for the first 3 months, 150-250 ng/dl at 3-6 months and 100-150 ng/dl after 6 months. Diltiazem was prescribed primarily as an antihypertensive agent. The dose ranged between 60-240 mg/day. Other antihypertensive agents were concomitantly used to optimize blood pressure control.

Data analysis

Demographic data were expressed as number and percent mean and SD as appropriate, unpaired t-test and Chi square test were used to test the difference between two groups. Survival analysis was done by Kaplan-Meier method and Cox proportional hazard regression. Primary outcome was the comparison of CsA dosage between the diltiazem and non-diltiazem group. Secondary outcome was the graft function (serum creatinine) and graft survival rate. The long-term outcome of each group was further assessed by determining the occurrence of chronic allograft nephropathy (CAN). CAN was diagnosed clinically by a syndrome of a progressive decline in renal function. This is recognized by an elevation of serum creatinine > 50 % from the baseline (with a value > 1.5 mg/dl) that other causes such as recurrent disease, transplant renal artery stenosis, and surgical complications were excluded. Suspected patients were advised to receive allograft biopsy and the diagnosis of CAN was then confirmed according to Banff criteria. A p-value of less than 0.05 was considered statistically significant.

Results

118 patients were enrolled. 48 were classified as the diltiazem group (Gr.1) and 70 as the non-diltiazem group (Gr.2). Details of demographic data are summarized in Table 1. In brief, mean SD age was 41.9 12.1 and 41.3 10.9 years respectively. Mean HLA mismatch was 3.1 1.6 and 2.9 1.4 for Gr. 1 and 2. Delay graft function occurred in 18.8 % and 11.4 % of Gr. 1 and 2 (p = 0.26). There was no significant difference for the following baseline characteristics between Gr. 1 and 2 namely: mean duration of dialysis (22.2 VS 20.5 months), mean systolic and diastolic blood pressure (132 VS 129 and 81 VS 80 mm Hg), the association with old donor age (>50 year; 8.3% VS 5.7 %) and the presence of diabetes mellitus (6.3% VS 4.3 %). The proportion of patients who received MMF triple therapy in Gr. 1 and 2 was 22.9% and 34.3% (p = 0.18). The incidence of acute rejection episodes did not differ between the two groups (16.7 % VS 14.3 %). Reversible CsA nephrotoxicity (acute elevation of serum creatinine more than 25 % of baseline that improved after CsA dose reduction) occurred in 2.82% in Gr. 1 and 1.37% in Gr. 2 (p=0.49).

Figure 1 shows that the difference of mean CyA dosage among Gr. 1 and 2 at the end of first month was 30 %. The mean difference was 11 % at the end of 12 months. At the end of 48 months, the mean CyA dosage did not differ between the two groups (2.65 1.23 VS 2.74 0.44 mg/kg/day; p = 0.85). Mean CsA levels at 1,12 and 48 months for diltiazem and non-diltiazem were 280 103 VS 290 102, 220 65 VS 210 71 and 210 74 VS 190 56 ng/dl . The latter showed a trend towards higher trough CsA level in the diltiazem group from the period of twelve months up to four years. However, this was not statistically significant (p = 0.08). Mean serum creatinine at 1,12 and 48 months for Gr. 1 and 2 was 1.5 0.53 VS 1.5 0.47, 1.6 0.87 VS 1.4 0.66 and 1.3 0.44 VS 1.3 0.30 mg/dl and were considered similar between both groups throughout the four year period.

Four patients in Gr. 1 and three patients in Gr. 2 had graft failure during the study period. Causes of graft failure in Gr. 1 included refractory acute rejection (n = 2), transplant renal artery stenosis (n = 1), and CAN (n = 1). Causes of graft failure in Gr. 2 included refractory acute rejection (n = 1), CA bladder with obstructive uropathy (n = 1) and cirrhosis with progressive renal failure (n = 1). The four year actuarial graft

