Effects of Losartan and Amlodipine on Intrarenal Hemodynamics and TGF-β1 Plasma Levels in a Crossover Trial in Renal Transplant Recipients

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Abstract. Hypertension and hyperfiltration are two important risk factors for the development of chronic allograft nephropathy. Transforming growth factor-β1 (TGF-β1) is the main cytokine involved in the fibrotic process that is involved in chronic rejection. Angiotensin II upregulates TGF-β1 production. Angiotensin II receptor antagonists therefore could not only control BP but also reduce TGF-β1 production in renal transplant patients. The aim of this study was to compare the effects of losartan and amlodipine on renal hemodynamics, as well as TGF-β1 and endothelin-1 (ET-1) plasma levels in a group of renal transplant patients who had normal renal function and who were treated with cyclosporine. Seventeen renal transplant patients who were receiving cyclosporine and who had normal graft function were included in a random 2 × 2 crossover trial with amlodipine and losartan (6 wk with each therapy). Three studies were performed (at baseline and at the end of both treatment periods) to determine renal hemodynamics, TGF-β1, and ET-1. Both treatments controlled BP to a similar degree, but only amlodipine increased GFR through an increase in the estimated glomerular hydrostatic pressure and filtration fraction. In contrast, losartan maintained GFR and reduced estimated glomerular hydrostatic pressure and filtration fraction significantly. Losartan and amlodipine had opposite effects on TGF-β1. Amlodipine did not affect TGF-β1 concentrations. In contrast, losartan reduced the plasma levels of TGF-β1 by approximately by 50% (from baseline, 5.2 to 2.6 ng/ml; P = 0.01); the majority of the patients reached normal levels of TGF-β1. ET-1 concentrations were significantly higher during amlodipine compared with losartan treatment. The present study documents that with similar control of BP, losartan and amlodipine have opposite effects on renal hemodynamics and on TGF-β1 concentrations. These differences could be important for the management of chronic allograft nephropathy.

Hypertension is a common clinical problem in renal transplant recipients: its prevalence ranges from 60 to 85% in transplant recipients who are treated with calcineurin inhibitors (1). Hypertension has been shown to correlate with increased cardiovascular mortality and morbidity (2), as well as with graft loss (3). Cyclosporine A (CsA) therapy is a major factor in the cause of hypertension. It also causes overexpression of angiotensin II (AngII) (4), thus increasing the synthesis of transforming growth factor-β1 (TGF-β1) (5), which is presumably involved in the development and progression of chronic allograft nephropathy (6) and induces interstitial fibrosis, glomerulosclerosis, and arterial proliferation (7,8). Production of TGF-β1 may be modulated either by the intrarenal renin-angiotensin system (9) or by a direct effect of CsA on synthesis and expression of TGF-β1. In agreement with this concept, Amuchastegui et al. (10) demonstrated in an experimental model that AngII receptor antagonists (AngIIA) clearly are better than calcium-channel blockers in protecting against progression of chronic allograft nephropathy.

The aim of the present study was to compare the effects of an AngIIA (losartan) and a calcium-channel blocker (amlodipine) on BP control, renal hemodynamics, TGF-β1, and endothelin-1 (ET-1) in renal transplant patients who had normal graft function and who were treated with CsA.

Materials and Methods

Patients

Seventeen renal transplant patients (11 men, 6 women) with a mean age of 53 ± 9 yr and a mean transplantation period of 90 ± 39 mo were included in the study. Immunosuppressive therapy consisted of CsA monotherapy in 10 patients and CsA plus prednisone in the rest. The inclusion criteria were (1) near normal renal function (serum creatinine < 1.6 mg/dl and proteinuria < 300 mg/24 h), (2) mild to moderate arterial hypertension (systolic BP [SBP] > 140 < 170; diastolic BP [DBP] > 85 < 100 mmHg) controlled by one antihypertensive drug, and (3) CsA-based immunosuppression. Diabetic patients were excluded. BP was adjusted during the study to values

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below 130/85 mmHg, introducing doxazosin when necessary. Before the run-in period, eight patients had been treated with calcium channel blockers (diltiazem and nifedipine), four patients had been treated with angiotensin-converting enzyme inhibitors (ACEi; captopril), three patients had been treated with β-blockers (atenolol), and two patients had been treated with α-blockers (doxazosin). All patients gave written informed consent, and the protocol was approved by the Ethical Committee of our hospital.

