Captopril-Induced Fall in Glomerular Filtration Rate in Cyclosporine-Treated Hypertensive Patients


ABSTRACT

It was found that two known renal vasodilators had different effects on RBF and GFR in the setting of therapeutic blood levels of cyclosporine in hypertensive renal transplant patients. Captopril lowered blood pressure in these patients but also lowered blood flow and GFR. Nifedipine lowered blood pressure to the same degree but without lowering either RBF or GFR.

Key Words: Transplantation, renal, blood flow, nifedipine, converting enzyme inhibitor

Cyclosporine is now routinely used in solid-organ transplantation and for an increasing number of immunologic diseases. Extensive studies with animals and humans suggest that, after both acute and chronic administration, cyclosporine commonly produces renal vasoconstriction, predominantly of the preglomerular small resistance vessels. At least up to the first year after renal transplantation, both the renal vasoconstriction and the hypertension in humans are reversible after cyclosporine is discontinued (1). The renal vasoconstriction precedes the development of hypertension (2), and the hypertension is volume dependent rather than renin dependent (3,4). Animal studies suggest a predominant effect of cyclosporine on the afferent arteriole, and no specific vasodilator that reverses this has been detected. As well as accounting for the development of hypertension, renal vasoconstriction probably eventually contributes to arteriopathy, nephrosclerosis, and interstitial fibrosis (5).

Calcium-channel blockers appear to act predominantly on the afferent arteriole in their renal vasodilatory effect, whereas converting enzyme inhibitors act predominantly on the efferent arteriole (6,7). One might, therefore, predict a more beneficial effect on renal hemodynamics in cyclosporine-induced hypertension from calcium-channel blockers rather than from converting enzyme inhibitors. Nevertheless, both types of antihypertensive drugs ameliorate the hypertension in cyclosporine-treated patients (8,9).

We have studied the effects of a converting enzyme inhibitor, captopril, and a calcium entry blocker, nifedipine, on RBF and GFR in hypertensive kidney transplant patients. Nifedipine was more effective as a vasodilator than was captopril. Moreover, treatment with captopril, but not nifedipine, resulted in a modest, reversible decrease in GFR. The decrease in GFR was not as dramatic or severe as that in transplant patients with renal artery stenosis (10), but it may be induced by a similar mechanism.

METHODS

We selected adult recipients of renal transplants who were hypertensive (mean arterial pressure [MAP], ≥105 mm Hg), with good allograft function (serum creatinine, ≤2.2 mg/dL). Eighteen patients who met these requirements were admitted to the General Clinical Research Center (GCRC) at the University of Alabama at Birmingham. All completed a 7-day, in-hospital evaluation, and all patients gave written informed consent. The study protocols were approved by the Institutional Review Board. All patients were taking cyclosporine as a single, daily dose as part of their immunosuppressive regimen, and all had cyclosporine blood levels in the therapeutic range. We studied six patients, while our center used the Sandoz polyclonal RIA (Sandoz Pharmaceuticals Corp., East Hanover, NJ). Their mean whole-blood cyclosporine level was 457 ± 220 ng/mL (therapeutic range, 250 to 1,000 ng/mL). The other 12 patients were studied while our center used the Sandoz monoclonal RIA and had a mean whole blood level of 248 ± 154 (therapeutic range, 100 to 300 ng/mL). All patients were also taking azathioprine (118 ± 19 mg/
24 h) and prednisone (13 ± 3 mg/24 h). We performed a "crossover" study in which the same patients were treated with each of two agents (captopril and nifedipine) and served as their own control. We randomly assigned the order of drug treatment (11 patients received captopril first), but neither patients nor investigators were blinded about the drug used.

The 18 patients in the "crossover" trial had a mean age of 35 ± 8 (mean ± SD) yr. Sixteen were men. Eleven (61%) received cadaveric allografts. The mean time between transplantation and entry into the GCRC study was 16 ± 12 months (range 4 to 35 months). None of the patients had received pulse steroids therapy for 6 months before the study, and none had been suspected of having acute rejection for 6 months before the study. Antihypertensive medications were held except for diuretics, which were kept constant throughout the study. All patients except for four were taking furosemide (31 ± 16 mg/day). All patients, except for three, had elevated blood pressures while on dialysis treatment, and all except for two had retained native kidneys. Half of the patients were African-Americans and the other half (50%) were white. Members of both races had similar responses in the study.

