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Renal hemodynamics and reduction of proteinuria by a vasodilating beta blocker versus an ACE inhibitor

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Renal hemodynamics and reduction of proteinuria by a vasodilating beta blocker versus an ACE inhibitor. The effects of a nonselective beta-adrenergic blocking drug with beta-2 agonist activity (dilevalol 200 mg) on proteinuria and renal hemodynamics were evaluated in a double-blind crossover study versus an ACE inhibitor (enalapril 5 mg) in eight patients with glomerulonephritis, moderate renal function impairment and proteinuria >1 g/24 hr. Patients were studied after a one week placebo phase while off all other medications, except steroids in a few cases, and after three weeks of treatment. A 10-day placebo washout period was included between the various drug treatments. During each period renal hemodynamics were measured by clearance techniques, and urinary protein excretion as well as fractional clearance of albumin and IgG were determined. Both drugs reduced mean arterial pressure and proteinuria to a similar extent [mean arterial pressure: placebo 108 ± 13 mm Hg; dilevalol 103 ± 11 mm Hg ($P < 0.05$); enalapril 103 ± 12 mm Hg ($P < 0.05$); protein excretion: placebo 5.1 ± 4.2 g/day; dilevalol 3.3 ± 3.0 g/day ($P < 0.05$); enalapril 2.8 ± 2.8 g/day ($P < 0.05$)]. The antiproteinuric effect was greater with enalapril than dilevalol. Dilevalol reduced GFR [baseline inulin clearance: 73.3 ± 38 ml/min/1.73 m^2; after dilevalol: 63.3 ± 28 ml/min/1.73 m^2 ($P < 0.05$)] and the decrease of proteinuria correlated positively with the reduction of GFR. Enalapril did not significantly lower the GFR (inulin clearance during enalapril 66.8 ± 23 ml/min/1.73 m^2) and the reduction of proteinuria did not correlate with the lowering of the GFR. Renal blood flow was not significantly changed either by enalapril or by dilevalol (baseline levels of PAH clearance: 363 ± 182 ml/min/1.73 m^2; after dilevalol 382 ± 185 ml/min/1.73 m^2 and after enalapril 397 ± 159 ml/min/1.73 m^2). Enalapril reduced the albumin excretion rate but dilevalol did not [baseline levels: 1.5 ± 1.0 mg/min, dilevalol 1.3 ± 1.0 mg/min, enalapril 0.9 ± 1.2 mg/min ($P < 0.05$)]. In conclusion, both drugs reduce proteinuria in patients with moderate renal function impairment and proteinuria >1 g/24 hr and show similar effects on hemodynamics. This reduction is supposed to be related to a reduction of GFR and FF in case of dilevalol. Enalapril showed a more pronounced reduction of proteinuria, which could be based on an increased charge selectivity of the glomerular barrier.

Proteinuria is considered to reflect damage of the glomerular capillary wall and glomerular hypertension in a variety of diseases involving the kidney [1, 2]. Drugs which are able to reduce proteinuria showed favorable effects on the progression of renal disease [3]. In the last few years a lot of work has been done concerning the effects of angiotensin converting enzyme inhibition with regard to this problem, especially in the rat model [3, 4]. ACE inhibiting drugs were also investigated in humans in conditions accompanied by proteinuria: diabetic nephropathy [5], glomerulonephritis [6, 7], hypertension [8, 9] and proteinuria associated with kidney transplantation [10]. Although mostly shown in retrospective studies with small sample sizes ACE inhibiting drugs seem to be able to reduce proteinuria and may preserve renal function in these conditions [8, 9, 11, 12]. These beneficial effects of ACE inhibition are considered to be based on its ability to reduce glomerular pressure by dilating the efferent arteriole of the glomeruli [2, 4, 6, 12, 13]. As this model has been developed in animal studies, there are doubts whether it may be applied to humans, too. Further investigations focused on alternative explanations indicated the presence of a possibly inherent impact of ACE inhibitors on the permeability of the membrane barrier itself [1, 13–15].

