Comparative Effect of Captopril and Nifedipine in Normotensive Patients With Incipient Diabetic Nephropathy*

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In these studies, the effect of a 6-wk treatment by placebo, the calcium-channel blocker nifedipine, or the converting-enzyme inhibitor captopril was assessed in normotensive patients with insulin-dependent diabetes and incipient nephropathy. In response to captopril and nifedipine, arterial pressure decreased slightly and to a similar extent. These drugs resulted in opposite effects on urinary excretion of albumin [i.e., increase in urinary albumin excretion (UAE) by 40% during nifedipine treatment and decrease by 40% during captopril treatment]. No change in UAE was observed in the placebo group. This observation of opposite changes in UAE in the presence of a similar fall in arterial pressure suggests that the effects of captopril and nifedipine on UAE result from some difference in their intrarenal action. The data do not present recommendations for the use or disuse of captopril or nifedipine in such a group of patients and do not allow extrapolation to hypertensive diabetic subjects well controlled by other conventional antihypertensive agents. *Diabetes Care* 11:850–53, 1988

Diabetic nephropathy characterized by persistent proteinuria (>0.5 g/24 h) developed in 41% of patients with insulin-dependent diabetes mellitus (IDDM) followed for at least 25 yr after the onset of the disease; however, ~57% of the patients did not develop persistent proteinuria during this follow-up period (1). Microalbuminuria defined as urinary albumin excretion (UAE) below the Albustix-detectable level of 0.5 g/L protein or 140 mg/L albumin has proved important in predicting the eventual development of clinical diabetic nephropathy (2,3). Viberti et al. (4) reported that within a 14-yr follow-up period, clinical proteinuria developed in 7 of 8 patients with UAE of 30–140 μg/min and in only 2 of 55 patients with UAE <30 μg/min on overnight urine collection at the first screening examination. This observation was confirmed by Mogensen and Christensen (2) during a similar follow-up period and with a lower limit of UAE of 15 μg/min. At initial examination, arterial pressure was higher in patients with UAE >15 μg/min than in those with UAE <15 μg/min; nevertheless, in all patients, arterial pressure was still within normotensive limits (WHO criteria). In more recent studies, a positive correlation was found between UAE and arterial pressure in normotensive patients with incipient diabetic nephropathy (UAE 15–200 μg/min) (5,6); moreover, careful analysis of the correlation found by Mogensen and Christensen (5) shows that an increase in mean arterial pressure of ~4 mmHg may be associated with the doubling of UAE.

Such observations, which demonstrate the important role of arterial pressure in the progression of diabetic nephropathy, raise the question of whether antihypertensive treatment is justified in diabetic patients in whom normotension is defined according to the WHO criteria in an attempt to slow down the course of incipient diabetic nephropathy. In this study, the influence of treatment by two antihypertensive agents, the converting-enzyme inhibitor captopril and the calcium-channel blocker nifedipine, was assessed in normotensive patients with incipient diabetic nephropathy.

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MATERIALS AND METHODS

Studies were conducted in 22 normotensive (diastolic arterial pressure <95 mmHg) patients with IDDM of 8–26 yr duration. All subjects presented with incipient diabetic nephropathy (avg baseline UAE 15–200 μg/min on 3 24-h urine collections and proteinuria below the detection limit of 0.5 g/24 h) (3). Informed consent was obtained from all patients.

After basal determinations of arterial pressure, serum electrolytes and creatinine, glycosylated hemoglobin, plasma renin activity, UAE (3 urine collections of 30 min each after oral water loading of 10 ml/kg in the supine position), patients were randomly assigned to treatment by slow-release nifedipine (20 mg twice daily, $n = 7$), captopril (25 mg twice daily, $n = 8$), or two placebo tablets ($n = 7$). After 6 wk of treatment, studies were repeated in all groups. In addition, in six of eight patients of the captopril group, assessment of the effect of treatment on UAE was performed after 6 mo of therapy.

All patients were trained to measure blood glucose level with the finger-stick technique with a glucometer (Ames, Miles, Paris) at 0800, 1200, and 1900. The glucose values reported in this study are the means of values measured during the last 2 wk of each study period.

Arterial pressure and heart rate were determined every 5 min with an automatic device (Dinamap 845 XT, Critikon, France) with the patient in the supine position and during the urine-collection periods. Plasma renin activity was estimated with a radioimmunoassay kit (CEA, Saclay, France), and urinary albumin was measured by radioimmunoassay (Pharmacia albumin radioimmunoassay, Uppsala, Sweden).

