Renal effects of losartan and amlodipine in hypertensive patients with non-diabetic nephropathy

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Abstract

Background. The objective of this study was to examine the effects of angiotensin II receptor blocker losartan versus the calcium channel blocker amlodipine on proteinuria, renal haemodynamics, glomerular sieving and tubular function in hypertensive patients with non-diabetic nephropathy.

Methods. The study design was a prospective, double blind, placebo controlled, randomized crossover trial on renal haemodynamics, proximal tubular function or glomerular sieving properties. ACE inhibitors with amlodipine and losartan. Renal parameters were measured at baseline and at the end of each 4-week active treatment period. Fifteen patients with a diagnosis of non-diabetic renal disease and hypertension were included.

Results. Mean arterial blood pressure decreased from 123 ± 13 mmHg at baseline to 113 ± 10 mmHg (P < 0.01) on losartan and to 114 ± 10 mmHg on amlodipine (P < 0.01). Urinary albumin excretion significantly decreased from 3510 ± 2586 mg/24 h at baseline to 2684 ± 2051 mg/24 h (P < 0.01) on losartan and increased non-significantly to 3748 ± 3355 mg/24 h on amlodipine. Filtration fraction significantly decreased from a baseline value of 22.8 ± 9.3% to 21.2 ± 10.2% (P < 0.05) on losartan and increased to 23.6 ± 8.9% (ns) on amlodipine. Either drug did not significantly alter glomerular sieving of neutral dextrans.

Conclusion. Our results demonstrate that losartan, but not amlodipine, decreased albumin excretion in hypertensive patients with non-diabetic nephropathy.

Key words: albuminuria; amlodipine; glomerular sieving; losartan; non-diabetic disease

Introduction

Short-term evaluation of antihypertensive drugs for renoprotection is often based on the therapy effect on the surrogate endpoint albumin excretion [1]. This short-term effect in reducing proteinuria may reflect a long-term protection of kidney function as demonstrated for ACE inhibitors and some calcium channel blockers [1]. The reduction in albumin excretion is mainly explained by the blood pressure lowering effect of an antihypertensive drug. However, for some classes of antihypertensive drugs, it has been demonstrated additional effects beyond the blood pressure lowering effect to explain the albuminuric sparing effect; an effect on renal haemodynamics, proximal tubular function or glomerular sieving properties. ACE inhibitors have shown to restore sieving function in some studies [2–4], but not all [5,6]. During treatment with verapamil [6], nitrendipine [5], and nifedipine [7], no change in glomerular sieving has been observed. Losartan has been shown to reduce proteinuria in short-term studies comparable to what is observed during ACE inhibition [8–10]. The beneficial effects of Angiotensin II receptor blockers in experimental studies on protein excretion have been proposed to be mediated by an improvement in glomerular sieving [11,12].

However, no studies have examined the effect on sieving function during losartan or amlodipine therapy in man. The objectives of the present study were to investigate the antiproteinuric effect of losartan and amlodipine and to investigate the effect of the drugs on renal haemodynamics, tubular function, and glomerular sieving function, in relation to the effect on protein excretion.

Subjects and methods

Fifteen hypertensive patients (12 male/3 female) with a clinical diagnosis of non-diabetic nephropathy were studied (median age 45, range 20–72 years). One patient had a renal disease due to Wegener disease, the renal disease for the rest of the patients were classified as chronic glomerulonephritis based on biopsy findings. Patients were selected on the basis of increased urinary albumin excretion rate above 200 μg/min on two occasions, mild to moderate hypertension with diastolic blood pressure 90–119 mmHg, and creatinine clearance between 20 and 80 ml/min.

