The Effects of Blood Pressure Reduction on Cyclosporine Nephrotoxicity in the Rat

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ABSTRACT
The effects of blood pressure reduction on cyclosporine nephrotoxicity were studied over 12 months in four groups of rats. Group 1 received no drugs and served as controls. Groups 2, 3, and 4 received cyclosporine (CyA), ~9 mg/kg-day, in their food. In addition, Group 3 received enalapril and Group 4 received minoxidil, hydrochlorothiazide, and reserpine. Time-averaged monthly systolic blood pressure was equal in Groups 1 and 2 (136±1 and 135±1 mm Hg, respectively). Antihypertensive agents reduced average systolic blood pressure in Groups 3 and 4 (116±1 and 117±1 mm Hg, respectively). Morphometric studies showed that 12 months of CyA treatment caused interstitial fibrosis with an increase in the fractional volume of cortical interstitium (Vvint: Group 2, 20±1%; Group 1, 11±1%) and a reduction in mean glomerular volume (Vg: Group 2, 2.00±0.06×10^6 μm^3; Group 1, 2.48±0.06×10^6 μm^3). These structural changes were accompanied by a significant reduction in GFR (Group 2, 2.27±0.10 mL/min; Group 1, 2.76±0.10 mL/min). Cotreatment with enalapril reduced interstitial fibrosis (Vvint, 14±1%) and maintained Vg (2.23±0.08×10^6 μm^3) and GFR (2.56±0.08 mL/min) at near-normal values in Group 3. In contrast, the combination antihypertensive regimen increased the extent of interstitial fibrosis (Vvint, 24±1%) and further lowered Vg (1.72±0.05×10^6 μm^3) and GFR (1.72±0.05 mL/min) in Group 4. These results show that sustained treatment with a moderate dose of CyA causes interstitial fibrosis and impairs renal function in rats. The administration of enalapril, but not minoxidil, reserpine, and hydrochlorothiazide, limits renal injury in this model.

Key Words: Cyclosporine, nephrotoxicity, blood pressure, glomerulus, interstitium
Food Intake and Drug Administration

To control food and drug intake, rats in each group were housed in separate cages and were provided daily with weighed portions of an agar gel containing both chow and any pharmaceutical agent(s). The gel was made by the suspension of 1,000 g of standard powdered rat chow in a solution of 45 g of agar dissolved in 1,500 mL of hot water. The resulting mixture was poured into shallow pans, allowed to solidify, and cut into weighed portions that were stored frozen until use. Pharmaceutical agents were blended into the powdered chow before the agar gel was prepared. CyA oral solution (Sandoz Pharmaceuticals, East Hanover, NJ) was diluted with olive oil to a concentration of 30 mg/mL. The diluted solution was blended into the chow of Groups 2, 3, and 4 to obtain a CyA concentration of 180 mg/kg of chow. An equal amount of olive oil without CyA was added to the chow of Group 1. In addition, enalapril (100 mg/kg) was added to the chow of Group 3, and minoxidil (150 mg/kg), hydrochlorothiazide (400 mg/kg), and reserpine (15 mg/kg) were added to the chow of Group 4. At 2 months, the mean serum CyA level was slightly lower in Group 3 than in Groups 2 and 4. The dose of CyA for Group 3 was therefore increased to ~11 mg/kg-day. By 4 months, the mean serum CyA level was higher in Group 3 than in the other two treated groups. The dose of CyA for Group 3 was then returned to ~9 mg/kg-day for the remainder of the study. Rats were initially provided with 40 g/day of the food-containing gel. After 5 months, this allotment was increased to 45 g/day. Residual chow was weighed once monthly in order to compare food intake among the groups.

Blood Pressure, CyA Levels, and Protein Excretion

Blood pressure was measured weekly for the first month and then monthly for the remainder of the study. Tail blood samples for the determination of serum CyA levels were obtained monthly for the first 6 months and then every 2 months for the remainder of the study. During the final month of the study, the rats were placed in metabolic cages for the determination of 24-h urine protein excretion.