Table 1. Demographic data of diltiazem and non-diltiazem group

Characteristics	Groups		p-value
	Diltiazem Cases 48	Nondiltiazem Control 70	
Gender*			0.289
Male	30 (62.50)	37 (52.86)	
Female	18 (37.50)	33 (47.14)	
Age of recipient** (years)	41.90 (12.09)	41.25(10.88)	0.733
SBP** (mmHg)	132.51(11.60)	129.49(10.30)	0.101
DBP** (mmHg)	81.22(5.43)	80.81(4.37)	0.614
Cause of renal failure*			0.238
IgA	6 (16.67)	3 (4.29)	
DM	3 (6.25)	3 (4.29)	
HT	3 (6.25)	4 (5.71)	
PKD	2 (4.17)	3 (4.29)	
SLE	2 (4.17)	1 (1.43)	
Other	5 (10.42)	15 (21.43)	
Unknown	25 (52.08)	41 (58.57)	
DM* Yes	3 (6.25)	3 (4.29)	0.633
No	45 (93.75)	67(95.71)	
Mode of dialysis*			0.290
HD	44 (91.67)	58 (82.86)	
CAPD	4 (8.33)	10 (14.29)	
Pre-emptive	0 (0.00)	2 (2.86)	
Duration of dialysis (months)**	22.17 (13.17)	20.45(16.95)	0.756
Gender of donor*			0.723
Male	29 (60.42)	40 (57.14)	
Female	19 (39.58)	30 (42.86)	
Age of donor (year)**			0.578
≤ 50	44 (91.67)	66 (94.29)	
> 50	4 (8.33)	4 (5.71)	
Type of transplantation*			0.254
CDKT	20 (41.67)	22 (31.43)	
LRKT	28 (56.33)	48 (68.57)	
CIT (hour)*	20.43 (4.60)	19.63 (6.47)	0.152
Delayed graft function*			0.266
No	39 (81.25)	62 (88.57)	
Yes	9 (18.75)	8 (11.43)	
HLA mismatch**	3.09 (1.58)	2.97 (1.41)	0.624
Immunosuppressive*			0.181
No MMF	37 (77.08)	46 (65.71)	
With MMF	11 (22.92)	24 (34.29)	
Acute Rejection Episodes*			0.724
No	40 (83.33)	60 (85.71)	
>1	8 (16.67)	10 (14.29)	

* number (%) for categorical data
** mean (SD) for continuous data

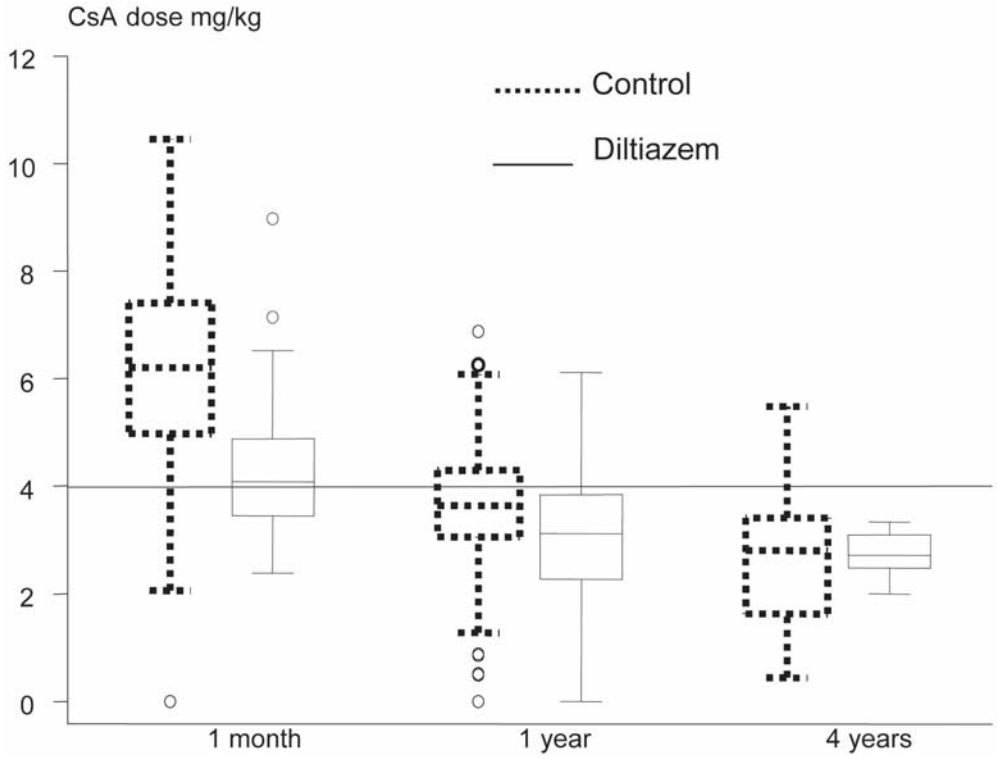

Fig. 1 Comparison of cyclosporin dosage (mg/kg/day) of diltiazem and non-diltiazem group (control) according to the time after transplantation

