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Effects of Cilazapril on Renal Haemodynamics and Function in Hypertensive Patients: A Randomised Controlled Study versus Hydrochlorothiazide

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In this study the efficacy and safety of short-term cilazapril administration on renal haemodynamics were evaluated in mild to moderate hypertensive subjects. Our final goal was to evaluate whether the reduction in blood pressure achieved by treatment was associated with maintained renal function. After a run-in period with placebo, 40 hypertensive subjects without renal or cardiac diseases were randomly allocated to a double-blind 4 week controlled trial with cilazapril 5 mg once a day (20 patients) or hydrochlorothiazide 25 mg once a day (20 patients). Renal haemodynamics measurements included effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) by radionuclide study using ^{131}I-hippuran and ^{99m}Tc, according to the methods described by Schlegel and Gates, respectively. Effective renal blood flow [ERBF = ERPF/(1-Ht)], filtration fraction (FF = GFR/ERPF) and renal vascular resistance (RVR = MBP×80/ERBF) were calculated. At the end of cilazapril and hydrochlorothiazide administration significant decreases ($p < 0.001$) in SBP, DBP and MBP vs baseline values were observed. In the cilazapril group a significant decrease ($p < 0.001$) in RVR and FF and a significant increase ($p < 0.001$) in ERPF and ERBF were also found. In the hydrochlorothiazide group a significant decrease ($p < 0.001$) in RVR was found. No important side effects were observed with either treatment. In conclusion our data indicate that both cilazapril and hydrochlorothiazide reduced blood pressure equally well but only cilazapril improved renal blood flow and reduced filtration fraction. *Key words:* ACE-inhibitors, cilazapril, essential hypertension, renal function.

INTRODUCTION

It is well known that the natural course of essential hypertension is characterized by a slow and progressive impairment of renal function related to age of patients and severity of disease [1, 2]. Experimental studies indicate that alterations in glomerular capillary pressure might be the main determinants of the development and evolution of renal impairment in hypertensives [3, 4].

Angiotensin converting enzyme (ACE) inhibitors have been shown to have favourable renal haemodynamics and excretory profile in the treatment of essential hypertension [5–7]. Some studies both on animals and on humans suggest that Ace-inhibitors may protect renal function by a mechanism other than simply lowering the systemic blood pressure [8, 9].

Cilazapril is the mono-ethyl ester prodrug of a potent specific long-acting ACE inhibitors and its antihypertensive effectiveness has been well documented (10). It appears to be well tolerated and with multiple pharmacological effects [11, 12]. Although the systemic effects of cilazapril are generally well known, its renal effects are only now being characterized.

In this study antihypertensive effectiveness, the safety of cilazapril and its effects on renal haemodynamics and function were evaluated in patients with mild to moderate hypertension. Our final goal was to ascertain whether the reduction in blood pressure induced by cilazapril administration was associated with maintained renal function.

Hydrochlorothiazide was chosen as the comparison drug because an equivalent expected efficacy and a completely different hypotensive action mechanism.

PATIENTS AND METHODS

Patients

Initially sixty-six consecutive hypertensive out-patients attending the antihypertensive center of the Internal Medicine Department at the University of Palermo (Italy) were enrolled. The diagnosis of essential hypertension was established by history and physical examination and by the absence of clinical findings suggestive of a secondary form of hypertension. During the recruitment period all the patients were totally unselected as far as preliminary investigations were completed. They included routine biochemical tests (including clearance of creatinine and oral glucose

tolerance test), chest X-ray, standard and 24 h EKG monitoring, M- and B-mode echocardiography and fundus oculi examination. Exclusion criteria included severe hypertension, cardiovascular disease (defined as myocardial infarction, chest pain, heart block, valvular disease and heart failure), renal failure (serum creatinine higher than or equal to 1.4 mg/dl), insulin-dependent or -independent diabetes mellitus, electrolyte imbalances, moderate or severe Keith-Wegener hypertensive retinopathy, alcoholism or psychiatric problems. Patients with concomitant left ventricular hypertrophy defined according to echocardiography criteria [13] or with other target organ damage were also excluded. Each patient gave informed consent after receiving a detailed description of the study procedure and the study was also approved by the Ethics Committee of our Institution.