**Study Design**

The study was a randomized, open, controlled 2 × 2 cross-over trial (11) in which the two treatments were amlodipine and losartan (Figure 1). It consisted of a 4-wk run-in period without medication, a wash-out period, a 6-wk active treatment with losartan or amlodipine (period 1), a 4-wk wash-out period, and a 6-wk treatment with the alternative treatment (period 2). At the end of the run-in period, patients were randomized to one of the two sequences: amlodipine/losartan (sequence 1) or losartan/amlodipine (sequence 2). The studies were performed at baseline and at the end of either treatment period. Plasma levels of TGF-β1 and ET-1 were determined at the same times and before starting period 2.

Losartan was used at a dose of 25 mg/d for the first week and 50 mg/d for the rest of the period. Amlodipine was administered at a dose of 5 mg/d during the whole study period.

**BP Measurement**

BP was measured every 2 wk at the out-patient department of the Renal Transplant Unit. BP determinations were performed according to World Health Organization recommendations. An automatic oscillometer (HEM-711; OMRON Healthcare, Inc., Vernon Hills, IL) was used to perform three consecutive measurements at 2-min intervals with the patient in supine position. The mean of the three determinations was used for calculations. Mean arterial pressure (MAP) was calculated as \[ \frac{[SBP + 2(DBP)]}{3} \].

All antihypertensive drugs or treatments known to affect BP or renal hemodynamics were discontinued before the run-in period. One and eight patients required doxazosin (2 mg/12 h) to control BP in the active and the wash-out periods, respectively.

**Biochemical Parameters, Hormones, and TGF-β1**

Serum creatinine, serum electrolytes (sodium and potassium), uric acid, total protein (TP), hematocrit (Hct), and white blood cell count were measured by routine techniques (Hitachi, Japan). Plasma renin activity (PRA) was estimated by RIA (Clinical Assay; Baxter, Cambridge, MA) of AngI generated after 3 h of incubation at pH 7.4 and 37°C under conditions to inhibit further conversion of AngI. Plasma concentration of AngII was determined by RIA (Nichols Institute, Whikjen, The Netherlands). Plasma concentration of ET-1 was measured by RIA (Nichols Institute) after extraction on Sep-Pak C18 cartridges (Water Associates, Milford, MA). Plasma samples (1 ml) were acidified with 4% acetic acid (4.5 ml) and applied to cartridges that were preactivated with methanol, distilled water, and 4% acetic acid. The cartridges were then washed with distilled water and 25% ethanol, and immunoreactive ET was eluted twice with 1 ml of 4% acetic acid in 86% ethanol. The eluted ET was then concentrated with distilled water and 25% ethanol, and plasma concentration of ET-1 was determined using a solid phase TGF-β1-specific sandwich ELISA (Quan-
tykine; R&D Systems, Minneapolis, MN). A TGF-β1 standard curve was constructed using 2000, 1000, 500, 250, 62.5, and 31.25 pg/ml recombinant human TGF-β1 protein. The minimum detectable level of TGF-β1 with the test was 7 pg/ml. Thrombomodulin was determined in some random samples to excluded TGF-β1 platelet contamination.

**Renal Hemodynamics and Calculations**

Samples of 4 ml of heparinized blood were taken at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 150, 180, and 240 min after the injection of a bolus of 70 μCi of 131I-orthoiodohippurate and 50 μCi de 125I-iodothalamate to determine the effective renal plasma flow (ERPF) and GFR, respectively. The compartmental model of Sapirstein et al. (12) and Blufoux et al. (13) was used to study the kinetics of 125I-iodothalamate and 131I-orthoiodohippurate.

Gomez’s equations were used to calculate afferent and efferent arteriolar resistance (AAR and EAR, respectively) (14,15). Data such as MAP, GFR, ERPF, renal blood flow (RBF), Hct, and TP were used to estimate quantitatively the intrarenal hemodynamics.

RBF was calculated as RBF(ml/min) = ERPF/(1 – Hct). The filtration fraction (FF) was calculated as FF = (GFR/ERPF) × 100.

Glomerular hydrostatic pressure (P G) was calculated from Gomez’s equations:

\[ P_G = (GFR/K_{FG}) + H_T + 5 \left( \frac{TP \times \log_e \left( \frac{1}{1 - FF} \right)}{1 - FF} - 2 \right) \]

where the filtration coefficient (K_{FG}) of glomerular capillaries was assumed to be 0.0812 (ml/s)/mmHg and the P_{G} in Bowman’s space (H_T) was assumed to be 10 mmHg.