Throughout the study, the patients were on an 88-mEq of sodium, 60-g of protein per day diet (prepared by the dietician in the GCRC) and maintained a fluid intake of 2 to 2.5 L/day. We obtained a baseline measurement of effective renal blood flow (ERPF) with \[^{131}\]Iorthodihippurate (11) and of GFR with \[^{99m}\]Te-ethylene diamine (12). Control values for supine blood pressure were obtained after the patients were in the hospital for 3 days and were off of all antihypertensive medications. We compared captopril (25 mg every 8 h) with nifedipine (10 mg every 8 h). The first drug was given for 48 h, and the measurement of ERPF and GFR was repeated. After an 8-h washout period, the patients were switched to the second drug for 2 days and ERPF and GFR were measured. Daily blood pressure was the average of five mercury sphygmomanometer readings per day by the GCRC nurses. MAP was calculated (one third of pulse pressure + diastolic pressure). Renal vascular resistance (RVR) was calculated (RVR = ERPF/MAP). Changes in blood pressure, ERPF, and GFR were derived from values at the end of the 3-day control period and from values after each of the 2-day treatment intervals.

A second comparison study of captopril and nifedipine was performed in similar hypertensive transplant patients receiving therapeutic doses of cyclosporine. This study was done as a parallel study in which patients were assigned to a 4-day course of captopril or nifedipine but did not crossover. This protocol was otherwise identical to the first protocol, except no drug change was made. This comparison was done to determine if the results of the first study might have been influenced by the crossover design. The parallel study had 10 patients; five received captopril, and five received nifedipine. The mean age of the captopril group was 40 ± 6 yr; four were men. All patients had cadaveric kidneys. The mean age of the nifedipine group was 43 ± 14 yr; three were men, and four had cadaveric allografts. The captopril group did not differ statistically from the nifedipine group in whole-blood cyclosporine blood levels via monoclonal RIA (155 ± 90 versus 122 ± 55 ng/mL), azathioprine dose (115 ± 22 versus 115 ± 14 mg/day), or prednisone dose (16 ± 5 versus 12 ± 3 mg/day). No patient in these two groups had participated in the crossover study.

All results are presented as mean ± standard deviation unless otherwise noted. A two-tailed paired t test was used to compare results of patients' values during the control and treatment periods of the crossover study. A two-tailed, unpaired t test was used to compare results of the captopril-treated with the nifedipine-treated patients in the parallel study. A P value <0.05 was considered significant.

RESULTS

In the crossover study, both the nifedipine and the captopril lowered MAP significantly: 10 ± 7 and 10 ± 9 mm Hg, respectively (P < 0.001) (Table 1). In the parallel study, the agents also produced similar decreases in MAP: 11 ± 7 mm Hg for captopril-treated patients and 12 ± 3 mm Hg for the nifedipine-treated patients.

This decrease in blood pressure was accompanied by a decrease in RBF in the patients treated with converting enzyme inhibitor. ERPF decreased from 261 ± 58 to 221 ± 49 mL/min (P < 0.0002) with captopril in the crossover study and decreased from 333 ± 90 to 273 ± 70 (P < 0.03) in the parallel study. Despite the decrease in MAP in patients receiving calcium-channel blocker, RBF did not change significantly. In the crossover comparison, ERPF during nifedipine treatment was 256 ± 73 mL/min compared with the baseline of 261 ± 58 mL/min (P = not