Dilevalol is a new antihypertensive drug with a dual mechanism of action combining vasodilatation due to selective β_2-agonism, with nonselective β-antagonism. In normal individuals and hypertensives without impairment of renal function dilevalol had no influence on GFR, ERPF, renal blood flow or renal vascular resistance [16]. In patients with some degree of renal involvement ERPF was maintained whereas GFR and FF were significantly reduced [17]. In contrast to other beta blocking agents renal vascular resistance was reduced by dilevalol [17, 18]. This closely resembles effects of ACE inhibiting drugs in patients with proteinuria and moderate renal function impairment [6]. The purpose of our study was to clarify whether drugs like dilevalol could mimic ACE inhibiting actions on renal hemodynamics and protein excretion, and to study the mechanism of reduction of proteinuria in patients with proteinuria and normal or moderately impaired renal function.

We investigated eight patients with proteinuria because of glomerulonephritis and moderately reduced renal function in a double-blind crossover mode. They received either dilevalol or enalapril, a long-acting angiotensin converting enzyme inhibitor, for a period of three weeks. Renal function and hemodynamics were investigated after a one week placebo phase and after both treatment periods.

Methods

Patients

Eight patients (3 females, 5 males) were enrolled in this study; their mean age was 30 ± 9 years. Informed consent was obtained and the study was approved by the Ethics Committee.

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Table 1. Patient characteristics at entry of the study

No	Sex	Age *years*	Diagnosis	MAP *mm Hg*	Medication	Creatinine *mg/dl*
1	W	30	MGP	101	Prednisolone	2.1
2	M	23	MSPGN	133	Nifedipine	1.3
3	W	31	FSGS	96	—	1.1
4	M	35	MGP	92	—	1.1
5	M	26	MGP	102	Thiazide	1.0
6	M	25	MGP	109	Thiazide	1.5
7	W	23	MSPGN	102	Prednisolone	0.9
8	W	50	FSGS	110	Nifedipine	1.0
Mean		30		106		1.3
SD		9		13		0.4

Abbreviations are: MGP, membraneous glomerulopathy; FSGS; focal segmental sclerosis; MSPGN, mesangioproliferative glomerulonephritis; SD, standard deviation.

Table 2. Blood pressure, protein excretion and renal hemodynamics during therapy with placebo, dilevalol and enalapril

	Placebo	Dilevalol	Enalapril
MAP *mm Hg*	108 ± 13	102.5 ± 11[a]	103 ± 12[a]
Protein excretion *g/day*	5.1 ± 4.2	3.3 ± 3.0[a]	2.8 ± 2.8[a]
Inulin clearance *ml/min/1.73 m²*	73.3 ± 38	63.2 ± 28[a]	66.8 ± 23
PAH clearance *ml/min/1.73 m²*	363 ± 182	382 ± 185	397 ± 159
Filtration fraction $C_{In}/C_{PAH} \times 100\%$	21 ± 9	17.4 ± 7[a]	18.1 ± 9[a]
Renal blood flow *ml/min/1.73 m²*	485 ± 312	500 ± 284	502 ± 230
Renal vascular resistance *dyn · sec · cm⁻⁵/1.73 m²*	22824 ± 11234	20457 ± 9611	19274 ± 7702

Abbreviation is MAP, mean arterial blood pressure.
[a] $P < 0.05$ compared to placebo

All subjects had a normal or only mildly impaired renal function, mild arterial hypertension and proteinuria above 1 g/day, with serum protein levels not lower than 55 g/liter. Two patients took diuretics because of mild edema for at least one year, two patients were on nifedipine because of mild hypertension and two others were on a long-term corticoid therapy. All drugs except prednisolone were discontinued at the beginning of the study. Patient characteristics are listed in Table 1. In all cases diagnosis was proven by renal biopsy. All patients were allowed to continue their normal diet (protein intake nearly 80 to 100 g/day; sodium intake nearly 10 g/day, fluid intake nearly 2000 ml/day). The sodium and protein content of the diet was unchanged. Except for the substances under investigation there was no concomitant medication.