AAR and EAR were calculated from the following equations:

\[ MAP - P_G = (AAR \times RBF)/1328 \]

\[ EAR = (GFR \times 1328)/K_{FG}(RBFG - GFR) \]

**Statistical Analyses**

The study had a standard AB/BA crossover design (in this study, AL/LA: A, amlodipine; L, losartan) (16), with baseline measurements taken at the beginning of the first period for all variables and, in the case of TGF-β1, also before the second period. A logarithmic transformation was applied for TGF-β1 values because TGF-β1 baseline data showed a non-normal distribution (Kolmogorov D_max = 0.299; P < 0.05). The treatment effect, period effect, and treatment-period interaction for logarithm of TGF-β1 were tested by the two-sample t test (17). The analysis of treatment effect, allowing for period effects, was performed by means of a spreadsheet, following the Hills-Armittage approach. The same analysis was used for each variable in the study.

**Results**

Tables 1 and 2 summarize the main biochemical and hemodynamic parameters during the study period.

**Effects on BP**

The control of BP was excellent with both treatments; all patients reached the target BP (<130/85 mmHg). Only one patient required administration of doxazosin during the active treatment period (losartan). Statistically significant differences from baseline were observed in both treatment groups; from baseline MAP, 107.9 ± 6 to 96 ± 10 mmHg with losartan (P < 0.0005) and 92 ± 7 mmHg with amlodipine (P < 0.0001). No significant differences with regard to the control of BP were observed between the two treatments (P = 0.124).

**Effects on Renal Function and Biochemical Parameters**

During the study, no significant changes of biochemical parameters (serum sodium, potassium, uric acid, albumin, TP) were observed with either treatment. Serum creatinine tended to increase slightly during losartan treatment (1.29 to 1.39 mg/dl), but this change was not statistically significant. Creatinine clearance tended to decrease from baseline on losartan and tended to increase on amlodipine, but this was not statistically significant. The difference between the two treatment periods was significant (P = 0.023), however. No significant changes in proteinuria were observed between baseline (108 ±

**Table 1.** Primary results of blood pressure, renal function, PRA, AngII, ET-1, and TGF-β1 during the study periodsa

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Losartan</th>
<th>Amlodipine</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>107.9 ± 6.0</td>
<td>96.0 ± 10.0</td>
<td>92.0 ± 7.0</td>
<td>P = 6.9E-06b; P = 1.4E-06c; P = NSd</td>
</tr>
<tr>
<td>sCr (mg/dl)</td>
<td>1.29 ± 0.3</td>
<td>1.38 ± 0.4</td>
<td>1.22 ± 0.3</td>
<td>P = NSb,c,d</td>
</tr>
<tr>
<td>CrCl (ml/min)</td>
<td>88.1 ± 31.0</td>
<td>82.0 ± 40.0</td>
<td>91.5 ± 42.0</td>
<td>P = NSb,c,d; P = 0.023d</td>
</tr>
<tr>
<td>K+ (mmol/L)</td>
<td>4.1 ± 0.4</td>
<td>4.4 ± 0.5</td>
<td>4.0 ± 0.3</td>
<td>P = NSb,c,d</td>
</tr>
<tr>
<td>Proteinuria (mg/24 h)</td>
<td>108.0 ± 103.0</td>
<td>88.0 ± 75.0</td>
<td>130.0 ± 90.0</td>
<td>P = NSb,c,d; P = 0.01d</td>
</tr>
<tr>
<td>bCsA (ng/ml)</td>
<td>97.1 ± 16.8</td>
<td>101.0 ± 32.0</td>
<td>103.0 ± 28.0</td>
<td>P = NSb,c,d</td>
</tr>
<tr>
<td>PRA (ng/ml per h)</td>
<td>0.42 ± 0.3</td>
<td>2.19 ± 2.6</td>
<td>0.75 ± 0.9</td>
<td>P = 0.008b; P = NSc; P = 0.009d</td>
</tr>
<tr>
<td>AngII (pg/ml)</td>
<td>23.7 ± 7.3</td>
<td>54.6 ± 42.0</td>
<td>32.4 ± 14.0</td>
<td>P = 0.008b,c; P = 0.01c; P = 0.04d</td>
</tr>
<tr>
<td>ET-1 (pg/ml)</td>
<td>7.3 ± 2.9</td>
<td>6.6 ± 2.0</td>
<td>8.2 ± 2.4</td>
<td>P = NSb,c; P = 0.03d</td>
</tr>
<tr>
<td>TGF-β1 (ng/ml)</td>
<td>5.2 ± 4.0</td>
<td>2.6 ± 1.0</td>
<td>4.41 ± 4.1</td>
<td>P = 0.018b; P = 0.09c; P = 0.045d</td>
</tr>
</tbody>
</table>

a Results are expressed as mean ± SD. PRA, plasma renin activity; AngII, angiotensin II; ET-1, endothelin-1; TGF-β1, transforming growth factor β1; MAP, mean arterial pressure; sCr, serum creatinine; CrCl, creatinine clearance; K+, serum potassium; bCsA, cyclosporine blood levels.