GFR

Osmotic constant infusion pumps (Alzet 2ML4; Alza Corporation, Palo Alto, CA) filled with lothalamate (ConRay 60%; Mallinckrodt Medical, St. Louis, MO) were installed ip under anesthesia provided by Brevital (Eli Lilly, Indianapolis, IN), 50 mg/kg ip. Rats were allowed 5 days to recover, and blood samples were then obtained for the determination of serum lothalamate levels. Values for GFR were derived from the infusion rate of the pumps and from measured serum and infusate levels of lothalamate.

Morphologic Studies

Rats were anesthetized with Brevital (50 mg/kg ip), and their kidneys were fixed by retrograde aortic perfusion with 1.25% glutaraldehyde in 0.1 M cacodylate buffer. Midcoronal slices of perfused kidneys were embedded in methacrylate, and sections were stained with trichrome (3-μm sections) and periodic acid–Schiff (5-μm sections) for morphologic analysis. The fractional volume of cortical components was determined on sections stained with trichrome with an 11×11-point eyepiece reticle grid and a magnification of ×400. A total of 1,089 points in the outer cortex of each animal was evaluated by the examination of nine fields on a single section. The volume fractions (Vv) of interstitium, tubule cells, tubule lumina, and glomeruli were calculated as the number of points falling on each structural component divided by the total number of points evaluated. The frequency of focal and segmental glomerular sclerotic lesions was determined on sections stained with periodic acid–Schiff. One hundred glomerular profiles were examined in a single section from each rat, and the number of glomeruli with segmental lesions was expressed as a percentage of the total. Segmental lesions were defined as areas of the tuft showing collapse of the glomerular capillaries accompanied by hyaline deposition and/or adhesion of the tuft to Bowman’s capsule. The average glomerular tuft volume (Vg) of each animal was determined as described by Weibel (15). For this purpose, the mean cross-sectional area (A0) was determined on glomerular tuft profiles in each animal with a computer-assisted morphometric unit. Vg was then calculated as

\[ V_g = B/K (A_0)^{3/2} \]

where B = 1.38 is the shape coefficient for spheres (the idealized shape of glomeruli) and K = 1.1 is a size distribution coefficient (15,16).

Analytical and Statistics

Systolic blood pressure (SBP) was measured by the tail cuff method. Urinary protein was measured by the Coomassie blue method. Serum CyA levels were determined by the use of a commercially available RIA kit (IncStar Corp, Stillwater, MN).lothalamate concentrations were determined by HPLC (17). The statistical significance of differences among values for individual parameters in the four experimental groups was determined by the analysis of variance. Scheffé’s test was used to assess the significance of difference between individual group means (six comparisons) with significance defined as P < 0.05. Results are expressed as means ± SE throughout.
RESULTS

Food Intake and Body Growth

Average food intake for Group 1 rats was 36±1 g/day. This was similar to the average intakes of 37±1, 40±1, and 37±1 g/day for Groups 2, 3, and 4, respectively. Body weight in the different groups was also similar at the close of the study (Table 1).

SBP

Mean SBP values in the four groups are depicted in Figure 1. The time-averaged value for SBP of 135±1 mm Hg in CyA-treated Group 2 rats was very close to the time-averaged value for SBP of 136±1 mm Hg in control Group 1 rats. Treatment with enalapril significantly lowered SBP so that the average SBP was 116±1 mm Hg in Group 3 rats. Treatment with nifedipine, reserpine, and hydrochlorothiazide caused a similar reduction in SBP so that the average SBP was 117±1 mm Hg in Group 4 rats. Values for SBP in Groups 3 and 4 rats were not different at any point during the study.