After a 14 day run-in period with placebo, 40 patients (24 women and 16 men, mean age 46.5 ± 8 years) with diastolic blood pressure persistently higher than 90 mmhg were eligible for the study. They were randomly assigned to a double-blind 4 week controlled trial of cilazapril 5 mg once a day (20 pts) or hydrochlorothiazide 25 mg once a day (20 pts). The drugs were supplied by Farmitalia Carlo Erba (Milano, Italy). Both hypertensive groups were maintained on a normal sodium diet, lower than 150 mEq/day. In view of this all the patients were advised to follow a diet with no added salt. The good adhesion to dietetic regimen was controlled through periodical and randomised examination of urinary excretion of sodium.

Clinical characteristics, renal haemodynamics investigation and laboratory tests were performed at the end of the run-in period and 24h after the last dose of cilazapril or hydrochlorothiazide. Clinical measurements included heart rate (HR), which was derived from the electrocardiographic trace; systolic (SBP) and diastolic (DBP) blood pressure were measured in triplicate using a mercury sphygmomanometer after 5 min in a supine position. Korotkoff phase V was used for DBP. Mean blood pressure (MBP) was calculated as the sum of DBP plus one third of the pulse pressure.

Methods

Laboratory tests included fasting blood sugar, sodium, potassium, chloride, urinary excretion of sodium, serum creatinine and clearance, uric acid, total and HDL cholesterol and triglyceride.

Renal haemodynamics: Renal haemodynamics was evaluated by radionuclide study according to methods described by Schlegel & Haway [14] and by Gates [15].

The methods used for measurements of effective renal plasma flow and glomerular filtration rate were based on the determination by scintillation camera of the fraction of the injected dose of Tc-99m DTPA and I-131 Hippuran present in the kidneys 1–3 min after its administration, as previously reported [16–18].

To calculate effective renal plasma flow and glomerular filtration rate the relative and fractional uptake were first determined by the computer and then related to the clearance values; relative and fractional uptake were related to clearance value by the empiric regression equations previously reported [14, 15].

Using radionuclide techniques effective renal plasma flow (ERPF; ml/min), effective renal blood flow [ERBF = ERPF (1-haematocrit); ml/min], glomerular filtration rate (GFR; ml/min) and filtration fraction (FF = GFR/ERPF; %) were calculated. Renal vascular resistance (RVR) was also measured by the formula $RVR = MBP \times 80/ERBF$ (dynes×s×cm^{-5}).

In our opinion, noninvasive radionuclide techniques are preferable to traditional methods utilized in evaluating the ERPF or GFR. In fact, the isotopic methods can estimate GFR or ERPF without blood or urine sampling. These methods allow determination of these measurements separately for each kidney and derive values for global renal function [19].

The accuracy and reliability of this technique in the evaluation of global renal function or unilateral kidney function have been well reported [19]. This method is in current use and has been validated in our laboratory [16–18].

In particular, inulin clearance correlated with fractional uptake of 99m-Tc DTPA measured between 2 and 3 min after renal tracer appearance ($r = 0.89$; $p < 0.0001$); PAH clearance correlated with fractional kidney uptake of 131-I-Hippuran measured between 2 and 3 min after renal tracer appearance for both global and unilateral renal function ($r = 0.81$; $p < 0.0001$). Both correlations were detected in 45 subjects with various levels of renal function, ranging from normal to anuric conditions.

A good correlation was observed between inuline clearance and GFR calculated by Gate's formula ($r = 0.85$; $p < 0.0001$) for global renal function and between PAH clearance and ERPF measured by Schelegel's formula ($r = 0.83$; $p < 0.0001$) for global renal function.

The reproducibility of isotopic GFR ($r = 0.90$) and ERPF ($r = 0.92$) determination was excellent. No significant differences between the calculated lines and line of identity were observed. Finally, the reproducibility of the processing (kidney outlining and creation of background region of interest) by successive analysis of renal function was good ($r = 0.97$ for GFR and 0.94 for ERPF).

Statistical analysis

Comparisons between baseline characteristics of the two treatment groups were analyzed by unpaired *t*-test. Comparisons between baseline and end-treatment measurements in the same group were analyzed by paired *t*-test. In addition, the Mann-Whitney U test was performed to compare percent change in blood pressure and renal haemodynamic measurements at the end of the two treatment groups. A p value < 0.05 was considered statistically significant.

All the data are expressed as mean value ± SD.

RESULTS

The results are summarized in Tables I and II.

There was no statistically significant difference between the two treatment groups in age, body weight, height and BMI. Baseline systolic, diastolic mean blood pressure and renal measurements did not differ between the two treatment groups.