<table>
<thead>
<tr>
<th>TABLE 1. Comparison of 18 patients on nifedipine and captopril</th>
<th>Control value</th>
<th>Nifedipine value</th>
<th>Captopril value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>110 ± 07</td>
<td>100 ± 11</td>
<td>100 ± 11</td>
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<tr>
<td>ERPF (mL/min)</td>
<td>261 ± 58</td>
<td>256 ± 73</td>
<td>221 ± 49(^a)</td>
</tr>
<tr>
<td>GFR (mL/min)</td>
<td>69 ± 17</td>
<td>66 ± 17</td>
<td>61 ± 16(^a)</td>
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\(^a\) P < 0.001.
significant (NS)). In the parallel study, ERPF increased (although not significantly) from 265 ± 47 to 288 ± 86 mL/min. Thus, the calculated RVR was significantly lower while the patients were taking nifedipine (Figure 1). The higher RVR observed during treatment with captopril was due entirely to the decrease in RBF rather than altered blood pressure.

GFR decreased significantly in patients taking captopril. In the crossover study, GFR decreased from 69 ± 17 to 61 ± 16 mL/min (P < 0.0003). In the parallel study group, GFR decreased from 79 ± 18 to 64 ± 10 mL/min (P < 0.04). Treatment with calcium entry blocker did not significantly change GFR in either study. In the crossover study, the GFR of patients taking calcium entry blocker was 66 ± 17 mL/min compared with the control value (69 ± 17 mL/min) (P = NS); in the parallel study, GFR increased, but not significantly (P = NS), from 76 ± 22 to 83 ± 34 mL/min.

Considering both trials, 23 hypertensive renal transplant patients were placed on captopril while taking cyclosporine. Twenty-one of the 23 had a decrease in GFR (Figure 2), which ranged from 0.5 to 25 mL/min. If only serum creatinine concentrations were considered, however, the difference was as not as striking: 1.8 ± 0.4 to 2.0 ± 0.5 mg/dL (P = NS).

**DISCUSSION**

Nifedipine and captopril had similar effects on blood pressure in these hypertensive, cyclosporine-treated, renal transplant recipients but had different effects on renal hemodynamics. Captopril therapy was accompanied by acute falls in ERPF and GFR that were not observed when blood pressure was lowered similarly by nifedipine. It is quite unlikely that this fall in GFR would have been observed in U.S. clinical practice because the changes in serum creatinine were minimal; furthermore, the acute antihypertensive effects of the two drugs did not differ. The different renal hemodynamic effects of the two antihypertensive agents are consistent with what is known about the predominant preglomerular vasoconstrictor effect of calcium-channel blockers, the predominant postglomerular arteriolar effect of converting enzyme inhibitors, and the mechanisms by which GFR is maintained in the setting of reduced RBF (13). Thus, if cyclosporine has a predominant renal arteriolar vasoconstrictive effect, it would likely interfere with the afferent arteriolar vasodilation. Afferent
arteriolar vasodilation is an important component of the maintenance of GFR in the setting of reduced RBF or perfusion pressure. To the extent that nifedipine reverses this cyclosporine-induced vasoconstrictive effect, the normal autoregulatory capacity would be restored. If cyclosporine does constrict the afferent arteriole, reducing glomerular perfusion pressure and GFR, the latter would be maintained by constriction of the efferent arteriole, dependent on angiotensin II. Captopril administration presumably interferes with this autoregulatory response, and GFR decreases. This hemodynamic response would be milder than that in patients with functionally active renal artery stenosis after treatment with converting enzyme inhibitors and diuretics (10). The decrease in RPF in cyclosporine-dependent hypertension would result from a failure of the afferent arteriole to dilate as captopril reduced systemic blood pressure and renal perfusion pressure fell, with a lesser vasodilatory effect on the efferent arteriole. In contrast, treatment with nifedipine may dilate the afferent arteriole to a greater extent as systemic blood pressure decreases. Additional support for the interferences by cyclosporine with renal autoregulatory capacity for GFR was seen in our recent studies of volume depletion (produced by a low-salt diet and furosemide) in posttransplant patients on cyclosporine or on azathioprine. The azathioprine patients maintained GFR in these circumstances, but GFR fell significantly in the cyclosporine-treated patients. In this case, both groups were normotensive, and the response in blood pressure after plasma volume contraction did not differ (4). It should be noted, however, that the changes observed in this study resulted from a 2- to 4-day exposure to each antihypertensive medication, which might not be sufficient time for potential compensatory response to come into play. Moreover, the low-sodium diet that our patients were placed on may exaggerate hemodynamic responses.