Serum CyA Levels

Mean serum CyA levels are depicted in Figure 2. As expected, CyA was undetectable in Group 1. In Group 2, the CyA level was stable throughout the study with a time-averaged value of 386±29 ng/mL. In Group 4, the CyA level was similar and also stable with a time-averaged value of 408±32 ng/mL. CyA levels in Groups 2 and 4 were not significantly different at any point during the study. The CyA level in Group 3 was slightly lower than the CyA levels in Groups 2 and 4 at 2 months. Therefore, the daily dose of CyA was increased from 9 to 11 mg/kg-day. The CyA level in Group 3 then rose to almost twice the CyA levels in Groups 2 and 4 at 4 months. The CyA level in Group 3 remained higher than the CyA levels in Groups 2 and 4 for the remainder of the study, even though the dose of CyA given to Group 3 was returned to the dose (9 mg/kg) given to the other two groups after 4 months. Overall, the time-averaged CyA level of 501±32 ng/mL in Group 3 was significantly higher than the time-averaged CyA levels in the other treated groups.

Table 1. Summary of studies at 12 months

<table>
<thead>
<tr>
<th></th>
<th>BW (g)</th>
<th>LKW (g)</th>
<th>GFR (ml/min)</th>
<th>VvInt</th>
<th>VvTub (%)</th>
<th>VvLum (%)</th>
<th>VvGlom (%)</th>
<th>Glom Scler</th>
<th>Vv &gt; 2.25x10^4 µm² (%)</th>
<th>A v &gt; 2.25x10^4 µm² (%)</th>
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<tr>
<td>Group 1</td>
<td>389±4</td>
<td>1.52±0.04</td>
<td>2.76±0.10</td>
<td>11±1</td>
<td>64±1</td>
<td>20±1</td>
<td>4±1</td>
<td>2.6±0.4</td>
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<td>Group 2</td>
<td>380±5</td>
<td>1.54±0.02</td>
<td>2.27±0.10</td>
<td>20±1</td>
<td>56±1</td>
<td>20±1</td>
<td>4±1</td>
<td>4.8±1.4</td>
<td>2.00±0.1</td>
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<td>(N=9)</td>
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<tr>
<td>Group 3</td>
<td>379±5</td>
<td>1.45±0.02</td>
<td>2.56±0.08</td>
<td>14±1</td>
<td>64±1</td>
<td>18±1</td>
<td>4±1</td>
<td>3.0±0.5</td>
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<tr>
<td>Group 4</td>
<td>391±9</td>
<td>1.29±0.11</td>
<td>1.59±0.07</td>
<td>24±1</td>
<td>54±1</td>
<td>18±1</td>
<td>3±1</td>
<td>9.8±0.8</td>
<td>1.72±0.1</td>
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<td>(N=9)</td>
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Abbreviations: BW, body weight; LKW, left kidney weight; Vv, fractional volume; Int, interstitium; Tub, tubular cells; Lum, tubular lumina; Glom, glomeruli; Glom Scler, prevalence of glomerular sclerotic lesions; A v > 2.25x10^4 µm², prevalence of glomerular profiles with area greater than 2.25x10^4 µm². b, Group 1 versus 4; c, Group 2 versus 4; d, Group 3 versus 4; e, Group 1 versus 2; f, Group 1 versus 3; g, Group 2 versus 3.
Figure 2. Serum CyA levels measured in tail blood samples. CyA levels were similar in groups 2 (open square) and 4 (open circle). Higher CyA levels were observed after 3 months in Group 3 (closed square). CyA levels were undetectable in Group 1 (closed circle). *P < 0.05 Group 3 versus 2; §P < 0.05 Group 3 versus 4.

Protein Excretion

After 12 months, the average protein excretion rate of 38 ± 6 mg/day in CyA-treated Group 2 rats was not different from the protein excretion rate of 35 ± 4 mg/day in control Group 1 rats. Slightly but significantly less proteinuria was observed in Group 3 rats and Group 4 rats; these rats had average protein excretion rates of 21 ± 2 and 22 ± 2 mg/day, respectively.