Cilazapril group

After cilazapril treatment a statistically significant ($p < 0.001$) decrease vs baseline values was observed for SBP, DBP and MBP (Table I). Blood pressure normalization (DBP≤90 mmHg) occurred in 14 of the 20 hypertensive patients. Cilazapril treatment induced a significant increase ($p < 0.005$) in ERPF and ERBF and a significant ($p < 0.001$) decrease in RVR and FF (Table I).

No clinically important modification occurred in the biochemical tests (Table II). Only transient and mild side effects were reported in two patients: flushing (one case) and dry cough (one case).

Hydrochlorothiazide group

After hydrochlorothiazide treatment a mild but not significant weight loss and a significant ($p < 0.001$) decrease in SBP, DBP and MBP were observed (Table I). Blood pressure normalization (DBP≤90 mmHg) occurred in 11 of 20 hypertensive patients. Moreover, a statistically significant ($p < 0.001$) decrease vs baseline value for RVR was found without a significant change in ERPF, ERBF, GFR and FF (Table I).

No clinically important modification occurred in the biochemical tests (Table II) except for a transient hypokaliemia, which occurred after 4 days of treatment and was corrected with oral K^+ (6 mEq once a day for 4 days).

Side effects were few and transient. Two patients complained of asthenia and three of dizziness.

Finally, Fig. 1 indicated that percent change in renal haemodynamic measurements was significantly ($p < 0.05$) different in the two treatment groups, whereas percent change in SBP, DBP and MBP was similar in the two treatment groups.

Table I. *Clinical characteristics (mean value ± SD) of two hypertensive groups before and after cilazapril or hydrochlorothiazide administration*

	Cilazapril		Hydrochlorothiazide	
	Baseline	Treatment	Baseline	Treatment
Cases n.	20	20	20	20
Age (years)	47±9	/	45±10	/
Weight (kg)	75±14	76±14	78±12	76±13
Height (cm)	166±8	/	166±7	/
BMI (kg/m^2)	27±3	27±3	28±2	28±3
SBP (mmHg)	155±11	144±9*	161±10	150±9*
DBP (mmHg)	99±6	92±5*	99±6	90±6*
MBP (mmHg)	118±6	109±6*	120±7	110±6*
HR (beats/min)	75±3	74±3	78±2	77±1
ERPF (ml/min)	496±67	544±63**	514±37	507±51
ERBF (ml/min)	903±124	984±115**	957±90	908±77
GFR (ml/min)	98±9	102±9	95±6	94±5
FF (%)	19.8±0.8	18.4±0.8*	19.3±0.2	19.7±0.1
RVR (dyn·s·cm^{-5})	10710±661	9004±676*	9596±492	8820±417*

BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MBP = Mean Blood Pressure; HR = Heart Rate; ERPF = Effective Renal Plasma Flow; ERBF = Effective Renal Blood Flow; GFR = Glomerular Filtration Rate; FF = Filtration Fraction; RVR = Renal Vascular Resistance.

*$p <$ 0.001 vs baseline.

**$p <$ 0.005 vs baseline.

Table II. *Biochemical tests (mean value ± SD) of two hypertensive groups before and after cilazapril or hydrochlorothiazide*

	Cilazapril		Hydrochlorothiazide	
Cases n.	Baseline 20	Treatment 20	Baseline 20	Treatment 20
Glycemia (mg/dl)	91±8	91±7.7	87±7	90±7
BUN (mg/dl)	30±4	31±3.5	30±3	34±3
Creatinine (mg/dl)	0.9±0.1	0.9±0.1	0.9±0.1	1.1±0.1
Sodium (mEq/l)	141±1	142±1	139±0.5	138±0.6
Potassium (mEq/l)	4.4±0.2	4.6±0.2	4.6±0.4	4.2±0.3
Uric acid (mg/dl)	3.8±0.9	3.9±0.8	4.0±0.5	4.7±0.6
Cholesterol (mg/dl)	187±19	186±15	200±8	210±8
HDL-CHOL (mg/dl)	41±2	41±1	44±2	43±2
Triglyceride (mg/dl)	161±12	161±11	160±6	170±6
GOT (IU/l)	23±4	24±4	17±1	16±1
GPT (IU/l)	26±6	27±6	20±1	20±1

None of differences are significant.

DISCUSSION AND CONCLUSIONS

This study demonstrated that cilazapril was effective to reduce blood pressure in mild to moderate hypertensive subjects, as well reported by other authors [10, 20]. Its antihypertensive efficacy was comparable to hydrochlorothiazide. Cilazapril (5 mg daily) normalized blood pressure (DBP≤90 mmhg) in 70% of treated hypertensives without significant side effects, whereas blood pressure normalization occurred in 55% of hypertensive patients treated with hydrochlorothiazide, but this difference was not significant.

