Amlodipine Increases Cyclosporine Levels in Hypertensive Renal Transplant Patients: Results of a Prospective Study[1,2]

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ABSTRACT

Calcium channel blockers (CCB) are considered the agents of choice to treat hypertension in cyclosporine (CsA)-treated renal transplant patients. Verapamil, diltiazem, and nicardipine, but not nifedipine or isradipine, can significantly increase CsA levels. The effect of a new CCB, amlodipine, has not been established. However, some hospitals are routinely switching patients to amlodipine from other CCB for reasons of cost. A case of a man with stable CsA levels who developed significantly increased CsA levels after being changed to amlodipine is presented along with a prospective trial to formally examine this issue. Eleven hypertensive, CsA-treated renal transplant patients were placed on amlodipine for an average of 6.9 wk and later withdrawn. Three measurements of CsA trough level, blood pressure, serum creatinine concentration, and BUN were obtained at baseline, during treatment with amlodipine, and after withdrawal of amlodipine. CsA levels on amlodipine increased an average of 40% above baseline (P = 0.003) and decreased to baseline (P = 0.001) after amlodipine was withdrawn, despite no significant change in CsA dose. Additionally, there was no change in serum creatinine, BUN, or mean arterial pressure values. Amlodipine can increase CsA levels

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by an average of 40% in hypertensive renal transplant patients, despite a stable CsA dose. This important effect must be considered when initiating or discontinuing amlodipine or when substituting amlodipine for other CCB.

Key Words: *Amlodipine, cyclosporine, calcium channel blocker, hypertension, renal transplant*

Calcium channel blockers (CCB) are widely used in renal transplantation. They are commonly used in the treatment of cyclosporine (CsA)-associated hypertension, in part, because of preferential dilation of the afferent arteriole (1), which may limit CsA toxicity. Additionally, CCB improve long-term allograft survival (2) and reduce the incidence of delayed graft function (3). The CCB verapamil and diltiazem, respective prototypes of the phenylalkylamine and benzothiazepine class, interfere with CsA metabolism and dramatically elevate CsA blood levels (4,5). This effect has not been shown with nifedipine or isradipine (6,7), agents in the dihydropyridine class. Recently, amlodipine, a newly released CCB of the dihydropyridine class, has proven effective in control of hypertension in patients with renal insufficiency (8). The effect of this agent on CsA metabolism has not been well studied although it has been presumed to behave similarly to nifedipine and isradipine. Given the similarities of these different agents, but their substantial cost differences, at least one military medical center is planning to systematically convert patients from long-acting nifedipine to amlodipine (9), whereas others are eliminating nifedipine from their formularies in favor of other, less expensive CCB, including amlodipine. Precipitation of allograft rejection or CsA toxicity could result if an unrecognized interaction between amlodipine and CsA metabolism exists. We present a patient who was changed from isradipine to amlodipine because of formulary restraints and showed markedly higher CsA levels. We discuss his clinical course and present results of a subsequent prospective trial, prompted by the index case, to determine whether amlodipine alters CsA levels.

CASE REPORT

A 59-year-old white man developed end-stage renal failure secondary to autosomal-dominant polycystic kidney disease. He received a cadaveric renal transplant in June 1992 and had an uneventful post-transplant course, specifically, without an episode of acute rejection with a baseline serum creatinine concentration of 1.8 mg/dL. His maintenance immunosuppression included cyclosporine 175 mg twice daily, azathioprine, and prednisone. Long-standing hypertension was well controlled with isradipine 5 mg twice daily. He had retired from the U.S. Air Force, and he therefore received his outpatient medications from a military pharmacy. Because isradipine was not a formulary item, he was changed to amlodipine 5 mg/day. His cyclosporine level, which had been stable at 236 ng/mL, became significantly elevated at 412 ng/mL after 2 months of therapy. However, his renal function remained stable with a serum creatinine concentration of 1.4 mg/dL, and his blood pressure was controlled (146/90). He was not receiving any other medications known to alter CsA levels. The elevated cyclosporine level prompted reduction of his cyclosporine dose to 125 mg twice daily. The CsA level returned to baseline, and renal function and control of blood pressure remain excellent.