GFR

Values for GFR measured in unanesthetized rats at the close of the study are presented in Table 1. GFR averaged 2.76 ± 0.10 mL/min in untreated Group 1 rats. This value is similar to GFR values obtained by inulin clearance in anesthetized rats in our laboratory (18). Treatment with CyA reduced GFR to 2.27 ± 0.10 mL/min in Group 2 rats. Cotreatment with enalapril prevented a significant decrease in GFR in Group 3 rats. The average GFR in this group was 2.56 ± 0.1 mL/min. However, cotreatment with minoxidil, reserpine, and hydrochlorothiazide resulted in a more pronounced decrease in GFR to 1.59 ± 0.1 mL/min in Group 4 rats. Three rats, one each from Groups 2, 3, and 4, died before the GFR was determined. In two rats, death was a complication of anesthesia; the third rat was euthanized after it developed a pelvic abscess.

Morphologic Studies

Results of morphologic studies are summarized in Table 1 and depicted in Figure 3. Reduction of the...
GFR in CyA-treated Group 2 rats was accompanied by the development of interstitial fibrosis. This change was most extensive in the subcapsular region but occasionally extended into the midcortex in bandlike fingers. Tubular atrophy and focal tubular dilation were readily apparent in areas where interstitial fibrosis was most marked. These areas also contained a scantly cellular infiltrate that appeared to be composed of lymphocytes. Vacuolization of proximal tubule cells was observed in some areas but was not a prominent finding. Significant vascular abnormalities were not observed. Morphometric studies confirmed that chronic CyA treatment caused expansion of the interstitium and atrophy of tubular cells. In control Group 1 rats, the fractional volume of the cortical interstitium (Vvlnt) averaged 11±1% and the fractional volume of the cortical tubule cells (VvTub) averaged 64±1%. In CyA-treated Group 2 rats, interstitial fibrosis increased Vvlnt to 20±1%. This increase in interstitial volume was accompanied by a reciprocal decrease in tubular cell volume so that VvTub averaged 56±1% in Group 2 rats although total kidney weight was unchanged. Of note, CyA treatment over 12 months did not cause prominent glomerular sclerosis. The prevalence of glomerular sclerotic lesions was 2.6±0.4% in Group 1 rats and increased only slightly and not significantly to 4.8±1.4% in Group 2 rats. CyA treatment did, however, cause a reduction in mean VvTub of 2.00±0.1×10⁶ μ³ in Group 2 rats was significantly less than the average value for VvTub of 2.48±0.1×10⁶ μ³ in Group 1 rats. The distribution of glomerular area profiles in the two groups suggested that the reduction in glomerular volume in CyA-treated rats was relatively uniform. In particular, the fraction of large profiles (A₀ > 2.25×10⁶ μ³) in Group 2 was not increased, indicating that the reduction in average glomerular volume in CyA-treated rats was not accompanied by the development of a subpopulation of enlarged glomeruli.

Cotreatment with enalapril not only preserved the GFR but also reduced the severity of renal injury in Group 3. Vvlnt in this group averaged 14±1%, a value less than that observed in Group 2 rats but still significantly greater than that observed in control Group 1 rats. Reduction in the extent of interstitial fibrosis in Group 3 was associated with maintenance of a normal fractional volume of tubule cells and a near-normal glomerular volume. In contrast, cotreatment with minoxidil, reserpine, and hydrochlorothiazide increased the severity of renal injury in Group 4. Vvlnt in this group averaged 24±1%, a value significantly greater than that observed in Group 2 rats receiving CyA alone. The increase in Vvlnt in Group 4 was associated with a marked reduction in VvTub that was proportional to the reduction in GFR observed in this group. A small but significant increase in the prevalence of glomerular sclerotic lesions was also observed in Group 4.

