

Contrasting effects of enalapril and metoprolol on proteinuria in diabetic nephropathy

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Abstract

Objective—To assess whether angiotensin converting enzyme inhibition reduces proteinuria in diabetic nephropathy more than blood pressure reduction with other antihypertensive treatment.

Design—Prospective, open randomised study lasting eight weeks in patients with diabetic nephropathy.

Setting—Outpatient nephrology clinics.

Patients—40 Patients with type I diabetes and diabetic nephropathy with reduced renal function.

Intervention—Antihypertensive treatment with enalapril or metoprolol, usually combined with frusemide.

Main outcome measures—Arterial blood pressure and urinary excretion of albumin and protein.

Results—Arterial blood pressure after eight weeks was 135/82 (SD 13/7) mm Hg in the group given enalapril and 136/86 (16/12) mm Hg in the group given metoprolol. Proteinuria and albuminuria were similar in both groups before randomisation. After eight weeks' treatment, the geometric mean albumin excretion was 0.7 (95% confidence interval 0.5 to 1.2) g/24 h in the patients given enalapril and 1.6 (1.1 to 2.5) g/24 h in the patients given metoprolol ($p < 0.02$). The proteinuria was 1.1 (0.7 to 1.7) and 2.4 (1.6 to 3.6) g/24 h respectively ($p < 0.02$).

Conclusions—Antihypertensive treatment with enalapril reduced proteinuria in patients with diabetic nephropathy more than an equally effective antihypertensive treatment with metoprolol. This points to a specific antiproteinuric effect of the angiotensin converting enzyme inhibitor independent of the effect on systemic blood pressure.

Introduction

Renal failure is the main cause of death in type I (insulin dependent) diabetic patients who have nephropathy.¹ The deterioration in kidney function is accelerated by the hypertension that usually accompanies the kidney disease. Pharmacological reduction of raised blood pressure is today the most powerful intervention to preserve kidney function.² It is not known with certainty, however, whether all antihypertensive drugs are equal in this respect, although angiotensin converting enzyme inhibitors may offer superior protection of renal function.³

To examine this issue further, we randomised 40 patients with diabetic nephropathy to treatment with either the angiotensin converting enzyme inhibitor enalapril or the β_1 selective blocker metoprolol. The aim was to achieve the same blood pressure levels in both groups and compare the effect of the two treatments on proteinuria and on kidney function in the long term. We report the effect of the first two months of treatment.

Patients and methods

Forty patients with type I diabetes and nephropathy were studied. The patients were required to have type I diabetes, diabetic nephropathy, reduced renal

function, and other diabetic complications such as retinopathy. They had a mean age of 42 (range 21-58) years and mean onset of diabetes at 17 (3-39) years of age. The mean duration of diabetes was 25 (13-45) years. All patients had retinopathy, and three patients were blind. The onset and development of the kidney disease had to be typical of diabetic nephropathy. If there was any suspicion of other renal disease then kidney biopsy was performed. This was done in four patients showing diabetic nephropathy only. Presence of hypertension was not an inclusion criteria, but only two patients were not being treated for hypertension before the study. The glomerular filtration rate was lower than our age adjusted normal value⁴ but higher than 24 ml/min/1.73 m².

Twenty two patients were randomised to enalapril and 18 to metoprolol. The initial goal was to include 60 patients but because previous treatment with angiotensin converting enzyme inhibitor was a criterion for exclusion there was a diminishing number of eligible patients in the participating centres owing to the increasing popularity of these drugs. The inclusion of new patients was therefore stopped after two years and 40 subjects. The study was performed after the patients' informed consent and approval by the local ethical committee had been obtained.

TREATMENT

Two weeks before the study, previous antihypertensive treatment was stopped except for frusemide. If this was considered unsafe, medication could be continued until two days before randomisation. The randomisation into two groups was done separately in the three centres and was stratified in three subgroups depending on renal function to ensure balance in this respect. On the day of the randomisation the patients received 5 mg enalapril or 50 mg metoprolol daily in addition to frusemide if it had been used before. Blood pressure was measured during the four hours after the first dose. The goal was a mean arterial blood pressure between 90 and 110 mm Hg when patients were supine. The dose of enalapril was doubled every week to the final dose of 20, 10, or 5 mg if the glomerular filtration rate was >50 , 30-50, or <30 ml/min/1.73 m² respectively. The dose of metoprolol was doubled every week to a maximum of 200 mg if the blood pressure was not satisfactory. If the blood pressure was not within the limits that had been set the dose of frusemide was increased or decreased. If necessary, hydralazine could be added.