DISCUSSION

CCB are widely used in renal transplantation and possess unique properties that make them ideal agents. CsA-associated hypertension, pervasive in renal transplantation, has as its cause not only sodium avidity but also the secretion of endothelin. The natriuretic properties, in addition to the vasodilatory effects of CCB, combine to effectively control this form of hypertension (10). CsA toxicity may be ameliorated by CCB in part because of preferential dilation of the afferent arteriole as well as the blocking of the vasoconstrictive effects of angiotensin II, norepinephrine, and endothelin (1). Additionally, CCB have been shown to improve long-term allograft survival and to minimize delayed graft function in the post-transplant period (2,3).

However, certain CCB possess the ability to alter CsA metabolism by inhibiting the hepatic cytochrome P-450 system (11). Verapamil, diltiazem, and nicardipine significantly elevate CsA levels when given concomitantly (4,5,12,13). By contrast, nifedipine and isradipine, members of the dihydropyridine class of CCB, do not significantly alter the metabolism of CsA (6,7). Recently, amlodipine, which is also in the dihydropyridine class, has been released and has been shown to be effective in controlling hypertension in patients with renal insufficiency (8). The effect of amlodipine on CsA metabolism has not been well studied although, as our case presentation exhibits, significant elevations in CsA levels upon initiation with amlodipine can occur. We undertook a prospective trial to determine whether this effect of amlodipine is widespread.

We recruited 11 adult, CsA-treated renal transplant patients from the outpatient transplant clinic at the University of Alabama at Birmingham. The study was approved by the university's Institutional Review Board for Human Use, and all patients gave written informed consent. All patients had been transplanted at least 6 months earlier and had not experienced an episode of acute rejection within 3 months of entering the study. All patients had well-functioning allografts with a serum creatinine concentration < 2.2 mg/dL. Patients were excluded if they were taking a CCB known to alter CsA levels, *e.g.*, verapamil or diltiazem. Additionally, no patient was receiving any medication, either at the initiation or at any other time in the

study, known to alter CsA blood levels. The characteristics of the study group are shown in Table 1.

The study had an open-label, cross-over design. Three consecutive trough CsA levels (whole blood, monoclonal TDX fluorescent assay; Abbott Diagnostic Laboratories, Chicago, IL), BUN, and serum creatinine levels were measured while the patient was taking a constant CsA dose (baseline period). Sitting blood pressure was measured and mean arterial pressure was calculated as the diastolic pressure plus one-third of the pulse pressure. Ten patients were started on amlodipine at 5 mg/day in substitution for one antihypertensive medication. Five patients were receiving long-acting nifedipine, three were receiving hydralazine, and two were taking isradipine. One patient had newly diagnosed hypertension but was not on antihypertensive medication and was started on amlodipine at 2.5 mg/day. While being treated with amlodipine, patients had three consecutive measurements of trough CsA level, BUN, creatinine, and blood pressure obtained at 1- to 4-wk intervals. Amlodipine was discontinued in all patients, and antihypertensive therapy reinstituted. The patient newly treated for hypertension was treated with isradipine. Three consecutive measurements of CsA level, BUN, creatinine, and blood pressure were again obtained at 1- to 4-wk intervals. Data were analyzed by paired t test. Probability values less than 0.05 were considered significant. The results are expressed as the mean ± SE.

Cyclosporine levels increased significantly (P = 0.003) after amlodipine was initiated as compared with the baseline value and decreased significantly (P = 0.001) after amlodipine was withdrawn. There was no difference in mean CsA levels before starting or after discontinuing amlodipine therapy ($P > 0.05$). CsA levels at baseline, during amlodipine therapy, and after withdrawal were 174 ± 34, 244 ± 42, and 174 ± 28 ng/dL, respectively, as shown graphically in Figure 1. Thus, the CsA level increased an average of 40% on amlodipine therapy. Of the 11 patients studied, only one did not have an increase in the CsA level while receiving amlodipine.