Results are presented as means ± SE. For comparison between basal and treatment values, Student's t test or Wilcoxon's test for paired data was used. Comparison between groups was carried out with Student's t test for unpaired data.

RESULTS

Pretreatment data. Before treatment, demographic data and results concerning arterial pressure, diabetes control, serum creatinine, plasma renin activity, and UAE were similar in the three groups.

When the whole population of patients was considered, it appeared that the UAE found at screening on 24-h urine collections was slightly but not significantly lower than the mean value found at the clinic and after oral water loading (60.7 ± 16.4 vs. 72.5 ± 30.4 μg/min). In addition, no correlation was found between pretreatment UAE and serum creatinine or basal plasma renin activity. However, there was a positive correlation between mean arterial pressure (MAP) and UAE (MAP = 8.1 log UAE + 83, $r = .47$).

Influence of 6-wk treatment. As summarized in Table 1, the placebo had no effect on any of the parameters that were assessed. Administration of captopril and nifedipine resulted in a similar fall in arterial pressure by −9 ± 2/−4 ± 1.6 mmHg for the captopril group and −7 ± 2/−3 ± 1 mmHg for the nifedipine group. No change in resting heart rate, body weight, serum creatinine, diabetes control, and insulin requirement was observed during treatment. Plasma renin activity did not change during nifedipine treatment and increased by 49 ± 27% (NS) during captopril treatment.

The most prominent finding of this study was that UAE decreased in all patients treated with captopril and increased in all subjects given the calcium antagonist ($P < .001$, Wilcoxon's test for paired data). There was no correlation between changes in UAE and changes in arterial pressure induced by either treatment. Although no side effects were reported in the captopril group, most patients treated with nifedipine complained of episodes of flushing shortly after drug administration and progressive ankle swelling throughout the day.

In six patients of the captopril group, UAE was measured after 6 mo of treatment. Mean values of UAE were 119 ± 58 μg/min before treatment, 59 ± 25 μg/min at 6 wk, and 64 ± 34 μg/min ($P < .05$ after log transformation) after 6 mo of therapy; in all subjects, UAE remained lower than baseline at the end of treatment. This indicates that the fall in UAE associated with captopril was maximal after 6 wk of treatment and remained constant thereafter.

DISCUSSION

In these studies conducted in normotensive IDDM patients with incipient nephropathy (UAE 15–200 μg/min), treatment for 6 wk by the converting-enzyme inhibitor captopril or the calcium-channel blocker nifedipine had opposite effects on UAE in the presence of a slight but similar fall in arterial pressure. UAE increased by 40% in the nifedipine group and decreased by 40% in the captopril group, whereas UAE was perfectly stable in the placebo group at the end of the observation period.

The observation made with captopril is in keeping with the results obtained by Marre et al. (7), who treated a similar group of patients with enalapril. Although the fall in arterial pressure was of a small magnitude, it may have contributed to the decrease in UAE in the captopril-treated patients due to the positive correlation between arterial pressure and UAE (5,6) and the fact that a small increase in MAP (3–5 mmHg) may be associated with a doubling of UAE in normotensive patients with incipient nephropathy.

The finding of an increase in UAE in the presence of a fall in arterial pressure during nifedipine therapy suggests that the contrasting effects of captopril and nifedipine on UAE may be independent of changes in renal

TABLE 1
Effect of 6-wk treatment on diabetes control, arterial pressure, and urinary albumin excretion

