Enalapril versus metoprolol in primary hypertension—effects on the glomerular filtration rate

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Abstract

Background. Hypertension is a significant cause of end-stage renal failure and effective treatment of hypertensive will reduce the progression rate of chronic renal failure in various kidney disorders. Different classes of drugs may be more effective than others in this respect. In this study we compared the effects on the glomerular filtration rate (GFR) of the ACE-inhibitor enalapril and the betablocker metoprolol in patients with mild and moderate primary hypertension during 6 years.

Methods. Patients with GFR in the normal range (≥80 ml/min/1.73 m² BSA) were included after a placebo treatment period of 4–8 weeks if diastolic blood pressure was 100–120 mm Hg. Target blood pressure was set to <90 mm Hg diastolic. One hundred and thirty patients were randomized in an open parallel study to receive either enalapril or metoprolol. No placebo group was included. GFR was measured using the ^51^Cr-EDTA clearance method and 81 patients completed the study.

Results. At inclusion, there were no significant differences regarding GFR or blood pressure between the groups. The blood pressure treatment goal was reached in all patients and was maintained during the whole observation period. A small but significant fall in GFR by 4 ml/min/1.73 m² BSA was noted in both groups after the first year of treatment but thereafter GFR decreased by only 1 ml/min/year/1.73 m² BSA, in both groups. Body weight, serum uric acid and triglycerides increased slightly with metoprolol treatment but no other differences between the two treatments were noted.

Conclusions. With the blood pressure maintained at the same level using either enalapril or metoprolol during a 6-year study period, GFR decreased to the same extent in the two groups both during the first year and thereafter. The overall magnitude of the GFR decline approached that of the normal age-related decrease of kidney function, i.e. GFR decreased only about 1 ml/min/year. Thus, treatment with an ACE-inhibitor, enalapril, and a beta-blocker, metoprolol, protected the kidney function to the same extent in this 6 year long study in mild and moderate primary hypertension.

Key words: ACE-inhibitors; antihypertensive treatment; beta-blockers; glomerular filtration rate; hypertension

Introduction

Hypertension is often claimed to be a significant cause of end-stage renal failure [1–4]. It has also been shown that effective treatment of hypertension will reduce the progression rate of chronic renal failure in glomerulonephritis, autoimmune disease and diabetes [5–8]. There is surprisingly little information, however, on the decline of kidney function in primary hypertension although recent evidence suggests that the progression decline is very slow indeed [9–11].

Normally, for an individual over 50 years of age the decrease in GFR is ~1 ml/min/year in Scandinavia as determined in a large group of individuals free of renal disease and hypertension [12]. In the case of untreated hypertensive patients there are no well controlled studies in recent decades with regard to decrease in GFR. However, it is a well-known fact that impaired kidney function, in some cases even uremia, was a common complication in primary hypertension when effective antihypertensive drugs were not available [13].

It was first shown for diabetic nephropathy that ACE-inhibitors may confer renal protection over and above what is obtained by lowering the blood pressure, especially in type I [14,15], where the ACE-inhibitors enalapril and captopril have been more beneficial than beta-blockers in protecting the kidney function. Studies have shown that this also might be valid in non-diabetic kidney disorders [16,17].

In 1986, Ljungman and co-workers [9] demonstrated that previously untreated patients with primary hypertension had a significant decline in GFR after 7 years of treatment despite being on effective antihypertensive
treatment using the selective beta-blocker metoprolol as basic therapy. The mean decrease in GFR was 2.5 ml/min/year but it was not clear if the decline was equally distributed over the observation period. At the same time Bauer and co-workers [19,20] showed that GFR in patients with primary hypertension who were treated with the ACE-inhibitor enalapril for several years did not decrease GFR.

The hypothesis was then forwarded that there was a difference in the kidney protection potential between these two classes of drugs. It would be possible to counteract the hypertensive effects on the kidney more effectively using the ACE-inhibitor enalapril compared to the beta-blocker metoprolol. As the two drugs, enalapril and metoprolol, are also the two most used drugs for hypertension treatment in Sweden today, it is obviously of interest to discover even small, long-term differences between these two drugs.

The present study was therefore designed to compare the effects of the ACE-inhibitor enalapril with those of the beta-blocker metoprolol on GFR in a study of 3 years and, if no clearcut response was obtained, continue for another 3 years, i.e. 6 years in total.

Patients and methods

Fifteen centres of general practice and primary health care co-operated in this open, randomised, parallel study over 6 years. Both patients with previously untreated hypertension and patients with previously treated hypertension with β-selective beta-blockade (atenolol, metoprolol) were included after a placebo treatment period of 4–8 weeks before inclusion. Inclusion criteria were a diastolic blood pressure of 100–120 mm Hg and a GFR in the normal range, i.e. >80 ml/min/1.73 m² BSA. The exclusion criteria were earlier stroke or myocardial infarction; angina pectoris, congestive heart failure, claudication and primary renal disease; albuminuria defined as plus two or more with dip-stick, microalbuminuria was not measured; diabetes mellitus or fasting blood glucose >7 mmol/l at two separate occasions; serum cholesterol >8 mmol/l; treatment with NSAIDs on chronic basis; and contraindications for beta-blockade, ACE-inhibitors and/or hydrochlorothiazide.