TABLE 1. Baseline clinical characteristics of subjects

Characteristic	Mean (± SD) (N = 11)
Age (yr)	42 ± 15 (24 to 64)
Sex	
Male	4
Female	7
Race	
Black	5
White	6
Blood Pressure (mm Hg)	
Systolic	134 ± 6
Diastolic	91 ± 6
Cyclosporine Dose (mg/day)	369 ± 88
Cyclosporine Trough Level (ng/dL)	174 ± 34
Serum Creatinine (mg/dL)	1.7 ± 0.1
BUN (mg/dL)	27 ± 3

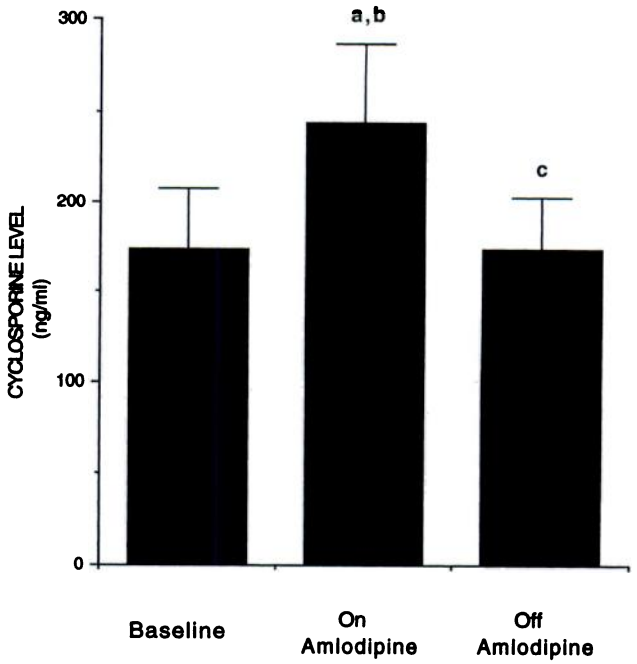

Figure 1. Effect of amlodipine on trough cyclosporine levels. a, P = 0.003 compared with baseline; b, P = 0.001 compared with level off amlodipine; c, $P > 0.05$ compared with baseline; values shown represent mean ± SE.

CsA dosage remained constant in eight of the 11 patients throughout the entire study. Three patients required minor dosage reductions of 50 mg/day, which is reflected in the third CsA level. One patient had renal dysfunction that improved after the CsA dose was decreased. Two other patients had CsA levels that were beyond the therapeutic range. Despite these minor adjustments, CsA dosage was not significantly different at 369 ± 88, 369 ± 87, and 358 ± 87 mg/day during the baseline period, on amlodipine therapy, or after withdrawal respectively. Table 2 summarizes the clinical and laboratory parameters at each time period.

Renal function, as measured by BUN and serum creatinine values, did not differ significantly throughout the study period. The serum creatinine concentration remained stable at 1.71 ± 0.1, 1.69 ± 0.2 and 1.73 ± 0.2 mg/dL, as did the BUN value at 27 ± 4, 26 ± 3, and 26 ± 5 mg/dL during the study periods.

Mean arterial pressure (MAP) did not differ significantly between study periods. MAP at baseline was 106 ± 6 compared with 108 ± 6 while patients received amlodipine and 104 ± 5 mmHg after it was withdrawn.

Our prospective study demonstrates that amlodipine significantly elevates CsA levels an average of 40% after therapy is initiated and confirms the findings of our case report. Importantly, in our study, this change

TABLE 2. Measurements before and after amlodipine[a]

Parameter	Baseline	On Amlodipine	Off Amlodipine	P Value[b]
Cyclosporine Level (ng/mL)	174 ± 59	244 ± 73	174 ± 49	A,B
Cyclosporine Dose (mg/day)	369 ± 152	369 ± 87	358 ± 150	NS
Mean Arterial Pressure (mm Hg)	106 ± 11	108 ± 10	104 ± 9	NS
Serum Creatinine (mg/dL)	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.4	NS
BUN (mg/dL)	27 ± 6	26 ± 5	25 ± 6	NS

[a] Values shown are mean ± SD.
[b] A, $P = 0.003$, level on amlodipine compared with baseline; B, $P = 0.001$, level on amlodipine compared with off baseline; NS, $P > 0.05$.

was confirmed when the CsA level returned to baseline after withdrawal of amlodipine. Furthermore, the CsA dosage did not differ in any phase of the study to explain the alteration of CsA levels.

Cyclosporine A undergoes hepatic metabolism through the very heterogeneous cytochrome P-450 enzyme system. Specifically, CsA is a substrate for the P-450 3A enzyme and undergoes *N*-demethylation and methyl hydroxylation (14). Some CCB, including verapamil, diltiazem and nifedipine, are also substrates for this enzyme system. Amlodipine is extensively oxidized in the liver and although the exact enzyme has not been determined, it presumably is via the P-4503A system similar to other calcium antagonists. Despite this similarity to other CCB, amlodipine has an exceedingly long half-life of 35 to 48 h (15) compared with 1 to 2 h for other calcium antagonists (16). This prolonged half-life makes steady state levels attainable only after 7 to 10 days of treatment.

