Sinus tachycardia related to tacrolimus after kidney transplantation in children and young adults

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Tacrolimus is a potent immunosuppressive agent widely used after organ transplantation. In this present study we present eight patients who complained of palpitation after kidney transplantation. Eight out of 31 patients who received tacrolimus after kidney transplantation suffered from tachycardia. Resting electrocardiography, 24 hours Holter monitorization, echocardiography were performed, and serum levels of cardiac troponin T, creatine kinase, CKMB, brain natriuretic peptide and tacrolimus were measured. The median time to palpitation after kidney transplantation was 30 days in seven patients, and one patient complained of palpitation five years after transplantation. Cardiovascular assessment revealed sinus tachycardia in all patients. Beta-blocker was instituted in five patients. After two months all patients were asymptomatic and their pulse rates were within normal limits. Transient sinus tachycardia is a frequent adverse event during tacrolimus therapy in children and young adults, at therapeutic levels. Patients may benefit from beta-blockers.

Key words: tacrolimus, sinus tachycardia, children, young adult.

Tacrolimus is a potent immunosuppressive agent widely used after organ transplantation[1,2]. Adverse effects of tacrolimus are neurotoxicity, nephrotoxicity, diabetogenicity, gastrointestinal disorders, and cardiovascular toxicity[1]. Alterations in cardiac morphology and pathology have been reported in patients receiving tacrolimus[3]. Agirbasliet al.[1] demonstrated that angiotensin-converting enzyme inhibitor or angiotensin receptor blockage could reverse the histopathological signs of tacrolimus induced cardiac toxicity in a rat model. In a multicenter prospective study on cardiovascular adverse effects of tacrolimus in kidney transplantation (68 patients, mean age 33.4 years old, range 16-58 years old), subjective cardiovascular symptoms were reported in 19.1% of patients; chest pain (13.2%), palpitation (8.8%), tachycardia (1.4%), electrocardiographic changes (20.5%), myocardial hypertrophy (1.5%)[3-5]. Chest pain and palpitation were both found to be related to elevated tacrolimus concentration ranging between 20-60 ng/ml. Elevation of troponin T was detected in 3 patients (4.4%), which was closely related to elevated tacrolimus concentration. In a rat model, Gardiner et al.[6] reported that infusion of tacrolimus leads to a dose-dependent rise in blood pressure and heart rate. They also observed that administration of propranolol reverses the tachycardia effect of tacrolimus but not its pressor effect[6].

In this study we present clinical evaluation of eight patients who complained of palpitation after kidney transplantation.

Material and Methods

Patients

From January 2002 to December 2007, a total of 31 patients had received tacrolimus after kidney transplantation in our clinic. We evaluated retrospectively clinical features of eight patients (6 female, two male; median age of 16.0 years, and range 8-23 years) who complained of palpitation, and compared them with those

without palpitation (n: 23). We excluded cases who experienced rejection. We evaluated our patients for the other reasons of tachycardia such as anemia, hyperthyroidism, and drug's side effects (Table I). Thyroid hormone levels were in normal range in all patients.

Immunosuppressive therapy after renal transplantation in our clinic

All patients received prednisolone and tacrolimus (Table I). Prednisolone was started at 60 mg/m^2/d (maximum daily dose 60 mg), and was tapered to 5- to 10 mg/d over 6 months. Tacrolimus was administered orally as capsules, every 12 h. The initial oral daily tacrolimus dose was 0.2-0.3 mg/kg. The target blood tacrolimus levels were 10 to 15 ng/ml in the first month, 5 to 10 ng/ml after 1 month. Twenty three patients received basiliximab (12 mg/m^2, maximum 20 mg, first dose at the time of transplantation, second dose four days post-transplant). All patients received azathioprine (2 mg/kg) or mycophenolate mofetil (800- 1000 mg/m^2/d; maximum 1500 mg/d, in two divided doses).

Cardiovascular assessment (Table II)

A detailed cardiovascular assessment including physical examination, resting electrocardiography (ECG), two-dimensional echocardiography, ambulatory electrocardiography device and 24 hour ambulatory blood pressure monitoring was made. Cardiac troponin T and CKMB, and brain natriuretic peptide levels were measured.