Informed consent was obtained according to the Declaration of Helsinki and the study was approved by the Regional Ethical Committee and also by the Norwegian Medicine Control Authority.
Renal effects of losartan and amlodipine in non-diabetic disease

Study protocol

The study followed a two period crossover design. It consisted of a 4-week run-in period without medication, followed by a 4-week active treatment period with losartan or amlodipine, then a 6-week placebo washout period, and lastly a 4-week crossover period with the alternate treatment. All antihypertensive treatment and any drugs known to affect blood pressure, renal haemodynamics, tubular function or glomerular function (in particular non-steroidal anti-inflammatory drugs and acetylsalicylic acid) were discontinued prior to the run-in period, except for diuretics (furosemide 40–80 mg) at constant dosage necessary for edema treatment. Prior to the run-in period, five patients had been using calcium channel blockers (3 nifedipine GITS, 2 amlodipine), 7 patients ACE inhibitors (three enalapril, four lisinopril), one patient β-blocker (doxazosin) and 3 patients were without antihypertensive medication. At the end of the run-in period, patients were randomized to one of the two sequences for active treatment. Losartan treatment was started at 50 mg once daily and amlodipine at 5 mg once daily. After 1 week of active treatment, if satisfactory blood pressure control was not achieved (DBP decreased by 10 mmHg from baseline and/or DBP fall to <85 mmHg), titration was carried out by doubling of the dose to losartan 100 mg once daily or amlodipine 10 mg once daily at the 1–3 week visits.

At study entry and completion, a complete physical examination and ECG were obtained. Throughout the study, the patients were seen at weekly intervals at the Renal Research Center at the National Hospital, University of Oslo. Blood samples and duplicate 24-h urine samples were collected at the end of the run-in period and at the end of the two active treatment periods. Renal clearance was performed as described below on the last day of the run-in period and the last day of each treatment period. Blood pressure was measured in an identical fashion throughout the study. The actual blood pressure reading was the mean value of the last two of three recordings taken with a standard sphygmomanometer with the patient seated for at least 5 min. Diastolic blood pressure was recorded as the disappearance of Korotkoff sound (phase 5).

Renal clearance studies

Renal clearance examinations were performed on the last day of the run-in period and on the last day of each treatment period. The evening before each clearance study, the subjects ingested 18 mmol of lithium citrate (Litihionit®) in order to obtain a plasma lithium concentration of about 0.3 mmol/l. Two intravenous cannulas were inserted, one for the infusion of inulin and para-amino hippurate (PAH) and the other in the opposite arm for repeat blood sampling. The subjects were initially hydrated orally with 20 ml/kg of tap water, thereafter the patients drank 250 ml of tap water every 30 min to maintain adequate urine flow. A priming dose of 30 ml of inulin (10% solution) and 7 ml of PAH (20% solution) was infused over 10 min followed by a continuous infusion of inulin and PAH designed to maintain blood levels of 200–300 mg/l and 20–40 mg/l, respectively. For the continuous infusion 13 ml of PAH (20% solution) and 54 ml of inulin (10% solution) were mixed with 920 ml of 0.9% NaCl, the infusion rate was 25 to 30 ml each were obtained by spontaneous voiding. Determined by a rate dependent modification of the Jaffé reaction using a creatinine analyser, Beckman creatinine assay kit (Pharmacia, Uppsala, Sweden). Total protein in serum and urine were measured by the biuret method. The sieving function was estimated by clearances of neutral dextrans of different sizes. After the priming dose of inulin, a dose of 130 mg/kg of Rheomacrodex (Pharmacia, Uppsala, Sweden) was infused i.v. over the course of 15 min. Rheomacrodex contains various-size dextrans, 90% ranging between 10 000 and 80 000 dalton, corresponding to a hydrodynamic or viscosity radius of 27 to 75 Å. The size of globular proteins was expressed as Stokes radius or as viscosity radius (hydrodynamic radius) are closely depicted by the Stokes radius of dextran. [13]. However, proteins and dextran do not lie on a common calibration curve when Stokes radius is used as size parameter for dextran [13]. We therefore used the measure of viscosity radius as a measure of globular proteins in solution in the calculation rather than the rather than Stokes radius [7,13]. The viscosity radius is calculated from the formula $R_V = 0.271 \times M^{0.498}$ whereas Stokes radius is given by $R_S = 0.33 \times M^{0.463}$ [13]. The difference appears from the formulas used for calculation and does not represent difference in the dextran method. The clearance of dextrans of different sizes was calculated after size separation by size-exclusion chromatography in serum and urine samples on a XK 16/100 macro-column with Sephacryl S-300 HR gel packed to a bed height of 93-cm (Pharmacia LKB Biotechnology AB, Uppsala, Sweden). The sample size applied on the column was 1 ml both for serum and undiluted urine, each separated into 20–30 fraction and measured the range of 30–60 Å of viscosity radius (each fraction contains dextrans within a range of 2 Å radius). Dextran were hydrolyzed with sulfuric acid and measured by the anthrone methods as described by Scott and Melvin [14]. The column was calibrated using a dextran standard possessing a broad molecular mass distribution, i.e. with a mass average ($M_a$) of 72 300 or number-average molecular mass ($M_n$) of 30 000 giving a polydispersity, $M_a/M_n$ of 2.4, which had been determined by size-exclusion chromatography (Pharco, LKB Biotechnology AB, Uppsala, Sweden). The fractional dextran clearance data were calculated by a data program (Sec-soft; © L. Hagel) with a simple spreadsheet (Excel) [13].