Study protocol

All patients were followed in our hypertension and nephrology unit on an out-patient basis. To obtain stable data, blood pressure was measured at least three times at entry of the study (Table 1). All medication except for corticoids was withdrawn at least two weeks before the start of the study. After a seven-day placebo period the patients were initially investigated clinically and blood samples for laboratory assays were drawn. Patients were without medication for three weeks except for steroids in two instances. During the following three weeks patients received the first drug (dilevalol 200 mg or enalapril 5 mg) in a double-blind fashion followed by another thorough examination. Blood pressure measurements were obtained daily by the patients themselves for the whole study period every morning before drug intake, and in the morning of

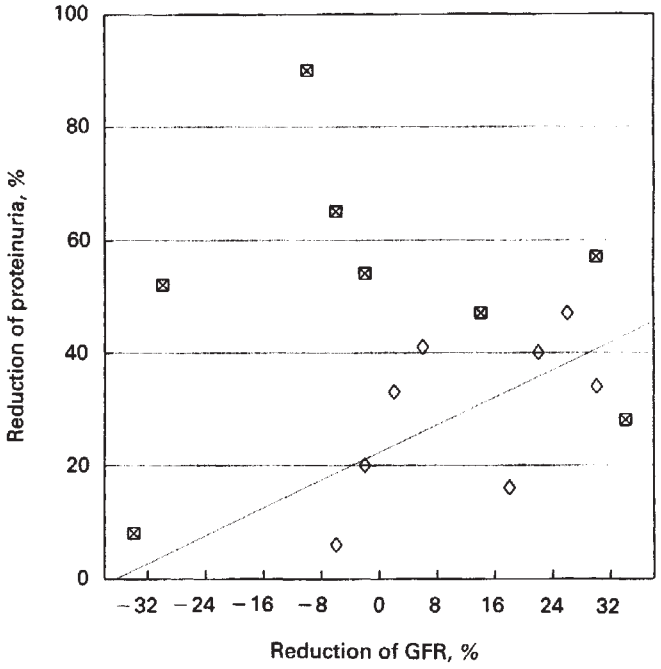

Fig. 1. *Correlation between reduction of proteinuria and reduction of GFR.* Symbols are: (◇) dilevalol group, rs = 0.86; (⊠) enalapril group, rs = 0.48.

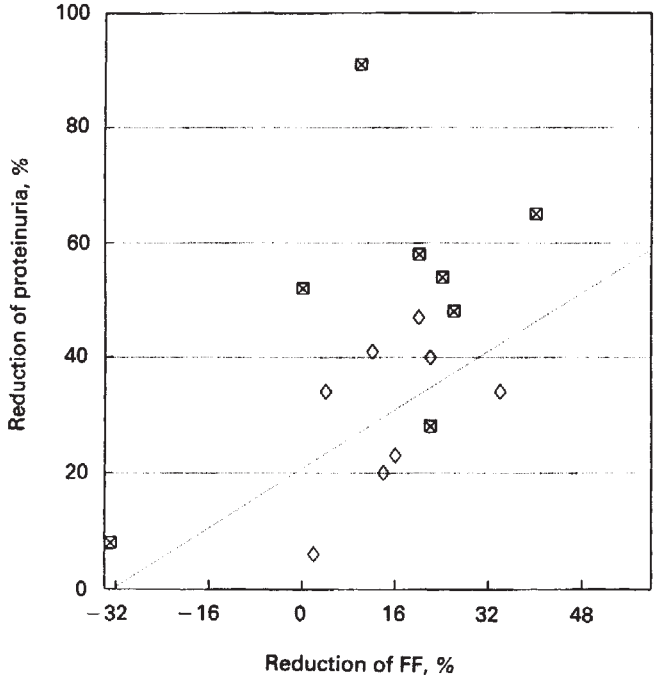

Fig. 2. *Correlation between reduction of proteinuria and reduction of FF.* Symbols are: (◇) dilevalol group, rs = 0.48; (⊠) enalapril group, rs = 0.19.