There are limited but conflicting data regarding the interaction between amlodipine and CsA. Toupance *et al.* reported no difference in CsA levels in patients treated with amlodipine for 4 wk (17). In our study, patients received amlodipine for an average of 6.9 wk and had it withdrawn for over 8.7 wk. Because of the unusually long half-life of amlodipine, the longer duration of our study may have allowed the inhibitory effect of amlodipine on CsA metabolism to manifest. Indeed, when patients were initiated on amlodipine, we noted a progressive elevation in CsA levels, which finally plateaued after the third level was obtained. In contrast to the findings of Toupance *et al.*, van der Schaaf *et al.* demonstrated increased CsA levels during treatment with amlodipine (18). In this study, the hemodynamic effects of amlodipine and lisinopril were compared in a double-blinded, cross-over trial. Their data showed a 23% elevation in CsA levels after patients were placed on amlodipine.

Why amlodipine should inhibit the metabolism of CsA whereas other members of the dihydropyridine class (including nifedipine, isradipine, and nitrendipine) (6,7) do not may relate to its unique structure and biochemical characteristics. Amlodipine is chemically related to nifedipine but structurally differs because of the presence of a basic amino side chain on the dihydropyridine ring. This amino group conveys the positive charge at physiologic pH and the resultant high affinity for its receptor. Importantly, receptor-binding experiments have demonstrated that amlodipine binds not only to the dihydropyridine ring but also interacts with the verapamil and diltiazem binding site (14). This latter feature may explain why amlodipine decreases CsA metabolism as do these other nondihydropyridine calcium antagonists. Lastly, nicardipine, also a dihyropyridine CCB, has been reported to substantially elevate CsA levels by as much as 250 to 370% (12–13). This observation indicates that not all dihydropyridine members alter CsA metabolism in a uniform manner. Table 3 (4–7,12,19) summarizes the well-known, substantiated interactions between various CCB and cyclosporine.

A decrease of CsA metabolism by CCB is not inherently detrimental. This property has been exploited by some transplant centers to lower the overall cost of cyclosporine therapy. Additionally, evidence suggests that CCB augment the immunosuppressive effect of CsA. Kunzendorf *et al.* has reported that diltiazem increases the intracellular concentration of the cyclosporine metabolite M-17 over five times the concentration of parent CsA (20). CsA metabolites, including M-17, have been correlated with a reduced incidence of kidney allograft rejection (21).

The concern about using agents that alter CsA levels is the initiation or discontinuation of therapy by physicians or other health care providers who are unaware of this potential drug interaction. Recently, at least one military medical center has made plans to systematically convert patients from long-acting nifedipine to amlodipine (9). As more hospitals and health maintenance organizations make formulary decisions on the basis of cost considerations, there is increased potential for unrecognized, significant drug-

TABLE 3. Interactions between calcium channel antagonists and cyclosporine

Effect of Interaction	Agent	Class of CCB[a]
Increases CsA level	Verapamil	Phenylakylamine
	Diltiazem	Benzothiazepine
	Nicardipine	Dihydropyridine
No effect on CsA level	Nifedipine	Dihydropyridine
	Isradipine	Dihydropyridine
	Nitrendipine	Dihydropyridine

[a] CCB, calcium channel blockers.

TABLE 4. Drugs that alter cyclosporine levels[a]

Decrease CsA levels
Carbamazepine
Phenobarbital
Phenytoin
Rifampin
Increase CsA levels
Danazol
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Metoclopramide

[a] Agents listed have substantiated interactions with cyclosporine.

drug interactions and resulting toxicity or precipitation of allograft rejection. It should also be noted that any medication that inhibits or induces the hepatic P-450 enzyme may result in changes in cyclosporine levels. Table 4 (19) summarizes drugs that have well-known, substantiated interactions with cyclosporine.

In conclusion, amlodipine is an effective antihypertensive agent in cyclosporine-treated renal transplant patients but can increase trough CsA blood levels by 40%. The increase of CsA levels may not be apparent for several weeks because of the long half-life of amlodipine. Close monitoring of CsA levels is important when initiating or discontinuing therapy with amlodipine.

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