Biochemical analyses

Serum sodium, potassium, chloride, bicarbonate, urea and urine sodium and potassium were measured by an autoanalyzer (Beckman Astra, Sweden). Serum and urine lithium was determined by atomic absorption. Haemoglobin and white blood count were determined by coulter counter. Commercial radioimmunoassay kit (Pharmacia AB, Uppsala, Sweden) and the assay kits determined plasma renin activity and plasma aldosteron. Inulin concentration was determined according to Schreiner [15]. PAH was determined according to Smith [16]. Serum and urine albumin was determined with a radioimmunoassay kit (Pharmacia AB, Uppsala, Sweden). Total protein in serum and urine were measured by the biuret method. Serum and urine β-2-microglobulin were assayed by a commercial radioimmunoassay kit (Pharmacia AB, Uppsala, Sweden). Urine samples for β-2-microglobulin were stored at pH > 6. Normal range for β-2-microglobulin in our laboratory is in serum 1010 to 3010/mg/l and normal excretion in urine is between 0.044 and 0.285 mg/24 h. Creatinine in serum and urine were determined by a rate dependent modification of the Jaffé reaction using a creatinine analyser, Beckman creatinine analyser model 2. Urinary N-acetyl-beta-glucosaminidase
Dextran clearance

Renin activity confirming the compliance during the statistical analyses

Table 1 shows no differences in serum haemoglobin, haematocrit, sodium, chloride, total protein, albumin, creatinine, beta-2-microglobulin, and uric acid from baseline to the end of either treatment period. Losartan therapy was as expected associated with an increase in renin activity confirming the compliance during the study. Serum aldosterone was unchanged from baseline during either treatment. Serum potassium increased significantly (P < 0.05) during losartan treatment.

Effects on blood pressure

The blood pressure measurements are summarized in Table 2. Sixty-nine percent of patients who received both treatments were titrated upwards to the higher dose of losartan (100 mg once daily) and 77% were titrated upward on amlodipine (10 mg once daily).

Mean arterial blood pressure decreased from 124 ± 13 mmHg at baseline to 113 ± 10 mmHg (P < 0.01) on losartan and to 114 ± 10 mmHg on amlodipine (P < 0.01). Diastolic blood pressure was reduced from 105 ± 12 mmHg to 96 ± 11 mmHg on losartan (P < 0.01) and to 96 ± 12 mmHg on amlodipine (P < 0.01) after 4 weeks of treatment. The mean decrease in DBP was similar on both treatments at each relative week. Losartan also significantly reduced systolic blood pressure from a baseline value of 162 ± 20 mmHg to 148 ± 15 mmHg (P < 0.01) after 4 weeks of treatment. Amlodipine reduced systolic blood pressure to 154 ± 17 mmHg (P = 0.09) after 4 weeks of treatment. At the end of the treatment periods there