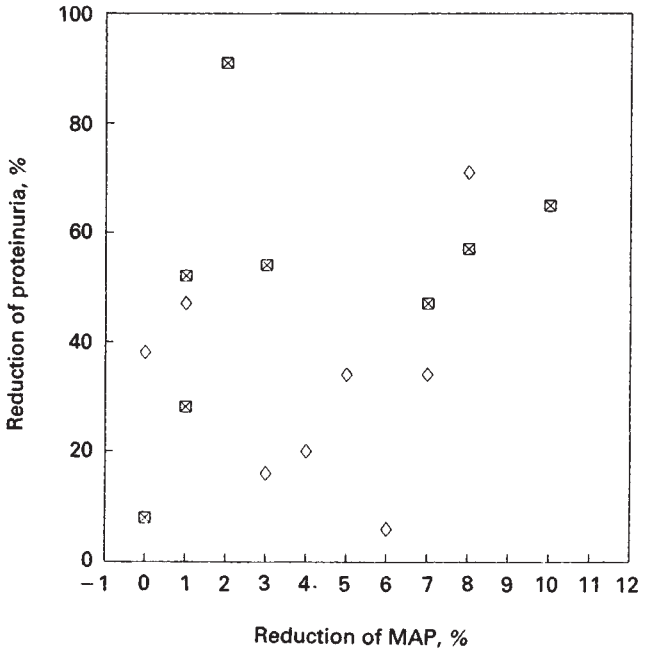

Fig. 3. *Correlation between reduction of proteinuria and reduction of MAP.* Symbols are: (◇) dilevalol group; (⊠) enalapril group.

each hospital visit. The blood pressure levels were obtained as mean values of these measurements (Table 2). Before entering the next treatment phase patients received placebo medication for 10 days. Subsequently another three week period of medication ensued.

Proteinuria was assessed after a three-day collection period starting at the fifth day of placebo intake and after 19 days of medication. The values of proteinuria given in Tables 2 and 4 were obtained from these three-day collection periods and are expressed as mean values ± SD. The differences between the collecting days were less than 10%. During out-patient follow-up, drugs were administered after blood pressure recordings and blood sampling had been finished, and just before starting the clearance measurements. Blood was also drawn for measurement of hormone activities (renin, aldosterone). Additionally, glomerular filtration rate (GFR) and renal blood flow (RBF) were determined with the patients in supine position the day before the first administration of the drug and after three weeks of treatment. Proteinuria and creatinine clearance were additionally assessed two weeks after ending the study when patients were seen for regular examination. At this moment proteinuria and creatinine clearance showed identical values in all cases when compared to those determined at the beginning of the study. Two weeks after withdrawing the drugs the protein excretion was 4.7 ± 4.35 g/day and thus reached the prestudy level.

Methods

Blood pressure was measured with a standard mercury sphygmomanometer. Measurements were performed in triplicate after 10 minutes of rest at supine position. GFR and RPF were measured by means of a constant infusion technique of inulin and PAH (para-aminohippurate) after an initial loading dose starting at 8:30 a.m. [15]. C_{In} and C_{PAH} parameters were calculated as urine concentration divided by plasma concentration, multiplied by urine volume in ml/min, and were corrected for standard body surface area (1.73 m^2). Filtration fraction (FF) was calculated as C_{In}/C_{PAH} and was expressed as a percentage of C_{PAH}. RBF was calculated from C_{PAH} by using the peripheral venous hematocrit and assuming 74% extraction of para-aminohippurate. Renal vascular resistance (RVR) was calculated as mean arterial pressure/renal blood flow × 80,000.

Serum and urinary potassium, sodium, calcium, creatinine, uric acid and albumin were measured by routine laboratory methods. The peripheral venous hematocrit was determined via a microhematocrit technique. Renin activities and aldosterone were measured by radioimmunoassays (renin: Serono Diagnostics; aldosterone: Diagnostic Products Corp.). Urinary protein was determined by Biuret method in three aliquots taken over a 24-hour collection.

Determinations of the extent of disruption of the glomerular permselective barrier have been done by measuring the urine and plasma concentrations of albumin, IgG and inulin. Urine albumin values were measured by ELISA technique [19]. Determination of IgG in urine and serum were done nephelometrically (Behring Nephelometer Analyzer, Behring Werke, Germany).

