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EFFECT OF MIBEFRADIL ON BLOOD CYCLOSPORINE LEVEL IN HYPERTENSIVE RENAL TRANSPLANT PATIENTS

HİPERTANSİF RENAL TRASPLANT HASTALARINDA MİBEFRADİL KULLANIMININ SİKLOSPORİN DÜZEYLERİ ÜZERİNE ETKİSİ

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SUMMARY

Calcium channel blockers (CCB) are preferred antihypertensive drugs in renal transplant patients. Mibefradil is the first drug of new class of CCB, which selectively blocks T-type calcium ion channels in contrast to other CCB which blocks only L-type channels. In this study, the effects on Mibefradil on blood cyclosporine trough levels were investigated.

Six adult hypertensive renal transplant patients (4 male, 2 female) were included in the study. All patients were using Isradipine and were switched to Mibefradil at 50 mg / day. Systolic and diastolic blood pressures, serum BUN, serum creatinine levels and whole blood cyclosporine trough levels were evaluated weekly while the patient was being treated with Mibefradil and after discontinuation of the therapy.

One week after the mibefradil treatment, CsA levels increased sharply and reached to approximately 350 % of pretreatment levels. Two weeks after resumption to isradipine treatment, blood CsA level decreased back to pretreatment level. Mean arterial pressure, BUN and serum creatinine levels did not show significant change throughout the study period.

Our results have shown that there wasn't any CCB that elevate blood CsA levels as high as Mibefradil. It should be used with great caution for the prevention of renal dysfunction due to cyclosporine toxicity.

Key Words: Renal transplantation, cyclosporine, calcium channel blokers, mibefradil

ÖZET

Kalsiyum kanal blokeıieri (KKB) renal transplant hastalarında tercih edilen antihipertansif ajanlardır. Mibefradil, L-tipi kalsiyum iyon kanallarını bloke eden diğer KKB' lerinden farklı olarak seleküf bir şekilde T-tipi kanalları bloke eden bir ilacıdır. Bu çalışmada, Mibefradil kullanımının siklosporin çukur düzeylerine olan etkisi araştırılmıştır.

Çalışmaya 4'il erkek, 2'si kadın toplam 6 hipertansif erişkin renal transplant hastası alındı. Hepsi Isradipine kullanmakta olan bu hastaların ilaçları 50 mg/gün dozunda Mibefradil ile değiştirildi. Mibefradil tedavisi öncesi, süresince ve Mibefradil kesiliminden sonra hastaları sistolik ve diastolik kan basınçları, serum BUN ve kreatinin düzeyleri ve siklosporin çukur düzeyleri haftalık olarak araştırıldı.

Mibefradil başlandıktan bir hafta sonra, siklosporin çukur düzeylerinin hızla artarak, tedavi öncesi düzeyin %350'sine ulaştığı saptandı. İlacın kesilmesinden iki hafta sonra siklosporin çukur düzeylerinin çalışma öncesi düzeylere döndüğü görüldü. Tedavi süresince ortalama arteriyel basınçlar, BUN ve kreatinin düzeylerinde anlamlı farklılıklar saptanmadı.

*Bulgularımız, Mibefradil'in siklosporin çukur düzeylerini önemli derecede yükselttiğini göstermektedir. Siklosporin nefrotoksisitesine bağlı renal disfonksiyonu önlemek amacıyla bu ilacın büyük bir dikkatle kullanılması gerektiğini **düşünmekteyiz.***

Anahtar Kelimeler: Böbrek transplantasyonu, siklosporin, kalsiyum kanal blokeri, mibefradil

INTRODUCTION

Calcium channel blockers (CCBs) are widely used in the treatment of hypertension (HT) in renal transplant patients. It has been reported that some of the CCBs also reduce the incidence of delayed graft function (1), improve the allograft survival (2) and limit CsA-induced nephrotoxicity (4). However, some CCBs can interfere with CsA metabolism and increase CsA blood levels. While amlodipine, verapamil, nitrendipine and diltiazem dramatically elevate cyclosporine A (CsA) blood levels (5), nifedipine and isradipine do not cause any change (6). Mibefradil is the first drug of new class of CCB, which selectively blocks T-type calcium ion channels in contrast to other CCB which block only L-type channels (7). It is an effective, safe and well tolerated therapy for the treatment of hypertension (8). The effect of mibefradil on CsA metabolism has not been determined yet. This pilot study was undertaken to determine whether mibefradil alters CsA levels in renal transplant patients.