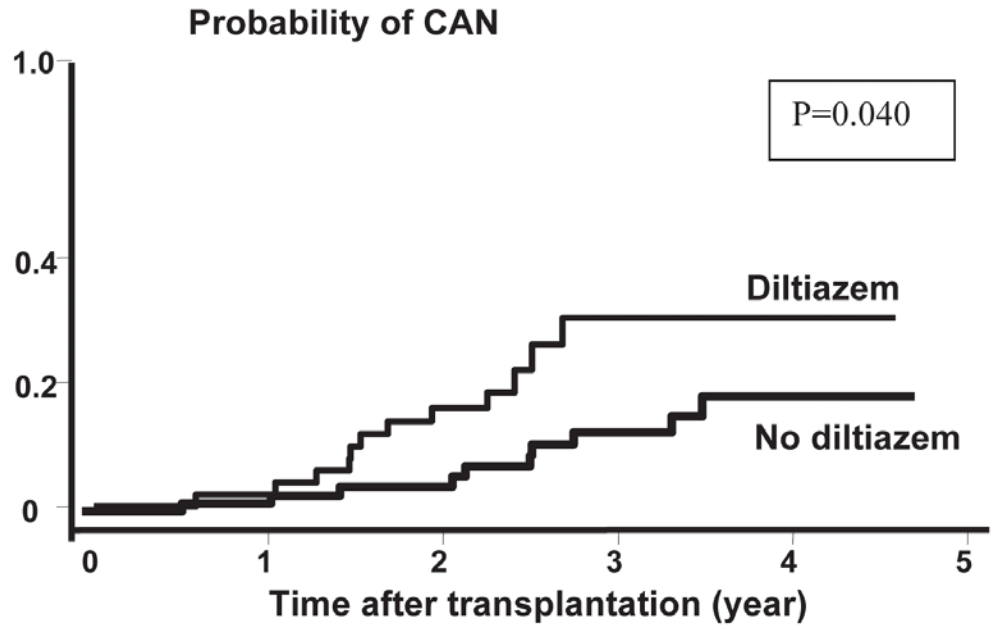

Fig. 2 Probability of CAN among diltiazem and non-diltiazem group

Table 2. Univariate analysis for predictive factors of CAN

Characteristics	Incidence rate of CAN per 100 person-year	Hazard ratio (95% CI)*	p-value
Treatment			
Control	3.75	Reference	
Diltiazem	8.45	2.79 (1.05-7.46)	0.040*
AR episodes			
0	4.28	Reference	
≥1	12.64	3.24 (1.134-9.28)	0.028*
Donor age, years			
≤ 50	4.98	Reference	
> 50	10.72	2.28 (1.12-4.62)	0.023*
Sex match			
Male to female	2.71	0.64 (0.14-3.18)	0.619
Identical	4.49	Reference	
Female to male	10.27	2.23 (0.81-6.17)	0.120
Type of transplantation+			
LRKT	3.02	Reference	
CDKT	6.35	1.86 (0.53-6.51)	0.327
Delayed graft function+			
No	2.60	Reference	
Yes	5.69	1.92 (0.32-14.56)	0.385
CsA trough level+			
≤ 150 ng/ml	7.57	Reference	
> 150 ng/ml	4.87	0.78 (0.25-2.47)	0.685
CsA dose mg/kg+			
≤ 4 mg/kg	5.57	Reference	
> 4 mg/kg	4.63	1.31 (0.41-4.10)	0.642

+ CI. Confidence interval
* Significant difference at $p < 0.05$

survival was 92 % for Gr1 and 95 % for Gr. 2 ($p = 0.31$).