Fractional IgG clearance and albumin clearance were calculated as

$$(U_{IgG}/P_{IgG})/(U_{in}/P_{in}) \text{ and } (U_{Alb}/P_{Alb})/(U_{in}/P_{in})$$

where U_{IgG} is urine IgG concentration in mg/dl; P_{IgG} is plasma IgG concentration in mg/dl; U_{In} is urine inulin concentration in mg/dl; P_{In} is plasma inulin in mg/dl; U_{Alb} is urine albumin concentration in mg/dl; and P_{Alb} is plasma albumin concentration in mg/dl.

Statistics

All data are expressed as mean ± standard deviation (SD). The Wilcoxon test was used to compare percentages and absolute values of blood pressure, renal hemodynamics, renin values, proteinuria, plasma renin activity and fractional clearances. The correlation between drug induced changes (in %) of FF, GFR, MAP and reduction of proteinuria (in %) was analyzed by Spearman's method with calculation of the rank coefficient value (rs). All statistical analyses were performed with an IBM Personal Computer System/2, Model 70.

Results

During dilevalol intake blood pressure decreased from a mean of 108 ± 13 mm Hg to a mean of 102.5 ± 11 mm Hg ($P < 0.05$ compared to placebo). Treatment with enalapril lowered blood pressure to nearly the same extent (from a mean of 108 ± 13 mm Hg to a mean of 103 ± 12 mm Hg; $P < 0.05$ compared to placebo; Table 2). Proteinuria was 5.1 ± 4.2 g/day during placebo, 3.3 ± 3.0 g/day during dilevalol ($P < 0.05$ compared to placebo) and 2.8 ± 2.8 g/day during enalapril therapy ($P < 0.05$ compared to placebo; Table 2). Reduction of proteinuria with reference to the individual percentage response data was 24.7 ± 13.9% induced by dilevalol compared to placebo ($P < 0.05$), and 47 ± 27.4% for enalapril versus placebo ($P < 0.05$). In contrast to enalapril, reduction of proteinuria induced by dilevalol was associated with a reduction of GFR (rs = 0.86; Fig. 1). The