We measured blood pressure and urinary protein and albumin excretion at baseline and weeks 1, 2, 3, 4, and 8; serum creatinine, sodium, and potassium concentrations at baseline and weeks 4 and 8; plasma renin activity at baseline and week 4; and haemoglobin A_{1C} concentration at baseline and week 8.

Blood pressure was measured with a mercury sphygmomanometer by a nurse after the patient had rested for five minutes in the supine position and after one minute of standing. The mean of two readings on each occasion was used. Mean arterial pressure was calculated as diastolic blood pressure plus one third of

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the difference between systolic and diastolic blood pressure and is shown as the mean of standing and supine values unless otherwise stated.

Urinary protein excretion was measured in 24 hour collections of urine with the biuret method. Albumin excretion was measured by immunochemical turbidometric assay, electrophoresis, or immunoprecipitation assay, depending on the hospital. Plasma renin activity was measured by radioimmunoassay.⁴ The reference range in a group of healthy people was 0.2-1.2 nmol/l/h. The glomerular filtration rate was measured before the study as the rate of disappearance of chromium-51 edetic acid in plasma after a single injection.

STATISTICS

Results are presented as means (SD or range) except urinary albumin and protein excretion, serum creatinine concentration, and plasma renin activity, which are expressed as geometric means (antilog 95% confidence interval of the logarithms). Student's two tailed *t* test for paired and unpaired comparisons was used. Urinary albumin and protein excretion, serum creatinine concentration, and plasma renin activity were analysed after log transformation because of the skewed distributions, and significance was taken as $p < 0.05$. Multiple linear regression analysis was used to determine the influence of mean arterial pressure and type of treatment on change in urinary albumin and protein excretion, which was fairly normally distributed, and on absolute values of urinary protein and albumin after log transformation. In addition, a sliding mean value method was used to describe the relation between blood pressure and urinary albumin and protein excretion. All urinary protein and albumin values were ranked according to the mean arterial pressure measured at the same time. A geometric mean was calculated on both albuminuria and proteinuria values for ranked measurements 1-19, and the mean of the corresponding mean arterial pressures was calculated; then calculations were made on ranked measurements 2-20, and so on. The successive points were joined to form curves for the enalapril and the metoprolol patients (see fig 2). The sliding mean

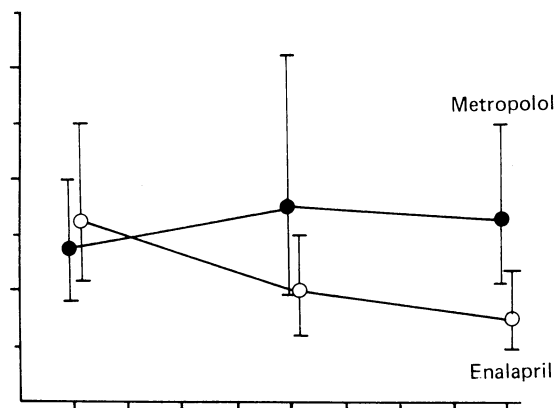


FIG 1—Blood pressure in 40 patients with diabetic nephropathy treated with enalapril or metoprolol. Values are means (SD) and are the mean of supine and standing blood pressure

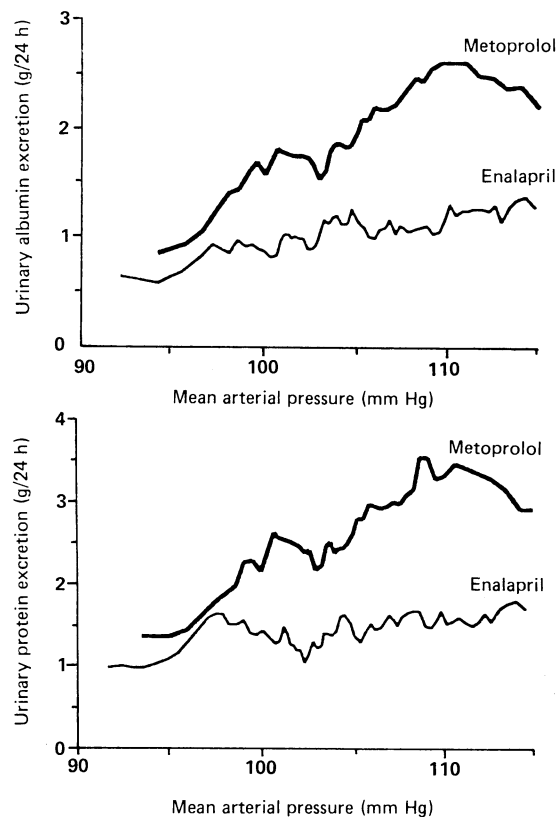


FIG 2—Relation between mean arterial pressure and albuminuria (top) and proteinuria (bottom) in 40 patients randomised to treatment with either enalapril or metoprolol. Lines represent sliding mean values of relation between all simultaneous measurements of mean arterial blood pressures and urinary albumin and protein excretion during treatment