On resting electrocardiography and ambulatory electrocardiography device monitoring heart rate, ST segment deviation or T wave inversion, and ventricular ectopies, atrial ectopies were evaluated. Sinus tachycardia is defined as heart rate >100 beats/minute (All patients in our study were >6 years old). Two dimensional echocardiography was done to determine left ventricular systolic functions (left ventricle end-systolic: LVESD and end-diastolic dimensions: LVEDD, left ventricular ejection fraction and shortening fraction) and left ventricle wall thickness. Left ventricle hypertrophy was defined as a left ventricle wall thickness more than normal measurement according to patient' body weight.

After cardiovascular assessment we prescribed

Table I. Clinical Characteristics of 31 Patients who Received Tacrolimus

	Patients with palpitation (n: 8)	Patients without palpitation (n: 23)	P
Sex (Male/Female)	2/6	16/7	0.043
Age [Median (range)] years	16.0(8-23)	15.0(7-28)	>0.05
Renal replacement therapy before transplantation			
- None	4	8	
-CAPD	4	6	
-Hemodialysis	0	9	
Time on dialysis (months)	Median 3 (0-60)	Median 12 (0-184)	>0.05
Immunosuppressive therapy before transplantation	3/8 (37.5%)	6/23 (26.1%)	>0.05
Donor type: Cadaveric /LRD	5 /3	8/15	>0.05
Immunosuppression			
Monoclonal antibody	7/8 (87.5%)	14/23 (60.9%)	>0.05
MMF	7/8 (87.5%)	15 / 23(65.2%)	>0.05
Azathioprine	1/8 (12.5%)	8 / 23 (34.8%)	>0.05
Antihypertensive treatment	7/8 (87.5%)	12 / 23 (52.2%)	>0.05
Calcium channel blocker	1/8 (12.5%)	11 / 23 (47.8%)	>0.05
Hemoglobin (g/dl)	Median 12.8 (11-13.5)	Median 12.2 (11.5-13)	>0.05
Median tacrolimus trough level (ng/ml)	5 (range 3-6.7)	4.8 (range 3.1-12)	>0.05

CAPVD: Continuous Ambulatory Peritoneal Dialysis, LRD: living renal donor, MMF: Mycophenolate Mofetil

Table II. Certain Clinical and Laboratory Features of Patients with Palpitation

Patients	Sex	Age years	Etiology of ESRD	Onset of palpitation after transplantation	BNP (pg/ml)	Tacrolimus level (ng/ml)	Ambulatory electrocardiography device after transplantation		Echocardiography before transplantation		Echocardiography after transplantation		Treatment with beta blockers
							Rhythm	Mean HR	IVSD (mm)	LVPW (mm)	IVSD (mm)	LVPW (mm)	
1	F	19	PAN	5 years	8	5.0	NSR	103 bpm	8	8	10	10	Metoprolol
2	F	16	Reflux	60 days	10	4.0	NSR	104 bpm	8	8.8	11	10	-
3	F	8	JNP	21 days	7	6.7	NSR	118 bpm	9	9	9.3	10	Metoprolol
4	F	18	MPGN	30 days	14	6.4	NSR	106 bpm	7	7.5	8	8.4	Metoprolol
5	F	23	Reflux	60 days	9	4.2	NSR	102 bpm	10	10	10	10	Atenolol
6	F	21	JNP	21 days	12	5.8	NSR	104 bpm	9	9	14	13.5	-
7	M	11	Idiopathic RPGN	30 days	5	5.5	NSR	120 bpm	9	8	10.5	8	-
8	M	11	Reflux nephropathy	27 days	8	3.0	NSR	125 bpm	9	8	9	8.5	Metoprolol

BNP: Brain natriuretic peptide, ESRD: end stage renal disease, IVSD: interventricular septum end diastolic diameter, LVPW: Left ventricular posterior wall end diastolic diameter, PAN: polyarteritis nodosa, JNP: juvenile nephronophytisis, MPGN: membranoproliferative glomerulonephritis, NSR: normal sinus rhythm, RPGN: rapidly proliferative glomerulonephritis

beta blocker to five patients for sinus tachycardia. Within the next routine visit after two months we asked about symptoms such as chest pain, chest discomfort, or palpitation; and evaluated physical examination, and resting electrocardiography.

Statistical analysis

Statistical analysis was performed using SPSS 11.0 for windows. Fisher's exact test and Mann-Whitney U test were used for comparison between groups. A p value <0.05 was considered statistically significant.