b Baseline versus losartan treatment.

c Baseline versus amlodipine treatment.

d Losartan versus amlodipine treatment.
103 mg/dl) and the end of both treatment periods (88 ± 75 with losartan and 132 ± 90 with amlodipine), although there was a significant difference between the two treatment periods (P < 0.01). No changes of the hemoglobin concentration were observed. CsA doses and blood levels did not change during the study periods (baseline, 97 ± 16 ng/ml; with losartan, 101.5 ± 32; with amlodipine, 103 ± 28; P = NS).

**Effects on Renal Hemodynamics**

GFR (iothalamate clearance) was unchanged during losartan treatment (71 to 69 ml/min; P = NS). A statistically significant increase was observed during amlodipine treatment, from 71 to 79 ml/min (P = 0.02). The difference between the two treatments reached statistical significance (P = 0.01). No statistically significant changes were observed in ERPF values during the study periods.

AAR decreased significantly with losartan and amlodipine (10.584 ± 4331 to 7917 ± 4065 and 7073 ± 3479 dyn/s per cm⁻², respectively; P = 0.0002 and 0.00003). There was no difference between the two treatment periods (P = 0.14). A completely different behavior was observed with respect to EAR. EAR at baseline was 2976 ± 951. The EAR significantly decreased with losartan (P = 0.05) and tended to increase with amlodipine (3137 ± 705; P = NS). There was a significant difference between the two treatment periods (P = 0.002).

Estimated P_G was 51.4 mmHg at baseline, 52 mmHg with losartan (P = NS), and 54.5 mmHg with amlodipine (P = 0.0014). The difference between the two treatment groups was significant (P = 0.02).

Significant differences in FF were observed with both treatments. FF at baseline was 23.7% and decreased to 21.4% with losartan (P = 0.07) and to 25.5% with amlodipine treatment (P = NS). The difference between the two treatment periods was significant (P = 0.008).

**Effects on PRA, AngII, and ET-1**

There was a significant increase in PRA during losartan treatment (0.42 ± 0.3 to 2.2 ± 2.6 ng/ml per h; P = 0.008) but not during amlodipine treatment (0.75 ng/ml per h; P = 0.109).

The difference between the two treatment periods was significant (P = 0.009). There was also a significant increase in the AngII concentration with both treatments from a baseline value of 23.7 ± 7.3 to 54.6 ± 42 with losartan (P = 0.008) and 32.4 ± 7 with amlodipine (P = 0.01). The difference between the two treatment periods was significant (P = 0.04). No significant changes in the ET-1 values from baseline were observed in study period, but the difference between these two periods was significant (P = 0.03; ET-1 at baseline, 7.3 ± 2.9 pg/ml; 6.6 ± 2 pg/ml with losartan; 8.2 ± 2.5 pg/ml with amlodipine).

**Effects on TGF-β₁**

The presence of a treatment effect on TGF-β₁ plasma levels was documented (P = 0.011; 95% confidence interval, 1.09 to 1.82). Losartan decreased TGF-β₁ plasma levels between 1.09 to 1.8 times more than amlodipine. The possible presence of a period effect in the sequence of the treatments could be excluded by the results of a period effect test (P = 0.129); the order in the treatments (A/L or L/A) did not change the results. The existence of a treatment-period interaction could also be excluded by the results of a carryover test (P = 0.6, i.e., the results in the first study did not condition the second study. TGF-β₁ plasma levels decreased significantly during losartan therapy (P = 0.018), reaching normal levels after 6 wk of therapy (5.1 ± 4 to 2.63 ± 1.07 ng/ml). During amlodipine therapy, the TGF-β₁ plasma levels tended to decrease (5.3 ± 4 to 4.4 ± 4.1 ng/ml), but this was not statistically significant (P = 0.09). Basal levels at the beginning of both treatment periods were similar, without any significant differences (5.3 and 5.1 ng/ml). The decrease in TGF-β₁ levels during losartan therapy was significantly greater than that observed with amlodipine (P = 0.045).