Effect of two months' treatment with enalapril or metoprolol in 40 patients with diabetic nephropathy. Values are means (SD) except for urinary protein and albumin values, serum creatinine concentration, and plasma renin activity, which are geometric means (antilog 95% confidence interval of the logarithms)

	Baseline	4 Weeks	8 Weeks
Supine blood pressure (mm Hg):			
Enalapril group	163/96 (17/9)	148**/87** (14/6)	141**/83** (13/8)
Metoprolol group	161/91 (25/9)	155/90 (23/8)	148*/89 (18/12)
Standing blood pressure (mm Hg):			
Enalapril group	147/91 (18/9)	131**/84** (15/8)	128**/81** (16/8)
Metoprolol group	140/87 (20/9)	128/83 (19/9)	123**/83 (19/13)
Mean arterial pressure (mm Hg)†:			
Enalapril group	114 (8)	103** (5)	99 (7)**
Metoprolol group	109 (10)	105 (10)	102 (11)*
Urinary protein excretion (g/24 h):			
Enalapril group	2.0 (1.3 to 3.0)	1.3 (0.8 to 2.1)**	1.1 (0.7 to 1.7)**‡
Metoprolol group	2.0 (1.4 to 2.8)	2.2 (1.5 to 3.2)	2.4 (1.6 to 3.6)
Urinary albumin excretion (g/24 h):			
Enalapril group	1.6 (1.1 to 2.5)	1.0 (0.6 to 1.5)*	0.7 (0.5 to 1.2)**‡
Metoprolol group	1.4 (0.9 to 2.0)	1.7 (1.0 to 3.1)	1.6 (1.1 to 2.5)
Serum creatinine (μmol/l):			
Enalapril group	159 (138 to 183)	168 (142 to 200)	171 (147 to 200)*
Metoprolol group	142 (123 to 164)	146 (125 to 170)	146 (125 to 171)
Serum sodium (mmol/l):			
Enalapril group	138 (5)	138 (4)	137 (4)
Metoprolol group	138 (4)	138 (3)	137 (3)
Serum potassium (mmol/l):			
Enalapril group	4.4 (0.5)	4.7 (0.5)*	4.8 (0.6)**‡
Metoprolol group	4.3 (0.4)	4.8 (0.5)**	4.2 (0.5)
Haemoglobin A _{1c} (%):			
Enalapril group	9.3 (1.6)		9.4 (1.9)
Metoprolol group	9.6 (2.1)		9.4 (2.4)
Plasma renin activity (nmol/h):			
Enalapril group	1.5 (1.2 to 2.0)	5.6 (3.6 to 8.6)	
Metoprolol group	1.7 (1.1 to 2.6)	1.2 (0.8 to 1.7)**	

* $p < 0.05$, ** $p < 0.01$ v baseline.

†Based on mean of supine and standing blood pressure.

‡ $p < 0.02$, enalapril v metoprolol.

calculations and graphs were made with Cricket Graph (Cricket Software, Malvern, Pennsylvania).

Results

After randomisation two patients given metoprolol were withdrawn from the study because of adverse reactions, but they are included in the results for as long as they participated. The first patient had a severe hypotensive response after the first 50 mg dose of metoprolol. The second patient had unacceptable drowsiness and was withdrawn from the study after two weeks' treatment.

On the day before randomisation the enalapril patients were treated with 58 (range 0-160) mg of frusemide and the metoprolol group with 117 (0-375) mg. After eight weeks the group given enalapril was treated with 96 (0-500) mg frusemide and 11 (SD 6) mg enalapril. The group given metoprolol received

168 (0-500) mg frusemide and 138 (67) mg metoprolol. One patient in the group given metoprolol was also given hydralazine, 75 mg daily. The table shows the results.