Results

A total of 8 patients suffered from palpitation (25.8%). The median time for the development of palpitation was 30 days (21-60 days). Clinical characteristics were presented on Table I.

Resting electrocardiography and two-dimensional echocardiographic examinations were normal before kidney transplantation in all patients.

We determined sinus tachycardia on physical examination and on resting ECG. On ambulatory electrocardiography device monitoring, mean heart rate of the patients ranged between 102 and 120 beat per minute (median 105 beat per minute) during the day. There was not any ST deviation or T inversion, ventricular or atrial ectopies on resting electrocardiography or on ambulatory electrocardiography device monitoring (Table II).

Two-dimensional echocardiography revealed thickening of left ventricular wall in one patient (patient 6). Left ventricle end-systolic and end-diastolic dimensions and measurements of left ventricular ejection fraction and shortening fraction measurements were all normal. Troponin T, CKMB and brain natriuretic peptide levels were in normal limits in all patients.

After cardiovascular assessment we diagnosed sinus tachycardia and beta blocker therapy was instituted in five patients (other three patients refused to use medication for palpitation). At the 2nd month-visit the patients had no palpitation, physical examination and resting ECG were normal in these five patients. Tachycardia was continued for 6-12 months in three patients who refused to use beta blocker therapy.

Discussion

Previous clinical trials of tacrolimus in recipients of kidney transplantation reported adverse cardiovascular events such as chest pain, palpitation, electrocardiographic abnormalities, or decrease in left ventricular ejection fraction[3-6]. Seino et al.[3] detected the incidence of cardiovascular adverse events slightly higher than these previous reports: the most frequent adverse event was chest pain and symptomatic events were closely related with elevated drug concentrations in the relatively early phase after transplantation[3]. They also demonstrated that troponin T elevation was also closely related with elevated levels of blood drug concentrations (>20 ng/ml) and was suggestive of minor or ongoing myocardial damage.

Our observations showed that sinus tachycardia may be also an adverse effect in the relatively early phase after kidney transplantation during oral tacrolimus therapy[7]. Sinus tachycardia was not related to tacrolimus concentration; the drug level ranged between 3.0-6.7 ng/ml in patients suffering from palpitation, contrary to the series reported by Seino et al[3]. In their series tacrolimus level ranged between 20-60 ng/ml in patients with chest pain or discomfort or palpitation. Echocardiographic examination did not reveal deterioration of left ventricular systolic functions in any of our patients. According to these observations we can interpret that sinus tachycardia in early phase after transplantation is not related to myocardial damage or to inappropriate tacrolimus dosage.

It should be remembered that ventricular arrhythmias coexist frequently in renal transplant recipients because of the underlying systemic diseases, anemia and influences of long-term hemodialysis performed before the kidney transplantation. None of the patients in our series had anemia during their complaints.

Myocardial hypertrophy in patients treated with tacrolimus was also reported as an adverse effect previously by Nakata, et al. [8]and Pirsch, et al.[9] in children. They observed that tacrolimus-induced myocardial hypertrophy correlated with tacrolimus blood levels and it was reversible. We observed border-line cardiac hypertrophy in one patient after initiation of tacrolimus. Blood tacrolimus, troponin T and

brain natriuretic peptide levels were in normal limits in all patients.

Gardiner et al.[6] showed that tacrolimus (450 μg/kg bolus i.v.) causes tachycardia in rats. Tacrolimus exerts its immunosuppressive effects by binding to FK binding protein (FKBP). In myocytes, FKBP couples with ryanodine receptors (RyR), which control intracellular calcium ion incorporation and enhances calcium ion release from sarcoplasmic reticulum by affecting the receptors[10]. Removal of FKB12.6 from RyR causes uncoupled channel gating in the ryanodine receptors, resulting in defective closure of these channels. And in an experimental study it has been shown that low dose propronolol corrects the defective interaction of FKBP12.6 with RyR resulting in an attenuation of intracellular calcium load. In our series response to beta blocker treatment is in accordance with the aforementioned information.

In conclusion; sinus tachycardia may be an adverse effect during tacrolimus therapy after kidney transplantation in children and young adults, at therapeutic levels. This effect was not found to be related to myocardial damage or blood tacrolimus level, and it was responsive to beta blocker treatment.

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