Group	Placebo (n = 7)		Nifedipine (n = 7)		Captopril (n = 8)	
	Basal	Treatment	Basal	Treatment	Basal	Treatment
Age (yr)	35 ± 5		33 ± 4		34 ± 5	
Duration of diabetes (yr)	15 ± 3		21 ± 3		16 ± 2	
Insulin dose (IU · kg^{-1} · day^{-1})	0.70 ± 0.10	0.80 ± 0.10	0.76 ± 0.07	0.70 ± 0.10	0.70 ± 0.10	0.70 ± 0.10
Glycosylated hemoglobin (%)	8.9 ± 0.3	9.1 ± 0.6	8.6 ± 0.4	8.9 ± 0.4	9.4 ± 0.7	8.8 ± 0.5
Body weight (kg)	58.4 ± 3.3	58.4 ± 3.1	59.1 ± 3.1	59.3 ± 3.1	62.3 ± 2.5	63 ± 2.9
Blood glucose (mg/dl)						
0800	156 ± 14	163 ± 17	175 ± 17	166 ± 14	147 ± 17	147 ± 13
1200	147 ± 28	149 ± 25	188 ± 40	151 ± 23	148 ± 25	144 ± 20
1900	243 ± 48	229 ± 23	200 ± 30	175 ± 15	205 ± 26	150 ± 6
Systolic arterial pressure (mmHg)	125 ± 7	125 ± 8	136 ± 8	129 ± 7*	131 ± 6	122 ± 4*
Diastolic arterial pressure (mmHg)	77 ± 2	76 ± 3	80 ± 3	76 ± 3*	78 ± 3	74 ± 3*
Heart rate (beats/min)	69 ± 5	74 ± 4	67 ± 3	71 ± 4	71 ± 4	70 ± 3
Serum creatinine (μM)	81 ± 4	79 ± 5	82 ± 4	87 ± 4	84 ± 4	87 ± 3
Plasma renin activity (ng · ml^{-1} · h^{-1})	2.5 ± 1	3.2 ± 0.5	3.8 ± 0.8	3.9 ± 1.1	2.1 ± 0.5	3.9 ± 1.5
Urinary albumin excretion (μg/min)	97 ± 70	95 ± 69	86 ± 70	122 ± 96*	86 ± 37	51 ± 19*

Values are means ± SE.
*P < .05 compared with pretreatment means.

perfusion pressure and rather are related to some difference in the intrarenal influence of the two agents. A similar observation was made by Jackson et al. (8), who showed that treatment of uninephrectomized rats made diabetic by streptozocin by the converting-enzyme inhibitor enalapril lowered blood pressure to normal and prevented the progression of proteinuria. In contrast, treatment by the calcium antagonist verapamil, which produced a similar fall in arterial pressure, did not influence the progressive increase in proteinuria in the diabetic rats. In experimental rat studies with the 5/6 renal ablation model, Anderson et al. (9) observed that, despite normalization of arterial pressure by enalapril or standard triple therapy, only enalapril afforded reduction in progressive proteinuria and glomerular sclerosis. Micropuncture data obtained by these investigators were in favor of a critical role for the decrease in intraglomerular pressure only produced by enalapril in the prevention of glomerular damage.

Although no assessment of renal hemodynamics and glomerular filtration rate was attempted in these studies, it can be anticipated that the converting-enzyme inhibitor may have induced renal vasodilation and no change in glomerular filtration rate, thus resulting in a fall in the filtration fraction, as observed in patients with essential hypertension (10). Such a decrease in filtration fraction, if it occurred, would suggest that inhibition of intrarenal generation of angiotensin II by captopril tends to preferentially dilate the efferent glomerular arteriole and lead to a fall in intraglomerular pressure and ultimately to a decrease in the glomerular permeability to albumin. Because exogenous angiotensin II increases the glomerular permeability to albumin mainly through intrarenal hemodynamic factors in animal studies (11,12), inhibition of intrarenal generation of angiotensin II by captopril would be expected to reduce UAE in our patients.

The effect of nifedipine on UAE observed in these studies was surprising. This treatment had no worsening influence on diabetic control, a factor known to affect UAE in patients with microalbuminuria (13). In experimental animals and humans, calcium-channel blockers induced renal vasodilation and an increase in glomerular filtration rate in some studies; however, in most studies, these agents did not modify the filtration fraction (14–16). This suggests that calcium antagonists may exert their vasodilatory action preferentially on the afferent glomerular arteriole (14). During verapamil infusion, no change in intraglomerular capillary pressure was observed in micropuncture studies, despite a fall in systemic pressure (17). If this were the case in our studies, no change in UAE should have occurred. Nifedipine may have induced an increase in the glomerular permeability to albumin through a mechanism independent of changes in intraglomerular capillary pressure.

The observation that treatment by captopril was associated with a sustained decrease in UAE (at 6 wk and 6 mo) in normotensive patients with incipient diabetic nephropathy is promising, whereas the increase in UAE induced by nifedipine is puzzling. Whether early (during the normotensive stage) treatment by converting-enzyme inhibitors affords prevention against the observed 20% yearly increase in UAE in these patients remains to be demonstrated together with the eventual slowing of the progression of diabetic nephropathy during long-term treatment (5). In contrast, the significance of the increase in UAE associated with nifedipine remains to be elucidated through studies with a better-tolerated and structurally different calcium antagonist.

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