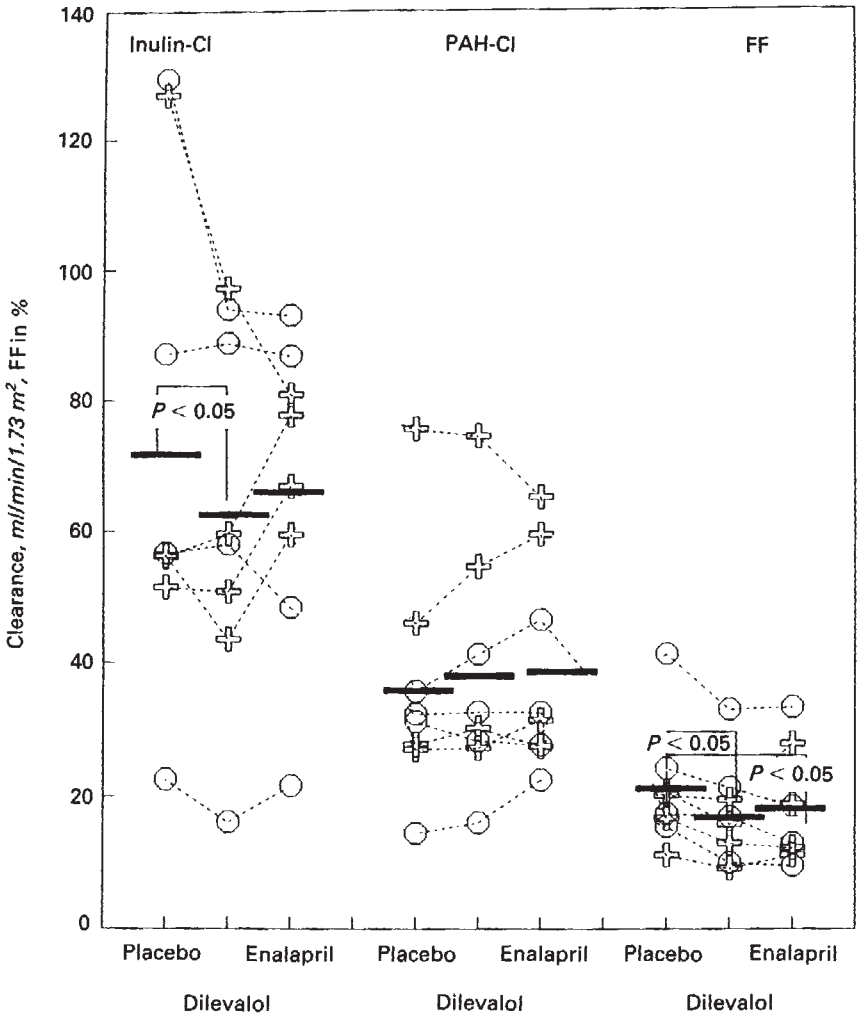

Fig. 4. *Individual data of renal hemodynamic changes with dilevalol and enalapril.* Circles received dilevalol first, crosses received enalapril first.

correlation coefficient for a reduction of FF and reduction of proteinuria was stronger for dilevalol, too (rs = 0.48 vs. rs = 0.19; Figs. 2 and 3). Table 2 summarizes blood pressure data, inulin and PAH clearances, filtration fraction, renal vascular resistance and 24-hour protein excretion during placebo and treatment periods. Figures 4 and 5 give the individual data concerning renal hemodynamics and protein excretion.

GFR measured by inulin clearance was slightly reduced by dilevalol from a mean of 73.3 ± 38 ml/min/1.73 m^2 to a mean of 63.2 ± 28 ml/min/1.73 m^2 ($P < 0.05$) and remained unaltered by enalapril (73.3 ± 38 ml/min/1.73 m^2 vs. 66.8 ± 23 ml/min/1.73 m^2). ERPF measured by PAH clearance was slightly elevated by both drugs (Table 2). Filtration fraction was significantly reduced by both drugs (dilevalol 21 ± 9% vs. 17.4 ± 7%, $P <$ 0.05 compared to placebo; and enalapril 21 ± 9% vs. 18.1 ± 9%, $P < 0.05$ compared to placebo).

Renin levels were significantly increased by enalapril and slightly decreased by dilevalol (Table 3). There was a concomitant but statistically not significant decline of plasma aldosterone concentrations for both drugs. Other parameters did not change significantly (Table 3).

Fractional albumin clearance was reduced significantly by enalapril in all patients except one (Table 4, Fig. 5). Dilevalol had no uniform effect on these values. We observed no clear-cut change of fractional IgG clearance with both drugs (Table 4).

Discussion

Urinary protein excretion was reduced by dilevalol and enalapril to nearly the same extent (Table 2). Renin levels were slightly lowered by dilevalol and significantly increased in case of enalapril treatment independent of sodium excretion. In contrast to other beta blocking agents no reduction in renal blood flow could be detected with dilevalol, and the renal vascular resistance was slightly but not significantly reduced (Table 2, Fig. 4). Interestingly, dilevalol showed the same strong effects on renal hemodynamics as enalapril, but reduction of proteinuria seemed to be more pronounced during enalapril (Table 2). In contrast to enalapril, reduction of proteinuria induced by dilevalol was associated with a reduction of GFR (rs = 0.86) regardless of the low number of patients (Fig. 1). The correlation coefficient for reducing FF and proteinuria was stronger for dilevalol, too (rs = 0.48 vs. rs = 0.19; Fig. 2). No correlation concerning the reduction of proteinuria could be