BLOOD PRESSURES

After the first dose the blood pressure fell in both groups to the same extent. During eight weeks' treatment similar blood pressure levels were obtained in both groups (table, fig 1). Systolic blood pressure was significantly reduced at eight weeks in the group given metoprolol (fig 1; $p < 0.01$). In the group given enalapril both the systolic and diastolic blood pressure was significantly reduced throughout. There were no significant differences in blood pressure between the groups.

The reduction in blood pressure compared with baseline was significantly higher in the patients given enalapril as they had had slightly higher blood pressure before randomisation than the patients given metoprolol. The fall in orthostatic blood pressure during treatment tended to be smaller in the patients given enalapril. Four hours after the first dose was given the mean arterial pressure fell a mean of 7 (12) mm Hg in the patients given enalapril and 16 (10) mm Hg in the patients given metoprolol ($p < 0.05$), and it differed significantly between the two groups after the first week of treatment, falling by 6 (8) mm Hg and 12 (9) mm Hg, respectively ($p < 0.05$).

PROTEIN EXCRETION

The urinary albumin and protein excretion decreased to half the initial value in the patients given enalapril but did not change in those given metoprolol (table). After eight weeks the urinary protein excretion was significantly correlated with mean arterial blood pressure ($r = 0.37$; $p < 0.05$). The reduction in proteinuria and albuminuria was, however, not correlated with the reduction in mean arterial blood pressure in all patients or in either group.

Thus both the type of treatment and blood pressure were related to proteinuria. This dual relationship between proteinuria, type of treatment, and mean arterial pressure is shown in figure 2. After further analysis with multiple linear regression both mean arterial pressure and the type of treatment were correlated with excretion of albumin and protein at eight weeks ($p < 0.05$ for both variables). In addition, when all simultaneous albumin excretion values and mean arterial pressure measurements throughout the study were analysed together, both the type of treatment and mean arterial pressure were correlated with albuminuria or proteinuria ($p < 0.001$ for both explanatory variables). With the same analysis, the type of treatment was related to reduction in albuminuria after two months ($p < 0.01$) but not to reduction in mean arterial pressure ($p = 0.56$). The same applied to reduction in proteinuria ($p < 0.01$ and $p = 0.71$, respectively). Generally, protein excretion was more closely correlated with mean arterial pressure, calculated as the mean of supine and standing blood pressure, than with either supine or standing mean arterial pressure. The initial frusemide dose was not correlated with proteinuria ($r = 0.057$).

Laboratory values—The glomerular filtration rate before the study was 48 (15) ml/min/1.73 m² in the patients given metoprolol and 46 (14) ml/min/1.73 m² in those given enalapril. Serum creatinine concentrations increased slightly but significantly in the patients given enalapril but not in those given metoprolol (table). Serum potassium rose after enalapril was given. There was no change in haemoglobin A_{1c} concentration in either group. The baseline plasma renin activity was significantly higher in patients than

in healthy controls ($p < 0.01$), and increased in the group given enalapril and decreased in the group given metoprolol.

Discussion

This study showed that proteinuria and albuminuria could be reduced by two months' treatment with enalapril to less than half the values obtained in a control group treated with metoprolol. As expected, higher blood pressure was linked to more proteinuria. The blood pressure was similar in both groups, and it is likely that the lower level of proteinuria during treatment with enalapril is produced by a mechanism independent of systemic blood pressure. This pressure independent effect is shown in figure 2. It seems plausible that this is an effect of changes in the renal haemodynamics caused by these drugs. Angiotensin converting enzyme inhibitors can induce and increase in renal blood flow without a concomitant reduction in glomerular filtration rate in this category of patients.³ This leads to a decrease in filtration fraction, which probably reflects a lowering of glomerular filtration pressure.

Reduction of blood pressure with different antihypertensive drugs in patients with incipient or overt diabetic nephropathy leads to a reduction in urinary protein excretion.^{2,6-8} Treatment with an angiotensin converting enzyme inhibitor usually⁹⁻¹⁵ but not always¹⁶⁻²⁰ results in reduced proteinuria in these patients. The experimental design in these studies, however, failed to distinguish between the effect of blood pressure reduction itself and other effects of angiotensin converting enzyme inhibitors; no control groups given other types of antihypertensive treatment were used.