Table 1. General parameters

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Losartan</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g l⁻¹)</td>
<td>12.4 ± 2.3</td>
<td>12.6 ± 2.8</td>
<td>12.4 ± 2.6</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>37.6 ± 6.8</td>
<td>37.6 ± 8.7</td>
<td>37.3 ± 7.7</td>
</tr>
<tr>
<td>Sodium (mmol min⁻¹)</td>
<td>139 ± 4</td>
<td>138 ± 2</td>
<td>139 ± 2</td>
</tr>
<tr>
<td>Chloride (mmol min⁻¹)</td>
<td>107 ± 5</td>
<td>107 ± 4</td>
<td>107 ± 4</td>
</tr>
<tr>
<td>Potassium (mmol min⁻¹)</td>
<td>4.3 ± 0.4</td>
<td>4.6 ± 0.6*</td>
<td>4.2 ± 0.5</td>
</tr>
<tr>
<td>Total protein (g l⁻¹)</td>
<td>104 ± 4.3</td>
<td>41.6 ± 4.2</td>
<td>39.6 ± 5.7</td>
</tr>
<tr>
<td>Creatinine (µmol l⁻¹)</td>
<td>284 ± 216</td>
<td>300 ± 288</td>
<td>294 ± 247</td>
</tr>
<tr>
<td>beta-2 microglobulin</td>
<td>5131 ± 2717</td>
<td>5554 ± 3416</td>
<td>5410 ± 3157</td>
</tr>
<tr>
<td>Uric acid (µmol l⁻¹)</td>
<td>417 ± 92</td>
<td>394 ± 98</td>
<td>389 ± 87</td>
</tr>
<tr>
<td>Aldosterone (µmol l⁻¹)</td>
<td>1012 ± 563</td>
<td>923 ± 520</td>
<td>1320 ± 1071</td>
</tr>
<tr>
<td>Renin (nmol l⁻¹ h⁻¹)</td>
<td>0.9 ± 0.6</td>
<td>2.6 ± 1.7**</td>
<td>1.4 ± 1.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *P < 0.05, **P < 0.01.

Table 2. Blood pressure responses to losartan and amlodipine

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Losartan</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>162 ± 20</td>
<td>148 ± 15*</td>
<td>154 ± 17</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>105 ± 12</td>
<td>96 ± 11**</td>
<td>96 ± 12**</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>124 ± 13</td>
<td>113 ± 10**</td>
<td>114 ± 10**</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *P < 0.05, **P < 0.01.

Statistical analyses

Efficacy data was based on all patients with data at baseline and both active treatment periods. The blood pressure and laboratory efficacy data were analyzed by the appropriate methods for two-period cross-over clinical trials, using changes from baseline (last observation at the end of the wash-out period), with untransformed data for blood pressures and log transformed data for laboratory data. The mean of two observations taken at two consecutive days was used for 24-h urine collection results. The mean of four observations taken during the 6-h ambulatory blood pressure measurement was used for clearance measurements.

T-tests were used to assess the presence of period and sequence effects, the between-treatment analyses using within-patient (crossover) differences, and the within-treatment changes from baseline using pooled data from both active treatment periods. The between- and within-treatment analyses were adjusted for a period effect. If a significant period (P < 0.05) or sequence (P < 0.10) effect was detected, an additional analysis was performed using only data from the first treatment period.

Untransformed and transformed data were reported as mean values at baseline and on-therapy. All statistical comparisons were based on two-sided tests. Statistical significance was declared if the probability value P was < 0.05 and borderline significance if P > 0.05 and < 0.10. Safety analyses were based on all randomized patients.

Dextran clearance

Wilcoxon’s two-tailed test for paired observations was used to evaluate the differences between the observations for each of the calculated fractional dextran clearances from 30 to 60 A of viscosity radius [20].

Results

General parameters

Table 1 shows no differences in serum haemoglobin, haematocrit, sodium, chloride, total protein, albumin,
were no significant difference in systolic blood pressure level between losartan and amlodipine treatment.