PATIENTS AND METHODS

Six adult hypertensive renal transplant patients were selected among the patient cohort followed in our outpatient transplant clinic at Akdeniz University, Medical School Hospital. Informed consents were obtained from all patients. All patients were on triple drug immunosuppresive protocol (prednisolone+azathioprine+cyclosporine) and taking isradipine for hypertension. They had been transplanted at least 6 months earlier and had not experienced an episode of acute rejection within the last 6 months. Blood CsA levels had been stable and the dosage of CsA had not been changed for the last 6 months. All patients had well functioning allografts with a serum creatinine less than 2 mg/dl. Patients taking any medication or CCBs that has been known to alter CsA levels were excluded.

The study had an open label, cross-over design. All patients were on isradipine before starting this study. Isradipine was switched to mibefradil in 6 hypertensive renal transplant patients. These patients were started on mibefradil at 50 mg/day in substitution for one antihypertensive medication. Three consecutive sitting mean arterial pressures (diastolic pressure plus one-third of pulse pressure), BUN, serum creatinine and blood CsA levels were obtained while the patients were taking a constant CsA dose (baseline period). We also obtained the same parameters weekly while the patient was being treated with mibefradil and after discontinuation of the therapy. Whole blood CsA levels were measured by TDx FLx® cyclosporine monoclonal whole blood assay (Abbott Laboratories, Abbott Park, IL 60064, 1996) that utilizes Fluorescence Polarization Immunoassay (FPIA).

All statistical analysis were done by SPSS for WINDOWS package program. Values before and after Mibefradil treatment were compared by paired t-test. The results are expressed as the mean+sem. P values lower than 0.05 were accepted as statisticaly significant.

RESULTS

One week after the mibefradil treatment, blood CsA levels increased sharply and reached to approximately 350% of pretreatmenl levels. Then, mibefradil treatment was stopped in order to prevent the occurence of CsA nephrotoxicity and this was followed by the decline of CsA blood level by weekly measurements. Two weeks after resumption to isradipine treatment, blood CsA level decreased back to pretreatment level. Mean arterial pressure, BUN and serum creatinine levels did not show significant change throughout the study period **(Table 1).**

DISCUSSION

This pilot study implies that mibefradil significantly increases blood CsA level an average of at least 350% **(Table 1).** This finding was confirmed when the CsA level returned to baseline after the discontinuation of mibefradil. Also there wasn't any change in CsA dosage that can alter CsA level throughout the study.

As known, CsA undergoes hepatic metabolism through cytochrome p450 3A enzyme by N-demethylation and methyl hydroxylation (9). Any drug that inhibits or induces hepatic p450 enzyme may cause changes in blood CsA levels. The interaction between the CsA and mibefradil may be due to the inhibition of the activity of cytochrome p450 1A2, 2D6 and 3A4. Studies which aim to determine the effects of mibefradil on CsA metabolism in the liver need to be done. CsA sparing effect of some CCBs has been used by some transplant centers to minimize the cost of cyclosporine therapy. The problem is that physicians who are unaware of this interaction may use this agent. There isn't any CCB that elevate CsA levels as high as mibefradil. So usage of this drug can raise the problems of CsA induced toxicity unless CsA levels should be monitored closely

In conclusion, mibefradil is an effective antihypertensive agent and seems to increase CsA level significantly in CsA-treated renal transplant patients. For the prevention of renal dysfunction due to CsA toxicity, close monitoring of CsA levels is essential when mibefradil therapy is instituted in CsA treated renal transplant patients. On the other hand, mibefradil treatment could also be considered to minimize the cost of CsA therapy.

Table 1: Clinical and laboratory data in renal transplant recipients.*

Parameter	Baseline	1" week	2[nd] week	3[rd] week
SBP mmHg	126+2.5	126+1.7	127+1.1	126+2.8
DBP mmHg	84+5.3	**79*1.5**	• 77+1.1	80±1.3
MAP mmHg	98+3.8	95+1.2	94+0.9	96+1.8
Creatinine (mg/dl)	1.42+0.16	1.45+0.15	1.46+0.13	1.54±.20
BUN (mg/dl)	21.8+3	22.7+2.8	24.5+3.3	25.0+3.11
CsA dose (mg/day)	191±10	**191+10**	187±8.5	187+8.5
Blood CsA **level** (ng/ml)	127±9.6	443+27**	289+33***	143+19#

* : Values are mean ± standard error of mean.
** : p=0.0000: level at 1 week compared with baseline
***: p=0.009: level at 2 week compared with baseline
: NS :level at 3 week compared with baseline

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