A total of eighteen patients had CAN diagnosed by the definition defined earlier. The median (and range) time for the diagnosis of CAN was 24(6-42) months after transplantation. 18 patients had proteinuria > 500 mg/day and 17 in 18 had hypertension. 14 out of 18 patients with CAN agreed to receive allograft biopsy and all had a confirmed pathology. Four patients refused to receive biopsy. All of these four patients did not have evidence of transplant renal artery stenosis, obstruction or other surgical complications. In addition, urinalysis of these four patients revealed no evidence of RBC cast other cellular cast or decoys cells.

Figure 2 compares the probability of CAN among Gr. 1 and 2. This showed that the grafts from the diltiazem group had significantly higher probability to develop CAN than the non-diltiazem group after one year of transplantation. The four-year probability of CAN was 31% VS 19% for diltiazem and non-diltiazem group. Calculation for the incidence rate of CAN per 100 person-year by univariate analysis revealed that CAN is significantly associated with diltiazem treatment ($p = 0.04$), acute rejection ($p = 0.028$), donor age

more than 50 years (p = 0.023) and is not associated with delayed graft function (p = 0.38), high maintenance trough Cs A level (> 150 ng/dl; p = 0.68) or high mean Cs A dosage (>4mg/kg/day; p = 0.64). (Table 2). However, multivariate Cox proportional hazard regression showed that only diltiazem therapy, and acute rejection were shown to be significantly associated with CAN. The mean (and 95 % confidence interval) of adjusted hazard ratio for diltiazem therapy was 2.93 (1.08-7.90; p = 0.03) and for acute rejection was 3.26 (1.14-9.36; p = 0.02).

Discussion

The authors have shown that the magnitude of CsA dose reduction by diltiazem co-administration ranged between 11-30 %. This is observed mainly in the first twelve months. In contrast, the mean CsA dosage of the two groups is not significantly different in the maintenance phase. To the authors' knowledge, studies determining the four-year outcome of diltiazem co-administration in KT recipients are limited. In addition, no study has confirmed the protective effect of diltiazem on the long-term graft function. A previous study reported that patients who received diltiazem (n = 17) had fewer rejection episodes than patients who did not receive diltiazem (n = 24) (18%VS 33%). This was also associated with better serum creatinine at one-year (1.7 VS 2.4 mg/dl)[5]. The present findings lead to a message that diltiazem co-administration with CsA is associated with benefit in terms of CsA dose reduction and indifferent serum creatinine at four years. Of particular note is that the graft survival rate of the two groups is similarly good. Interestingly, the prevalence of patients who had more than 50 % elevation of serum creatinine in the present study was higher in the diltiazem than non-diltiazem group.

The underlying mechanism why diltiazem co-administration is associated with higher incidence of CAN needs to be further clarified. For practical reasons, trough level was used to adjust CsA dosage in the present study. This may not be ideal in kidney transplant recipients who receive diltiazem co-administration. The present result shows that the trough CsA level of the diltiazem group is slightly (but not significantly) higher than the non-diltiazem group from 12 months onwards. This may be a reason why the diltiazem group is associated with a higher incidence of graft dysfunction. However, other debatable issues need to be discussed. Due to the known effect of diltiazem to inhibit cytochrome p 450 3A4, diltiazem can lead to retention of parent compound of CsA and cause elevation of CsA blood level. In addition, diltiazem may also lead to retention of metabolites of CsA. Some CsA metabolites can be nephrotoxic and lead to chronic allograft nephropathy. It is not clear whether the retained metabolite can cross react with the parent compound that is measured by monoclonal FPIA method or not. A previous study has shown that HPLC is the gold standard method to assay CsA level[12]. This may be particularly true in patients who receive CsA sparing agents. However, HPLC is impractical for routine services and hence FPIA and other enzyme immunoassay are still widely used to measure cyclosporine level in clinical practice.

The present results have confirmed the importance of acute rejection as a strong predictor of CAN and suggest that diltiazem co-administration should be avoided in recipients who have a previous episode of acute rejection. Further studies are needed to determine whether optimizing CsA dosage by C2 monitoring will help to reduce the incidence of allograft dysfunction in kidney transplant recipients who received diltiazem co-administration.

In summary, diltiazem co-administration with CsA is found to be associated with CsA dose reduction, good graft survival rate and good serum creatinine at four years. However, the hypothesis that diltiazem may have a protective effect on long-term graft function can not be confirmed in the present study.