DISCUSSION

The first aim of this study was to assess the effects of chronic CyA treatment on kidney structure and function in the rat. Biopsy studies have documented interstitial fibrosis and tubular atrophy in humans receiving CyA at doses averaging ~10 mg/kg-day for 1 yr (19,20). In this study, interstitial fibrosis and tubular atrophy were observed in rats receiving CyA at a dose of ~9 mg/kg-day for a similar period. These changes were accompanied by a reduction in β₂ and a reduction in GFR. Despite the long duration of the study, CyA treatment did not cause proteinuria or a significant increase in glomerular segmental sclerosis.

Progressive interstitial fibrosis and tubular atrophy have previously been observed in rats treated with CyA for 4 to 20 wk (9–12,21–25). It is difficult to compare the extent of this injury among different studies, because quantitative methods have not generally been used to assess morphologic changes. One difference between these findings and those of many previous studies, however, was the relatively mild degree of tubule cell vacuolization in this study. Tubule cell vacuolization could be identified but was not apparent in every field examined and did not cause the extensive derangement of tubule architecture that has often been observed in rats treated with CyA (21–25). This difference may be related to the dose of CyA used. In most previous studies, higher doses of CyA have been administered for shorter intervals, and high doses of CyA have been shown to cause rapid development of tubule cell injury in the proximal nephron (9,22). These results are similar to those obtained by Backman et al. (26), who observed tubular atrophy and interstitial fibrosis but not tubule cell vacuolization in rats receiving 5 to 6 mg/kg-day of CyA for 66 wk. These results suggest that rats receiving low-dose CyA develop progressive interstitial fibrosis and tubular atrophy in the absence of the severe tubule injury caused by high-dose CyA.

The finding of interstitial fibrosis and tubule atrophy without marked tubule vacuolization is also characteristic of chronic CyA nephrotoxicity in humans (20,27–29). Several differences between the effects of CyA on the kidney in rats and humans, however, should be noted. First, CyA nephrotoxicity in humans is regularly associated with hypertension (1,2,28,30). Results of this study show that CyA nephrotoxicity develops without elevation of the blood pressure in rats. This has been a common finding in rats given CyA (5,11,25,31). Second, arteriolar injury is a common feature of CyA nephrotoxicity in humans but is not observed in CyA nephrotoxicity in rats.
toxicity in rats (10–12,21–29). Finally, recent studies have described the development of a subpopulation of enlarged glomeruli and of glomerular segmental sclerosis in cardiac transplant patients receiving CyA (28,29). These changes have been considered to represent hypertrophy and subsequent sclerotic injury in glomeruli whose blood supply is least compromised by CyA. Neither glomerular enlargement nor increased glomerular segmental sclerosis was observed in CyA-treated rats in this study. This may be because renal injury was less severe in the rats we studied than in the cardiac transplant recipients who have been subjected to renal biopsy (28,29). Rats given a larger dose of CyA than was used in this study have recently been shown to develop a subpopulation of enlarged glomeruli as well as a larger population of shrunken, presumably ischemic glomeruli (31).

The second aim of this study was to determine whether blood pressure–lowering drugs would limit CyA nephrotoxicity in the rat. At present, the mechanism(s) responsible for CyA nephrotoxicity remain largely undefined. Increased renal vascular resistance, however, has been observed in many, although not all, studies evaluating the early effects of CyA administration in rats (3–7,32,33). Increased renal vascular resistance was also observed in a recent study of the effects of CyA administration in humans (8). These observations suggest that renal ischemia could contribute to CyA nephrotoxicity and have prompted interest in the possibility that antihypertensive drugs could limit the severity of this disorder (2,8,20,25,34,35). This study assessed the effect of enalapril and of a combination of minoxidil, reserpine, and hydrochlorothiazide on CyA nephrotoxicity in rats. It should again be emphasized that rats given CyA alone did not develop hypertension. Antihypertensive agents were therefore administered in doses sufficient to induce controlled hypotension.