Patients were randomised to either enalapril 20 mg (Renitec, MSD) or metoprolol 100 mg (Seloken Zoc, Astra) once daily to be taken in the morning at 8 am. Target blood pressure was set to <90 mm Hg diastolic blood pressure. After drug titration the maximal dose was 40 mg of enalapril and 200 mg of metoprolol. If this was not sufficient to control diastolic blood pressure, hydrochlorothiazide 12.5–25 mg o.d. was added. If this was not sufficient to control blood pressure the patient was withdrawn from the study. No other drugs for hypertension treatment were allowed. The treatment period was 6 years.

The study was approved by the Ethics Committee of the Medical Faculty, Göteborg University, Göteborg, Sweden.

A total of 130 patients were randomised into the study and after 3 and 6 years 107 and 81 remained, i.e. 82 and 62% of the patients. There was no difference in drop out rate between the enalapril and metoprolol groups and at the end of the study there were 41 patients on metoprolol and 40 patients on enalapril. Hydrochlorothiazide was added to the treatment with metoprolol in 11 patients and in 9 patients with enalapril in the dose of 19±9 and 13±8 mg/day, respectively. Main reasons for leaving the study were need of other therapy due to uncontrolled hypertension with the study drugs in 4 patients in the metoprolol group and 2 patients in the enalapril group after 3 years and a total of 5 and 3 patients after 6 years. Other reasons for leaving the study were a wish to withdraw and adverse effects, e.g. cough was the reason for withdrawal in 6 patients in the enalapril group. There were no unexpected adverse effects. Only 3 patients were lost to follow-up. Clinical data for the two groups of patients at the start of the study are given in Table 1. There were no differences between the groups regarding any of the variables.

Blood pressure was measured using a mercury manometer after 5 min rest in the supine position and after 1 min in the standing position. Measurements were repeated three times and the average of the last two measurements was calculated for measurements in the supine position. For standing blood pressure only one measurement was made. Patients were instructed not to take the drugs before the blood pressure measurements on clinical visits, which were scheduled for 8–10 am.

After randomisation, patients were seen after 1, 3, 6 and 12 months during the first year and every 6 months during the following 5 years.

Renal function (GFR) measurements were made twice before randomisation within 2 months, every 12 months for the first 3 years, at the end of the study after 6 years. GFR was measured using the plasma clearance of 51Cr-EDTA [21]. The correlation between the two initial GFR measurements is given in Figure 1, demonstrating the high degree of precision of the method. The mean of the two first GFR measurements were used as the baseline value for calculation of the rate of decline of GFR over 6 years. Haematology, serum electrolytes and liver test were performed yearly using standard methods.

Differences between groups were tested using the Student’s t-test. Linear regression was used to calculate decline rate in GFR over time. To detect a statistical significant difference between the treatment groups of 4.5 ml/min in GFR a power of 80% was chosen at the 0.05% level with a two-sided test. Taking the multicenter design into account it was calculated that 130 patients should be randomised to treatment, equally divided between enalapril and metoprolol and that at least 30 patients in each group should complete each treatment.

### Table 1. Baseline characteristics on 130 patients with primary hypertension randomised to E or M. There were no significant differences in any parameter

<table>
<thead>
<tr>
<th></th>
<th>Enalapril</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>63</td>
<td>67</td>
</tr>
<tr>
<td>Male/female</td>
<td>42/25</td>
<td>42/25</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55±8</td>
<td>54±8</td>
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<tr>
<td>Blood pressure</td>
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<tr>
<td>Systolic (mmHg)</td>
<td>162±16</td>
<td>163±15</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
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<td>104±5</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>124±7</td>
<td>124±7</td>
</tr>
<tr>
<td>GFR (ml/min/1.73m²)</td>
<td>94.7±15.8</td>
<td>93.9±4.3</td>
</tr>
<tr>
<td>Uric acid (mmol/l)</td>
<td>310±79</td>
<td>300±84</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>6.4±1.3</td>
<td>6.2±1.0</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.6±1.4</td>
<td>1.5±0.9</td>
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Results

Blood pressure management

Initial systolic and diastolic blood pressures were the same in the two groups and the treatment blood pressure goal was reached in all patients. Mean systolic and diastolic blood pressures during the study are shown in Figure 2a. The mean arterial blood pressure (Figure 2b) was slightly and significantly more reduced in the enalapril group than in the metoprolol group after 12 and 24 months, but not after 30 months and thereafter. The mean systolic and diastolic blood pressure in the two groups during the study were 143\pm13/87\pm5 mm Hg for enalapril and 147\pm12/89\pm6 mm Hg for metoprolol (NS).