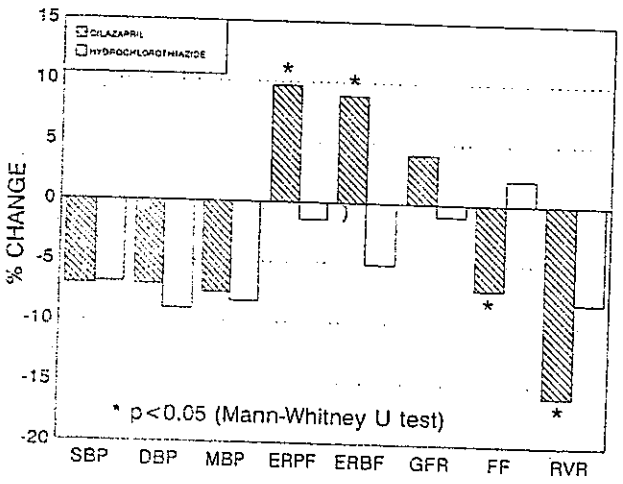

Fig. 1. Per cent change of blood pressure and renal haemodynamics at the end of cilazapril and hydrochlorothiazide treatments. SBP = Systolic blood pressure; DBP = Diastolic blood pressure; MBP = Mean blood pressure; ERPF = Effective renal plasma flow; ERBF = Effective renal blood flow; GFR = Glomerular filtration rate; FF = Filtration fraction; RVR = Renal vascular resistances.

In addition, effects on renal haemodynamics and function after short term cilazapril treatment were more favourable than those detectable after hydrochlorothiazide treatment. In fact, increased renal plasma and blood flow and decreased filtration fraction were found only in cilazapril group, whereas reduced vascular resistance was observed in both treatments. Despite these differences, both treatments are actually characterized by maintained renal function, but increased in filtration fraction after hydrochlorothiazide therapy may be considered unfavourable effect on long term renal function. In view of this, it is well known that glomerular hyperfiltration is a risk factor for a progressive deterioration in renal function in hypertensive subjects [17–19, 21].

This is actually considered an important goal of antihypertensive treatment. In fact, although uncontrolled hypertension may be associated with an increased rate of decline in renal function, this does not necessarily imply that correction of the hypertension will be associated with a reversal of this effect. It is generally accepted that treatment of hypertensive subjects with or without reduced renal function will protect the kidney from further injury induced by increased blood pressure [21–23]. Furthermore, it has been reported that not all antihypertensive agents are equally effective in preserving against that deterioration [24]. However, drugs with favourable effects both on systemic pressure and on intraglomerular pressure appear to have advantages compared with treatments that only reduce systemic pressures [23].

Moreover, some experimental studies indicated that early administration of ACE inhibitors might preserve renal function in rat model of renal failure. In fact,

Anderson et al. reported that enalapril was effective to control both glomerular hypertension and systemic hypertension without reducing single-nephron GFR [25].

Our data indicated that renal effects of cilazapril are consistent with a preferentially efferent arteriolar vasodilation and thus reduction of glomerular pressure.

In this way damage to the glomerular endothelium, or movement of macromolecules into the glomerular mesangium, may be reduced and the development of the glomerular sclerosis diminished.

On the other hand, some data suggest that all ACE inhibitors do not seem to be equally beneficial. In fact lisinopril was less effective than enalapril to improve renal haemodynamics in hypertensive subjects [26]. The explanation given was based on possible differences in tissue uptake, distribution and metabolism of the two ACE inhibitors.

The favourable effects on renal haemodynamics promoted by short-term cilazapril administration were not observed in hydrochlorothiazide group, although it was effective to reduce renal vascular resistance. This is in agreement with other data indicating that some antihypertensive agents may depress renal function by fall in renal blood flow and may not confer full renal protection, despite controlling systemic blood pressure [27].

In fact, it is well known that decreased systemic pressure is not the only solution for a reduction in the progression of renal function impairment and more specific goals for antihypertensive treatments will have to be defined [8, 27].

In conclusion, our data indicate that both cilazapril and hydrochlorothiazide reduced blood pressure equally well but only cilazapril improved renal blood flow and reduced filtration fraction. This leads one to speculate that short term cilazapril treatment might be suitable to protect renal function in mild to moderate hypertensive subjects. In view of this, prospective randomised long term studies have to be provided to ascertain whether the effects of cilazapril on renal haemodynamics have the potential to modify the clinical course of hypertensive renal disease.

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