Treatment with enalapril significantly reduced the severity of renal injury in rats receiving CyA for 1 yr. This benefit was seen despite significantly higher plasma levels of CyA. These results contrast with those recently obtained by Gillum and Truong (25), who found that enalapril conferred no protection against renal injury in rats receiving CyA for 1 months. One factor that could account for this discrepancy is the dose of CyA used. Gillum and Truong (25) examined renal injury in rats receiving CyA, 25 mg/kg·day by ip injection. CyA levels obtained with this regimen are considerably higher than those observed in this study (11). Together, results of the two studies would suggest that enalapril cannot prevent acute tubular injury and interstitial fibrosis in rats receiving a high dose of CyA but can limit the less-rapid development of interstitial fibrosis in rats receiving a lower dose of CyA.

A notable finding of this study was that converting enzyme inhibition reduced renal injury in a disease model characterized by interstitial fibrosis, tubular atrophy, and reduction in glomerular volume. Previous studies have, for the most part, assessed the effect of converting enzyme inhibition in models of renal disease characterized by the development of proteinuria and glomerular segmental sclerosis (13,14,36–38). Converting enzyme inhibition has almost invariably been shown to retard the progression of glomerular injury in such models. In some studies, the protective effect of converting enzyme inhibition has been related to reduction of glomerular capillary pressure (13,14). In other studies, the protective effects of enalapril have been attributed to limitation of glomerular growth and to preservation of glomerular barrier function (36–38). None of these mechanisms provides a ready explanation for the finding that enalapril reduces CyA nephrotoxicity in rats. Micropuncture studies have shown that CyA-treated rats exhibit normal or slightly reduced values for glomerular pressure, and this study showed that CyA-treated rats have normal values for protein excretion rate and reduced values for $V_G$ (7,32,39).

Whereas cotreatment with enalapril had a beneficial effect, cotreatment with minoxidil, reserpine, and hydrochlorothiazide increased the severity of renal injury in rats receiving CyA for 1 yr. The reason for the different effect of the two treatment regimens is not apparent. Studies by Anderson et al. (13,14) have shown that converting enzyme inhibitors and combinations of hydralazine, reserpine, and hydrochlorothiazide are equally effective in reducing renal vascular resistance in rats with experimental diabetes and in rats subjected to renal ablation. As previously noted, preferential reduction of efferent resistance would seem an unlikely explanation for the protective effect of enalapril we observed in CyA nephrotoxicity. It should be emphasized that this study does not identify the mechanism by which enalapril limited the development of interstitial fibrosis in CyA-treated rats. Measurements of circulating renin angiotensin system activity in both CyA-treated rats and humans have yielded variable results, with the majority of studies detecting no increase in renin activity (20,28,40–43). Converting enzyme inhibitors, however, have proven effective in many conditions in which circulating renin angiotensin system activity is not elevated. In some of these conditions, converting enzyme inhibitors may prevent injury by increasing kinin or prostaglandin levels rather than by inhibiting angiotensin II (All) production. In other conditions, converting enzyme inhibitors may prevent tissue damage by blocking the activity of local tissue renin angiotensin systems. Recent studies have suggested, for instance, that inhibition of local All production contributes to the
ability of converting enzyme inhibitors to limit cardiac hypertrophy and fibrosis in experimental hypertension and to limit arterial wall thickening after experimental endothelial injury (44-46). The beneficial effect of converting enzyme inhibition in these cardiovascular disease models has been attributed both to the blockade of All-mediated muscle cell growth and to the blockade of All-mediated production of cytokines and matrix components. Presumably, the blockade of similar local actions of All could contribute to the beneficial effects of converting enzyme inhibition in renal disease models. In particular, the blockade of local All activity could counteract potential effects of CyA on renal cell cytokine release and matrix production (2). At present, It is not possible to selectively block any of the local actions of All without also blocking the effect of All on arteriolar tone. It is thus difficult to determine in an individual disease model whether converting enzyme inhibition limits renal injury by opposing vasoconstriction or by preventing some other action of All within the kidney.

Results of this study do indicate, however, that agents that cause similar reductions in blood pressure may have markedly different effects on the development of CyA nephrotoxicity.

ACKNOWLEDGMENTS

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