Insua *et al*, however, made this comparison and investigated the effect on microalbuminuria of six weeks' treatment with captopril in eight type I diabetic patients and of nifedipine in seven and found that captopril reduced but nifedipine increased microalbuminuria.²¹ In contrast, Baba *et al* found nicardipine to be as effective as enalapril in reducing microalbuminuria in seven type II diabetic patients.²² One explanation for these diverging results is given by Heeg *et al*, who found that lisinopril reduced proteinuria in patients with the nephrotic syndrome only if sodium was reduced in the patients' diet.²³ This indicates that an active renin-angiotensin system enhances the anti-proteinuric effect of angiotensin converting enzyme inhibitors. As higher renin concentrations could be anticipated in the patients with type I diabetes studied by Insua *et al*²⁴ they could have been more susceptible to this effect of the angiotensin converting enzyme inhibitor than the type II diabetic patients in the study by Baba *et al*. The baseline plasma renin activity was higher in the present study than our normal value. We found earlier that patients with type I diabetes and nephropathy had higher renin levels than patients with other types of renal disease provided that overhydration was treated with frusemide.²⁵ In our previous prospective long term study of captopril in patients with diabetic nephropathy we did not observe an anti-proteinuric effect of that angiotensin converting enzyme inhibitor.³ Most patients showed a reduction in proteinuria, but this did not reach statistical significance during the long term follow up.

In the present study the reduction in blood pressure in the patients given enalapril was somewhat greater than in those given metoprolol owing to a tendency to higher blood pressure before the study in those given enalapril. The blood pressure was comparable in both groups during treatment, so this is unlikely to explain the difference in level of proteinuria. During treatment, both blood pressure and treatment with enalapril had a

significant influence on the degree of proteinuria, as shown in figure 2. There was no correlation between the fall in blood pressure and the reduction in proteinuria in either group or in the whole study population. The mean supine and standing blood pressure was best correlated with proteinuria and may therefore reflect the blood pressure throughout the day more accurately than either supine or standing blood pressure.

Although the blood pressure was similar for both treatments a tendency to higher supine and lower standing blood pressure was found in the group given metoprolol. When this was calculated as the orthostatic fall in blood pressure, there was a trend towards more orthostatic hypotension in the group given metoprolol, and this difference was significant after the first test dose and after one week. Enalapril therefore offers an advantage in this respect in these patients, who are prone to orthostatic hypotension. Enalapril was well tolerated, but two patients given metoprolol had side effects severe enough to require withdrawal of metoprolol.

The group given enalapril showed a small increase in serum creatinine concentration. If this represents a true fall in glomerular filtration rate the reduction is too small to explain the 56% reduction in albuminuria in this group. For unknown reasons there was a transient increase in serum potassium concentration in the group given metoprolol at four weeks. In the group given enalapril serum potassium concentration rose at eight weeks, although this increase was moderate and did not necessitate change of treatment in any patient. However, this supports the conclusion that angiotensin converting enzyme inhibitors should be used in these patients only after treatment with a diuretic, to ensure that they do not develop hyporeninaemic hypoaldosteronism, which could aggravate hyperkalaemia. It has been argued that diuretic treatment might increase proteinuria and worsen the prognosis in diabetic nephropathy,²⁶ but this fear does not seem warranted because the lowest rate of deterioration so far reported in diabetic nephropathy is during treatment with a combination of antihypertensive drugs including high doses of frusemide.² It can also be speculated that the antiproteinuric effect of enalapril might have been smaller without pretreatment with a diuretic.²³

It is uncertain whether reducing proteinuria will benefit the kidneys in the long term, but it seems logical to assume that this antiproteinuric effect reflects a beneficial effect on mechanisms harmful to the kidneys. In addition, proteinuria, irrespective of origin, has been claimed to perpetuate the process of glomerulosclerosis.²⁷

Our results points to the conclusion that angiotensin converting enzyme inhibitors reduce proteinuria in diabetic nephropathy by a mechanism independent of the effect on systemic blood pressure. Whether the specific renal effects of angiotensin converting enzyme inhibitors lead to better preservation of kidney function, as indicated in our previous report,³ has to be verified by long term studies.

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ONE HUNDRED YEARS AGO

The danger of kissing a greasy book, so often tendered in police and law courts to a witness about to be sworn, is at last appreciated by some officials and in some quarters. We see it stated that when the Duke of Fife appeared lately at Stratford in a prosecution the Testament on which he took the oath was enveloped in some clean white paper for his use—a precaution

which might with advantage be more generally adopted. Why should not the formula and method of taking the oath in English Courts of Justice be altered and adopted, possibly in imitation of the method adopted in Scotland, which is that of raising the hand in lieu of kissing the book? (*British Medical Journal* 1890;i:1494.)