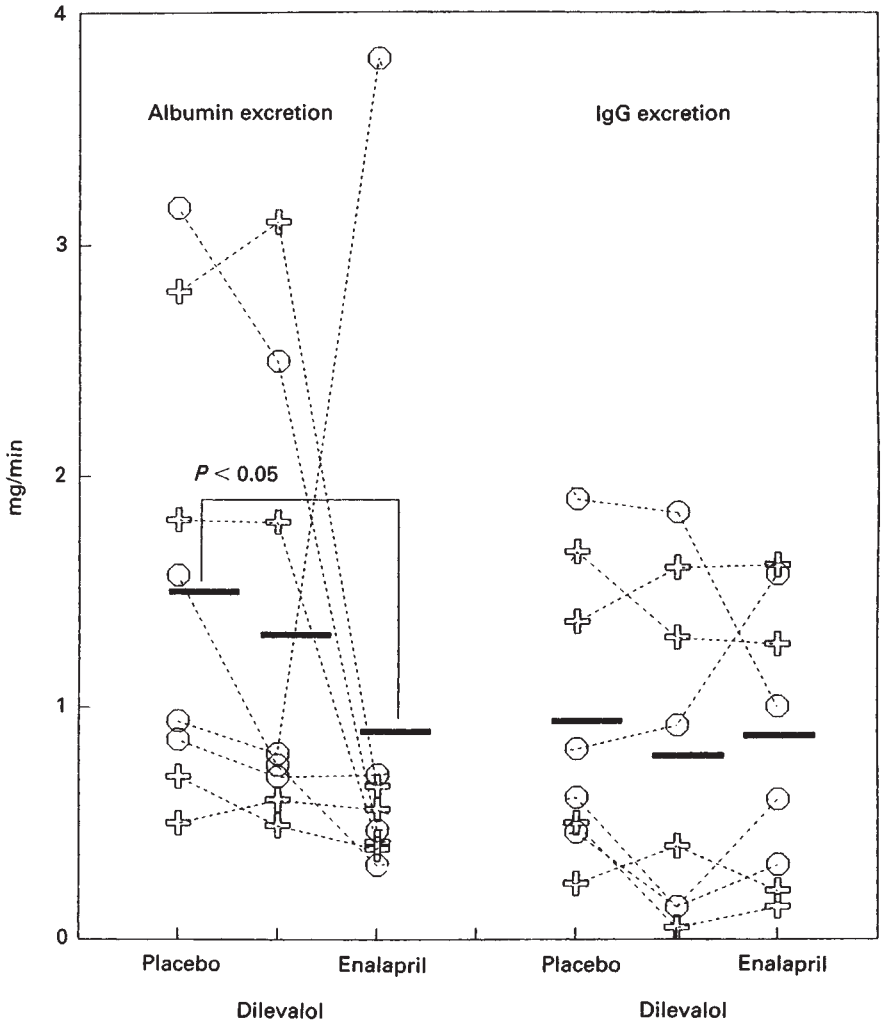

Fig. 5. *Individual data of albumin and IgG excretion during treatment with dilevalol and enalapril.* Circles received dilevalol first, crosses received enalapril first.

Table 3. Selected serum and urine values after treatment with placebo, dilevalol and enalapril

	Placebo	Dilevalol	Enalapril
PRA *ng/ml/hr*	1.5 ± 1	1.1 ± 0.7	5.6 ± 3[a]
Aldosterone *pg/ml*	166 ± 99	148 ± 70	90 ± 58
Serum creatinine *mg/dl*	1.6 ± 0.7	1.6 ± 0.7	1.6 ± 0.7
Creatinine clearance *ml/min/1.73 m²*	82.1 ± 21	73.0 ± 22	76.4 ± 16
Serum sodium •*mval/liter*	142 ± 2.4	140 ± 3.2	142 ± 3.2
Serum potassium •*mval/liter*	4.0 ± 0.3	4.0 ± 0.4	4.1 ± 0.4
Serum total protein *g/dl*	6.1 ± 0.8	6.2 ± 0.6	6.2 ± 0.6
Urinary phosphate *mg/day*	916 ± 365	831 ± 262	761 ± 188
Urinary sodium •*mval/day*	189 ± 71	165 ± 40	169 ± 90.5
Urinary potassium •*mval/day*	68 ± 8.5	62 ± 17.7	64 ± 16.2

Abbreviation is PRA, plasma renin activity.
[a] $P < 0.05$ compared to placebo and values under dilevalol

Table 4. Renal protein handling in patients with glomerulonephritis during treatment with dilevalol and enalapril