It is well established that converting enzyme inhibitor therapy (especially when combined with diuretics) may abruptly decrease GFR in conditions with markedly reduced RBF such as volume contraction, severe heart failure, functionally significant renal artery stenosis, and severe nephrosclerosis. We suggest that at least some patients with cyclosporine-dependent hypertension (because of the afferent arteriolar vasoconstriction) also depend on angiotensin II-mediated vasoconstriction of the efferent arterioles to maintain GFR. Thus, the administration of a converting enzyme inhibitor or circumstances that increase the need for afferent dilation (such as lower blood pressure or acute vascular rejection in patients taking converting enzyme inhibitors) may cause a drop in GFR. Several investigators have recently reported cases (14,15) of reversible acute renal dysfunction in renal transplant patients taking both cyclosporine and converting enzyme inhibitor. These patients did not have transplant renal artery stenosis, and the renal dysfunction reversed when converting enzyme inhibitor was stopped.

Not all renal transplant recipients on cyclosporine have cyclosporine-dependent hypertension (16). Native kidney-dependent hypertension in these patients is related to renin secretion by the old kidneys and responds well to converting enzyme inhibitors. However, in patients on cyclosporine with an otherwise unexplained drop in GFR, in the absence of high blood levels of cyclosporine, the possibility of this hemodynamic effect akin to that seen with functionally active renal artery stenosis should be considered.

Bantle et al. (17) recently reported that cyclosporine-treated patients (eight heart transplant recipients and one pancreas transplant recipient) had a 20% increase in ERPF when given converting enzyme inhibitor for 2 days. This finding is in marked contrast to the decreases in ERPF we observed in the 23 kidney transplant recipients taking cyclosporine in this study. Their report prompted us to add the parallel study to determine if the difference in study design might account for the differing results. In both portions of our studies, GFR decreased significantly in hypertensive renal transplant patients who were taking cyclosporine and a converting enzyme inhibitor. Our observations are consistent with animal studies from the Minnesota group (18,19) in which captopril did not reverse the vasoconstriction induced by cyclosporine. We think our results differ from those of Bantle et al. because we studied kidney transplant recipients rather than heart transplant recipients. Heart transplant recipients may not react to cyclosporine therapy in the same fashion as do other organ transplant patients (20). Unlike renal patients, heart transplant recipients have innervated kidneys and sympathetic renal stimulation. Such patients also lack ventricular sympathetic innervation and accompanying cardiac negative feedback to sympathetic stimulation of the heart. Furthermore, in our study, blood pressure was lowered by captopril, but did not change in the other report. It is also likely that the longer-term study of Bantle et al. may have resulted in an after-load reduction and increased cardiac output in their heart transplant patients, which could have favorably influenced ERPF. Abu-Romeh et al. (21) have reported that ERPF decreased 26% in 13 hypertensive renal transplant recipients taking cyclosporine and given enalapril for 2 wk. This report agrees with our observations and suggests that the effect may persist for more than the 2- to 4-day observation in our patients.

Our studies are all short term, and we cannot directly extrapolate to beneficial effects of channel blockers for long-term therapy in cyclosporine-treated renal transplant recipients. Moreover, the
drug exposure was only 2 days in the crossover trial that had a short washout period and 4 days in the parallel study. Nonetheless, others have shown long-term effects consistent with this position (22). In carefully controlled studies of animals with one-clip, two-kidney hypertension, converting enzyme inhibitor therapy has been associated with atrophy of the ischemic kidney on long-term therapy (23). Furthermore, the chronic interstitial fibrosis and glomerular hyalinization in patients with chronic cyclosporine nephropathy may be related to persistent renal vasoconstriction (24). Thus, as in the antihypertensive treatment of renovascular hypertension, calcium-channel blockers may be drugs of choice to treat cyclosporine-induced hypertension, although further, prospective controlled studies in renal transplant recipients will be required.

REFERENCES