**Effects on albumin and protein excretion**

Urinary albumin excretion rate significantly \((P < 0.01)\) decreased from a baseline value of 3510 ± 2586 mg/24 h to 2684 ± 2051 mg/24 h (27.7% reduction from baseline) on losartan, Table 3. Amlodipine therapy increased albumin excretion to 3748 ± 3355 mg/24 h (n.s.). Mean albumin/creatinine ratio significantly \((P < 0.01)\) decreased from 273 ± 221 mg/mmol at baseline to 215 ± 131 mg/mmol during losartan therapy, whereas there was no change from baseline on amlodipine therapy.

Urinary total protein excretion rate significantly decreased \((P < 0.01)\) from a baseline value of 4.0 ± 2.8 g/24 h to 3.1 ± 2.3 g/24 h on losartan (24.3% reduction from baseline) and increased to 4.5 ± 3.8 g/24 h on amlodipine at week 4. The mean protein 24-h excretion rate was significantly lower \((P < 0.05)\) on losartan compared with amlodipine.

**Effect on renal haemodynamics**

The data are summarized in Table 4. Effective renal plasma flow (ERPF) increased from a baseline value of 192 ± 153 ml/min to 204 ± 172 ml/min on losartan while GFR (inulin clearance) slightly decreased from 37 ± 24 ml/min to 36 ± 287 ml/min. This resulted in a slightly, but significant lower filtration fraction of 21.2 ± 10.2 during losartan therapy compared to baseline filtration fraction of 22.8 ± 9.3. Amlodipine did not change ERPF from baseline (192 ± 153 ml/min vs 196 ± 155 ml/min) nor GFR (37 ± 24 ml/min vs 37 ± 250 ml/min) and no significant change in filtration fraction.

**Effect on renal markers**

The baseline values and the effects of both drugs on renal markers are shown in Table 5. The urinary excretion of markers for proximal tubular function, NAG and ALP, were pathologically elevated in the patients in our study. The proximal markers ALP and NAG were unchanged during either drug period as compared to baseline. The low molecular protein \(\beta\)-2-microglobulin is also excreted in an abnormal high rate in these patients consistent with a proximal tubular dysfunction in patients with nephropathy. The excretion of \(\beta\)-2-microglobulin tended to decrease during losartan therapy and increase during amlodipine therapy, although the changes were not statistically significant. Amlodipine significantly increased lithium clearance from 18 ± 10 ml/min to 23.0 ± 11 ml/min \((P < 0.05)\), whereas losartan therapy was without effect on lithium clearance. Uric acid excretion was not changed during treatment periods. Neither drug affected the excretion of kallikrein. Sodium excretion was unchanged from baseline in either drug period.

**Effect of sieving of neutral dextrans during the clearance periods**

Figure 1 shows the mean clearance values of dextran relative to that of inulin in the 30–60 Å ranges of dextran viscosity radii. Each collected fraction corresponds to a range of 2 Å. No significant change was found at any point between the fractional dextran clearance curve during baseline compared to either the losartan or amlodipine period.

**Discussion**

This study demonstrates that the angiotensin II receptor blocker losartan significantly reduced urinary albumin and total protein excretion rates in hypertensive, non-diabetic patients with nephropathy whereas

Table 3. Twenty-four hour urinary protein excretion in response to losartan and amlodipine

<table>
<thead>
<tr>
<th>Protein Type</th>
<th>Baseline</th>
<th>Losartan</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (mg/24 h)</td>
<td>3510 ± 2586</td>
<td>2684 ± 2051**</td>
<td>3748 ± 3355</td>
</tr>
<tr>
<td>Total protein (g/24 h)</td>
<td>4.0 ± 2.8</td>
<td>3.1 ± 2.3**</td>
<td>4.5 ± 3.8</td>
</tr>
<tr>
<td>Albumin creatinine ratio (mg/mmol)</td>
<td>273 ± 221</td>
<td>215 ± 131**</td>
<td>282 ± 257</td>
</tr>
</tbody>
</table>

Values are mean ± SD. **P < 0.01.