	Placebo	Dilevalol	Enalapril
Serum albumin concentration *g/dl*	3.9 ± 0.6	3.9 ± 0.4	3.9 ± 0.4
Serum IgG concentration *g/dl*	0.9 ± 0.3	1.0 ± 0.4	1.0 ± 0.4
Albumin excretion rate *mg/min*	1.5 ± 1.0	1.3 ± 1.0	0.9 ± 1.2[a]
IgG excretion rate *mg/min*	0.9 ± 0.6	0.8 ± 0.7	0.8 ± 0.6
Fractional albumin clearance ($\times 10^{-5}$)	30.6 ± 20	33.2 ± 22	11.7 ± 3.8[a]
Fractional IgG clearance ($\times 10^{-5}$)	9.7 ± 7.9	10.4 ± 12.7	9.0 ± 7.6
C_{IgG}/C_{Alb} %	45.4 ± 48.5	46.2 ± 54.1	74.8 ± 59.1

[a] $P < 0.05$ compared to placebo

seen for either drug with regard to the lowering of arterial blood pressure (Fig. 3). The observations concerning the reduction of proteinuria by ACE inhibiting drugs independent of a reduction of systemic blood pressure and without correlation between the

reduction of GFR and FF are in line with those of other authors [6, 7]. In contrast to recently published data, proteinuria was reduced in all patients regardless of the renin status [7].

In addition to changes of renal hemodynamics and systemic blood pressure ACE inhibitors exert other effects which may promote a reduction of proteinuria. There is evidence for a change of membrane protein selectivity [12, 13, 15, 20–22]. We could not demonstrate a homogeneous alteration for either the fractional albumin and IgG clearance, except that in all instances except one the fractional albumin clearance was significantly decreased by enalapril compared to placebo and dilevalol (Table 4, Fig. 5). Albumin clearance was considered to reflect a selective property of the anionic constituents of the glomerular capillary wall [20]. As shown for diabetic glomerular disease [23], it has been proposed that loss of barrier charge selectivity provides a basis for proteinuria in glomerular disease [15]. Data from other investigators show that dextran sieving profiles do not change over the whole radius range during ACE inhibition, which may be considered as an indicator for an increased charge selectivity, although ACE inhibition lowered the IgG-cl/Alb-cl ratio in this study [21]. These data by de Zeeuw, Heeg and de Jong [21] are in contrast to recently published results by Remuzzi et al [24], who showed that the transglomerular passage of large dextrans (radii 54 to 62 Å), but not of lower size (26 to 52 Å), were significantly lowered by enalapril in patients with IgA nephropathy. The same study showed that fractional albumin clearance was also reduced by enalapril, and this is in contrast to their above-mentioned results, as albumin has a radius of 36 Å but is negatively charged. Data of Yoshioka et al [25, 26], obtained with two rat models, showed that saralasin infusion leads to a partial decrease of excretion of large dextrans, whereas fractional clearances of smaller dextrans remained unaffected. We think these differences can be explained by patient characteristics (nephrotic patients vs. patients with normal plasma albumin; hypertensive vs. normotensive patients, differences in the underlying renal disease), and probably by duration and choice of treatment. The fact that ACE inhibition induces different changes in protein excretion may also be a result of differences in charge, as we only measured negatively charged proteins with different molecular radii.

Although there was only a short second placebo phase after the first drug administration period without another urine sampling period, we assessed the same extent of reduction of proteinuria for both drugs when given in the first period. We did the last evaluation of proteinuria two weeks after ending the study. In the interim patients were without medication. These tests showed that proteinuria had returned to baseline levels at this point in all cases (proteinuria 4.7 ± 4.35 g/day). We cannot exclude that after a longer time period the effects of both drugs might differ. Unfortunately we had to discontinue our studies on dilevalol, because there was a notification of possible drug-related non-infectious hepatitis from Japan. Subsequently the manufacturer withdrew dilevalol from clinical application. Nevertheless, we consider our results interesting with regard to work in progress on other beta blocking agents with vasodilating activities, and for other agents affecting the permselectivity characteristics of glomerular filtration.

In conclusion, our results strongly suggest that there are other drugs which show ACE inhibitor-like effects on renal hemodynamics. Yet, these drugs were not able to reduce proteinuria to the same extent as ACE inhibitors. Concerning the mechanism of action of both drugs we found that, compared to dilevalol, enalapril showed additional effects on the fractional albumin excretion, indicating an increased charge selectivity of the glomerular barrier.

Acknowledgments

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