**Discussion**

In the present study, we demonstrated that despite similar control of BP with both losartan and amlodipine, the effects on renal hemodynamics and on profibrogenic cytokines were different. Whereas amlodipine increased the GFR through an increase in the FF and in the estimated glomerular capillary

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**Table 2. Main results of renal hemodynamic studies during the study periods**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Losartan</th>
<th>Amlodipine</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dl)</td>
<td>3.9 ± 0.2</td>
<td>4.1 ± 0.2</td>
<td>4.0 ± 0.2</td>
<td>P = NS&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>6.5 ± 0.6</td>
<td>6.7 ± 0.4</td>
<td>6.5 ± 0.4</td>
<td>P = NS&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>71.1 ± 29.0</td>
<td>69.0 ± 30.0</td>
<td>79.0 ± 33.0</td>
<td>P = NS&lt;sup&gt;b&lt;/sup&gt;; P = 0.02&lt;sup;c&lt;/sup&gt;; P = 0.01&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>ERPF (ml/min)</td>
<td>300.0 ± 111.0</td>
<td>313.0 ± 108.0</td>
<td>306.0 ± 107.0</td>
<td>P = NS&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>P&lt;sub&gt;G&lt;/sub&gt; (mmHg)</td>
<td>51.4 ± 6.4</td>
<td>52.0 ± 7.5</td>
<td>54.5 ± 7.8</td>
<td>P = NS&lt;sup&gt;b&lt;/sup&gt;; P = 0.014&lt;sup&gt;c&lt;/sup&gt;; P = 0.02&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>FF (%)</td>
<td>23.7 ± 5.9</td>
<td>21.4 ± 5.0</td>
<td>25.2 ± 4.9</td>
<td>P = 0.07&lt;sup&gt;b&lt;/sup&gt;; P = 0.14&lt;sup&gt;a&lt;/sup&gt;; P = 0.008&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>AAR (dyn/s per cm⁻²)</td>
<td>1058.0 ± 4331.0</td>
<td>79170.0 ± 4065.0</td>
<td>70730.0 ± 3479.0</td>
<td>P = 0.00026&lt;sup&gt;b&lt;/sup&gt;; P = 0.00003&lt;sup&gt;c&lt;/sup&gt;; P = 0.14&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>EAR (dyn/s per cm⁻²)</td>
<td>2976.0 ± 951.0</td>
<td>2559.0 ± 648.0</td>
<td>3173.0 ± 705.0</td>
<td>P = 0.05&lt;sup&gt;b&lt;/sup&gt;; P = 0.46&lt;sup&gt;a&lt;/sup&gt;; P = 0.002&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Results are expressed as mean ± SD. GFR, glomerular filtration rate; ERPF, effective renal plasma flow; AAR, afferent arteriolar resistance; EAR, efferent arteriolar resistance; P<sub>G</sub>, glomerular hydrostatic pressure; FF, filtration fraction.

<sup>b</sup> Baseline versus losartan treatment.

<sup>c</sup> Baseline versus amlodipine treatment.

<sup>d</sup> Losartan versus amlodipine treatment.
pressure ($P_G$), losartan did not cause a significant change of GFR but a significant decrease in FF and in estimated $P_G$. Contrasting effects were also observed with respect to plasma levels of the profibrogenic cytokine TGF-$\beta_1$. Losartan caused a significant decrease, whereas amlodipine caused no significant change. The effects on plasma ET-1 concentration also were different: losartan tended to cause a slight decrease and amlodipine a slight increase. This different effect on renal hemodynamics and profibrogenic cytokines between losartan and amlodipine could have potential repercussions for chronic allograft nephropathy.

Hypertension is a very important cardiovascular risk factor in renal transplant patients and has been related clearly to the development of chronic allograft nephropathy. Opelz et al. (3) demonstrated the negative impact of hypertension on graft survival. An inverse relationship was found between the severity of arterial hypertension and graft survival. Following the World Health Organization recommendations (18), control of BP in this specific high-risk population must be strict. SBP and DBP should be lowered to values less than 130/80 mmHg, respectively (19). Although the control of BP is essential in renal transplant patients, many issues remain unresolved. Calcium channel blockers are the most frequently used antihypertensive drugs in renal transplantation, essentially because they are highly effective in the control of BP, are easy to use, and have an acceptable side effect profile (20). The risk of renal artery stenosis and initial reports on transplant patients with a slight increase of serum creatinine on ACEi have limited the use of ACEi or AngII receptor blockers (21,22). In the present study, the control of BP was excellent with both calcium channel blocker and AngII receptor blocker, without any significant difference between the two drugs. Only one patient needed doxazosin during the study period to reach the target BP. Both treatments were tolerated without any relevant side effects. Biochemical parameters or blood levels of CsA did not change during either treatment. With both treatments, BP control was excellent and well tolerated.