Table 4. Renal haemodynamic responses to losartan and amlodipine

<table>
<thead>
<tr>
<th>Haemodynamic Parameter</th>
<th>Baseline</th>
<th>Losartan</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (Inulin, ml/min)</td>
<td>37 ± 24</td>
<td>36 ± 28</td>
<td>37 ± 25</td>
</tr>
<tr>
<td>ERPF (PAH, ml/min)</td>
<td>192 ± 153</td>
<td>204 ± 172</td>
<td>196 ± 155</td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>22.8 ± 9.3</td>
<td>21.2 ± 10.2*</td>
<td>23.6 ± 8.9</td>
</tr>
</tbody>
</table>

Values are mean ± SD. GFR = glomerular filtration rate. ERPF = effective renal plasma flow. *P < 0.05.

Table 5. Effect of losartan and amlodipine on renal markers

<table>
<thead>
<tr>
<th>Renal Marker</th>
<th>Baseline</th>
<th>Losartan</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium clearance (ml/min)</td>
<td>18 ± 10</td>
<td>22 ± 14</td>
<td>23 ± 11*</td>
</tr>
<tr>
<td>(\beta)-2-microglobulin (mg/24 h)</td>
<td>21 ± 30</td>
<td>19 ± 26</td>
<td>27 ± 37</td>
</tr>
<tr>
<td>NAG (U/mmol/creatinine)</td>
<td>0.7 ± 0.3</td>
<td>0.7 ± 0.4</td>
<td>0.7 ± 0.4</td>
</tr>
<tr>
<td>Kallikrein (U/mmol/creatinine)</td>
<td>2.6 ± 2.6</td>
<td>2.7 ± 3.4</td>
<td>2.8 ± 2.7</td>
</tr>
<tr>
<td>ALP (U/mmol/creatinine)</td>
<td>0.5 ± 0.5</td>
<td>0.5 ± 0.5</td>
<td>0.5 ± 0.6</td>
</tr>
<tr>
<td>Uric acid (mmol/24 h)</td>
<td>2.4 ± 1.3</td>
<td>2.5 ± 1.3</td>
<td>2.8 ± 1.4</td>
</tr>
<tr>
<td>Sodium (mmol/24 h)</td>
<td>156 ± 55</td>
<td>168 ± 63</td>
<td>160 ± 65</td>
</tr>
</tbody>
</table>

Values are mean ± SD. NAG = N-acetyl-beta-glucosaminidase. ALP = Alkaline phosphatase. *P < 0.05.
Fractional dextran clearance, e.g., the urine-to-plasma (U/P) concentration of dextran relative to the U/P ratio of inulin as a function of dextran size, is shown on the abscissa. Dextran hydrodynamic (viscosity) radii are given in Angstroms. The curve marked with full boxes displays the placebo period (reference), the curve marked with open squares represents the losartan period and the curve marked with full circles represents the amlodipine period. The horizontal bars on the curve represent 1 SD.

Amlodipine was without effect. The novel approach in this study was the use of dextran clearance to characterize pore size selectivity during losartan or amlodipine therapy in man.

Effects of angiotensin II receptor blockers on glomerular sieving have been suggested from experimental studies [11,12]. The study of Mayer et al. [11] in the remnant rat model demonstrated that angiotensin II receptor blockade restored glomerular size-selectivity, but not the defect in glomerular charge-selectivity. Remuzzi et al. [12] showed that long-term treatment of diabetic rats with losartan prevented the loss of sieving function of the glomerular membrane as assessed by Ficoll fractional clearance. One could argue that the reduction in proteinuria in our study could be attributed to a change in charge selectivity as the dextran clearance measures only size selectivity. However, the experimental studies indicate that the improvement of sieving function obtained by losartan is probably mediated by restoration of size selectivity [11,12]. The contribution of losartan to the observed antiproteinuric effect is probably not mediated by alterations in glomerular size selectivity, at least not in non-diabetic patients with advanced renal impairment and macroalbuminuria.