At the end of the study 31 patients had only enalapril and 30 patients had only metoprolol while 9 patients had enalapril and 10 patients metoprolol in combination with hydrochlorothiazide.

Glomerular filtration rate

There was no difference in GFR between the two groups when comparing means of the two initial measurements before randomization at the start of the study being 95\pm16 ml/min for the enalapril group and 93\pm14 ml/min for the metoprolol group (NS).

Calculating the rate of decline in GFR in the two groups shows there was no difference as shown in Figure 3. The rate of change of GFR for the whole period was $-1.4 \pm 2.6$ and $-1.1 \pm 2.4$ ml/min/year for enalapril and metoprolol, respectively (NS). Half of the decrease in GFR took place during the first year and the rest during the following 5 years and to the same extent in the two groups. During the last 5 years the mean decline in GFR was <1 ml/min/year.

Calculating the rate of decline for those patients that completed all 6 years yielded similar results as shown in Figure 4. GFR decreased during the first year by $-3.1$ and $-4.1$ ml/min and thereafter by $-0.6$ and $-1.0$ ml/min/year for enalapril and metoprolol, respectively (NS).

Additional observations

During the first 3 years, serum uric acid, triglycerides and body weight increased significantly during metoprolol treatment as shown in Figure 5. These differences then disappeared.

Discussion

With the sophistication of today’s antihypertensive treatment it would be interesting to note any differences
between treatment regimes even if they are small. With the success of ACE-inhibitors came the idea that kidney function might be preserved better with these drugs than with the previous antihypertensive drugs, i.e. ACE-inhibitors may confer renal protection. In fact, this was shown in diabetes mellitus [14,15] and subsequently also in other kidney disorders [16,17].

In mild and moderate primary hypertension representative data are sparse. The most convincing data of progression of kidney function has been given by Ljungman et al. [9,18,26] showing that groups of hypertensive patients defined on an epidemiological basis progressed rather slowly when given effective antihypertensive treatment. Nevertheless, the progression rate for the glomerular filtration rate was more than double that of normal ageing, i.e. 2.5 vs. 1 ml/min/year. Obviously, to detect differences between groups of patients within these narrow limits would require really long term studies and methods with good precision.

We have now concluded a 6-year study aiming at detecting differences in kidney function between the drugs enalapril and metoprolol in mild and moderate primary hypertension. However, we could find no difference in GFR between the two groups of patients over this long period of time. The patients were successfully maintained on the same blood pressure level, i.e. ACE-inhibitors may confer renal protection. In fact, this was shown in diabetes mellitus [14,15] and subsequently also in other kidney disorders [16,17].

We have also observed that the deterioration in kidney function is slower than anticipated from the early studies of Ljungman et al. [9,18]. We would have expected GFR to be reduced by 15 ml/min during the study period of 6 years, but in fact it was only decreased by 7–8 ml/min, i.e. half the anticipated rate of decline. In fact, the rate of GFR decline by 1 ml/min/year in this study with target blood pressure below 90 mm Hg.
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diastolic is no more than could be expected as age-related which was also the findings in a recent study by Fliser et al. [11].

These findings are interesting both from theoretical and practical points of view. Blood pressure reduction to levels of 90 mm Hg or less may eliminate the hypertension damage to the kidneys completely and there seemed to be no difference between metoprolol and enalapril in this respect. The major implication is of course that patients with well treated primary hypertension do not develop chronic renal failure.

A recent study by Himelman et al. [22,23] using a protocol very similar to ours has demonstrated a small difference between the beta-blocker atenolol and the ACE-inhibitor cilazapril in a 3-year study. There were no differences at two years but a small one developed in the third year. For the total period cilazapril decreased by 1 ml/min/year while the progression rate for atenolol was 2 ml/min/year. There is no obvious explanation for this divergent result compared to the present study, but one would have liked to see a longer follow up. Interestingly for enalapril and cilazapril, the results were very much the same, i.e. the rate of GFR decline was 1 ml/min/year, but there may be a small difference between the beta-blockers atenolol and metoprolol to explain the results.

The risk of developing kidney failure in well treated primary hypertensive patients have also been addressed in epidemiological studies. Two studies may be cited in this connection, namely the Framingham Study and the Primary Preventive Trial [24,25] demonstrating a very small risk indeed. In these studies, however, kidney function has only been estimated using the serum creatinine which may conceal a decrease in GFR to some extent. Our results clearly indicate that kidney function is in fact well preserved in treated primary hypertensive patients as the rate of decline in GFR was no more than could be expected from age-dependent decrease in kidney function.

We conclude therefore that the decline rate of kidney function in well treated mild and moderate primary hypertension is in fact indistinguishable from the normal age-dependent rate of decline. There was no difference between the ACE-inhibitor enalapril and the beta-blocker metoprolol in this respect, which may indicate that the control of blood pressure per se is the important factor. In the present study the target diastolic blood pressure <90 mm Hg was maintained during the study period and this excellent blood pressure control might have been important for the results.

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