Opposite effects on renal hemodynamics were observed: the calcium channel blockers acted exclusively through vasodilatation of the afferent arteriole and the AngIIA through vasodilatation of both the afferent and efferent arterioles. Although the Gomez equations have a limited accuracy, they represent the only available method for determining glomerular hemodynamics in humans (14,15). The vasodilatation of the afferent arteriole achieved with amlodipine tended to be more intensive than that with losartan, but the effects on the efferent arteriole were diametrically opposed: losartan significantly decreased EAR, whereas amlodipine tended to increase it. These contrasting effects on EAR explain the contrasting effects on glomerular hemodynamics. Amlodipine significantly increased GFR in renal transplant patients, whereas losartan maintained GFR. Presumably the increase in GFR during amlodipine was caused by the marked vasodilatation of afferent arterioles, without any change of efferent arterioles, thus increasing FF and estimated $P_G$. In contrast, treatment with losartan was associated with a decrease in FF and estimated $P_G$. These different effects of losartan and amlodipine on glomerular hemodynamics could be important in the genesis of chronic allograft nephropathy, a condition characterized by high FF and $P_G$. High FF and $P_G$ play a role in the genesis of glomerulosclerosis, and this deleterious effect may in part be mediated through the synthesis of several growth factors, such as TGF-$\beta_1$, AngII and ET-1 (23,24). The use of only one kidney for renal transplantation, the immunosuppressive therapy with nephrotoxic side effects, and the progressive increase in the age of organ donors are factors that facilitate the development of a hyperfiltration syndrome. In this scenario, antihypertensive agents that decrease the FF and the PGc could have beneficial effects on the long-term results of renal transplantation.

TGF-$\beta_1$ has also been implicated in the development of chronic allograft nephropathy, inducing interstitial fibrosis and glomerulosclerosis (6). We recently demonstrated that treatment with losartan significantly decreased the plasma levels of TGF-$\beta_1$ in renal transplant patients with chronic allograft nephropathy. The decrease of TGF-$\beta_1$ observed was approximately 50% from the initial levels (25), similar to what is found in different experimental models of renal damage (9). The same effect on TGF-$\beta_1$ plasma levels was also recently demonstrated with ACEi (captopril) in diabetic patients with proteinuria (26). In the present study, we documented that losartan has a similar effect on TGF-$\beta_1$ plasma levels in renal transplant patients with normal function. The decrease in the TGF-$\beta_1$ plasma levels was approximately 50% from the initial level. We emphasize that after 6 wk of treatment with losartan, the plasma levels of TGF-$\beta_1$ were within the normal range. This is the first demonstration that a pharmacologic treatment normalizes the plasma levels of TGF-$\beta_1$. In contrast, no significant changes were observed with amlodipine. The different effects of losartan and amlodipine on this important growth factor and profibrogenic cytokine also could be important in the prevention of chronic allograft nephropathy. Moreover, an opposite effect on ET-1 was observed between losartan and amlodipine. Losartan decreased plasma levels of ET-1; amlodipine tended to increase the concentration of this potent vasoconstrictor and remodeling factor. The different effects of losartan and amlodipine on TGF-$\beta_1$ could partially explain the different effects on ET-1, because in vivo and in vitro studies have demonstrated that AngII and TGF-$\beta_1$ are important stimuli for the synthesis of ET-1 (23,27,28).

In summary, the present study demonstrated that losartan and amlodipine were highly effective in the control of hypertension in renal transplant patients with normal renal function. Analysis of the effects on renal hemodynamics and the plasma concentration of profibrogenic cytokines (TGF-$\beta_1$ and ET-1) suggest that losartan could be more beneficial than amlodipine in interfering with progression of chronic allograft nephropathy than amlodipine. Prospective studies with the use of these drugs in the immediate posttransplant period with consecutive renal biopsies would be the only way to confirm our hypothesis that the blockade of the AngII receptor with losartan could reduce or even prevent the development of chronic allograft nephropathy in renal transplant patients who are treated with calcineurin inhibitors.
Acknowledgments

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