The effect on sieving function during ACE inhibition also varies. In patients with non-diabetic renal disease and well-preserved renal function, Remuzzi et al. [3] demonstrated that enalapril improved glomerular size-selectivity. However, in a recent report Hemmelder et al. [6] were unable to show any effect of trandolapril on dextran clearance in non-diabetic patients with proteinuria. Morelli et al. [2] documented that enalapril improved size selectivity in IDDM patients with macroalbuminuria and well-preserved renal function. Remuzzi et al. [4] using enalapril reported similar findings on glomerular permselectivity in patients with IDDM and more advanced renal dysfunction. However, in NIDDM patients with overt proteinuria and reduced renal function Mosconi et al. [5] failed to demonstrate an effect of size-selectivity by perindopril.

The observed antialbuminuric effect of losartan in this study is consistent with results from previous studies that angiotensin II receptor blockers may reduce proteinuria [8–10]. Gansevort et al. [9] indicated that the effect could be due to a fall in intraglomerular pressure and/or changes in glomerular basement membrane characteristics. The unchanged dextran clearance and the reduction in filtration fraction during losartan therapy supports the findings of Gansevort et al. [9] that haemodynamic factor may contribute to the albuminuric sparing effect during losartan treatment. However, with the relatively small reduction in filtration fraction in this study the result should be interpreted with caution. The haemodynamic effects manifested by a fall in filtration fraction are usually more pronounced with ACE inhibitors. This phenomenon may be related to the inactivation of kininase II resulting in an accumulation of bradykinin.

Fig. 1. Fractional dextran clearance, e.g. the urine-to-plasma (U/P) concentration of dextran relative to the U/P ratio of inulin as a function of dextran size, is shown on the abscissa. Dextran hydrodynamic (viscosity) radii are given in Angstroms. The curve marked with full boxes displays the placebo period (reference), the curve marked with open squares represents the losartan period and the curve marked with full circles represents the amlodipine period. The horizontal bars on the curve represent 1 SD.
in albumin excretion is not likely to be mediated by a increased tubular reabsorption of albumin.

The calcium channel blocker amlodipine documented no antiproteinuric effect despite a comparable antihypertensive effect. The effect of amlodipine on proteinuria in patients with reduced renal function and hypertension has previously been reported by August et al. [29]. In a small number of patients who received amlodipine, lowering of blood pressure was associated with a decrease in protein excretion in three patients.

Amlodipine has been applied in several studies regarding microalbuminuria in non-diabetic and diabetic patients. Amlodipine has been demonstrated to have an albumin sparing effect [30] or no effect on albumin excretion [31,32]. This variable effect is in accordance with studies with other calcium channel blockers [1]. As our study is a short-term study it will not rule out a long-term beneficial effect of amlodipine. Dihydropyridines might have some antiproteinuric effects in patients with low albumin excretion, whereas the effect observed in patients with albuminuria in above 500 mg/24 h varies [33].

The glomerular sieving of neutral dextrans during amlodipine therapy has not previously been examined. However, the finding with unchanged glomerular sieving in this study is in accordance with previous studies in man with other calcium channel blockers such as nitrendipine, verapamil and nifedipine [8–10]. Amlodipine affected proximal electrolyte reabsorption as judged by increased lithium clearance. Amlodipine may therefore share this effect with other dihydropyridine calcium channel blocker nifedipine [25]. A potential favourable effect of amlodipine on albumin excretion might therefore be counteracted by suppression of proximal tubular reabsorption of albumin. However, even if a decreased reabsorption of albumin in the proximal tubules could offer some protective effect, the burden of the albumin load to the more distal segments would be augmented.

In conclusion, this study demonstrates that albumin excretion significantly decreased with losartan without changing glomerular sieving properties or tubular function in hypertensive patients with non-diabetic nephropathy. Amlodipine was without effect on albumin excretion.

References

18. Hartmann A, Høloaas H, Steen PA, Kiil F. Evidence for the burden of the albumin load to the more distal segments would be augmented.

In conclusion, this study demonstrates that albumin excretion significantly decreased with losartan without changing glomerular sieving properties or tubular function in hypertensive patients with non-diabetic nephropathy. Amlodipine was without effect on albumin excretion.

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