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ผลของการบริหารยาดิลไทอะเซ็มร่วมกับยาไซโคสปอรินสำหรับผู้ป่วยที่ได้รับการปลูกถ่ายไต : การติดตามผลที่ระยะเวลาสี่ปี

อติพร อิงค์สาธิต, วสันต์ สุเมธกุล, พนัส เฉลิมแสนยากร, โสภณ จิระสิริธรรม

ยาดิลไทอะเซ็ม และ ไซโคสปอริน มีกลไกการเผาผลาญคล้ายคลึงกัน โดยผ่านเอนไซม์ ไซโตโครมพี 450 ตระกูลย่อยสามเอสี่ ดังนั้นการบริหารยาดิลไทอะเซ็มร่วมกับไซโคสปอรินในผู้ป่วยที่ได้รับการปลูกถ่ายไต จะมีผลทำให้สามารถลดขนาดยาไซโคสปอริน, ช่วยควบคุมความดันโลหิต และอาจป้องกันการเสื่อมของไต

วัตถุประสงค์ *: เพื่อศึกษาผลลัพธ์ของการรักษาที่เวลาสี่ปี สำหรับผู้ป่วยที่ได้รับการปลูกถ่ายไตและได้รับการบริหารยาดิลไทอะเซ็มร่วมกับไซโคสปอริน เปรียบเทียบกับผู้ป่วยที่ได้รับยาไซโคสปอรินโดยไม่ได้รับยาดิลไทอะเซ็ม โดยคัดเลือกเฉพาะผู้ป่วยที่มีระดับความดันโลหิตและปัจจัยพื้นฐานคล้ายคลึงกัน*

วัสดุและวิธีการ *: จำแนกผู้ป่วยเป็นสองกลุ่มคือกลุ่มดิลไทอะเซ็ม (จำนวน 48 ราย) และกลุ่มที่ไม่ได้รับดิลไทอะเซ็ม (จำนวน 70 ราย) ผู้ป่วยได้รับการปรับยาไซโคสปอรินโดยใช้ค่าระดับยาที่วัดก่อนรับประทานยา และตรวจด้วยวิธีฟลูโอเรสเซ็น อิมมูโนเอสเส*

ผลการศึกษา *: พบว่าทั้งสองกลุ่มมีอัตราการอยู่รอดของไตที่สี่ปีใกล้เคียงกัน (92 และ 95 เปอร์เซนต์) และมีค่าเฉลี่ยของซีรัมครีอะตินิน เท่ากัน (1.3 มิลลิกรัมต่อเดซิลิตร) ค่าเฉลี่ยปริมาณยาไซโคสปอรินที่ใช้ในกลุ่มดิลไทอะเซ็มต่ำกว่ากลุ่มที่ไม่ใช้ดิลไทอะเซ็ม 30 เปอร์เซ็นต์ที่หนึ่งเดือนแรก และยังคงต่ำกว่ากลุ่มที่ไม่ใช้ดิลไทอะเซ็ม 11 เปอร์เซ็นต์ที่เวลาหนึ่งปี อย่างไรก็ตาม กลุ่มดิลไทอะเซ็มมีโอกาสเกิดการเสื่อมของไตมากกว่ากลุ่มที่ไม่ได้รับดิลไทอะเซ็มอย่างมีนัยสำคัญ (31เปอร์เซ็นต์เทียบกับ 19 เปอร์เซ็นต์) (อัตราเสี่ยง 2.93 เท่า; p = 0.03)*

สรุป *: การบริหารยาดิลไทอะเซ็มร่วมกับไซโคสปอริน โดยใช้ระดับยาก่อนการรับประทานยาเป็นเครื่องมือในการปรับขนาดยาไซโคสปอริน มีประโยชน์ในแง่ของการลดปริมาณการใช้ยาไซโคสปอรินต่อวันลงได้อย่างมีนัยสำคัญ และมีความสัมพันธ์กับการทำงานของไตและซีรัมครีอะตินินที่ดี อย่างไรก็ตาม ผลการศึกษาพบว่ายาดิลไทอะเซ็มไม่สามารถป้องกันการ เสื่อมของไตที่ได้รับการปลูกถ่ายแล้วได้*