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Antihypertensive Efficacy and Effects of Nitrendipine on Cardiac and Renal Hemodynamics in Mild to Moderate Hypertensive Patients: Randomized Controlled Trial Versus Hydrochlorothiazide

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Summary. **In this study antihypertensive efficacy, safety, and the effects of short-term nitrendipine administration on central and renal hemodynamics were evaluated in mild to moderate hypertensives. Our final goal was to ascertain whether the reduction in blood pressure induced by nitrendipine treatment was associated with maintained renal function. After a run-in period with placebo, 26 hypertensives without cardiac or renal disease were randomly assigned to a double-blind 8-week controlled trial with nitrendipine (N) 20 mg once a day (13 pts) or hydrochlorothiazide (HCT) 25 mg once a day (13 pts). Renal hemodynamic measurements included effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) by radionuclide study using I-131 hippuran and Tc-99m, 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 also calculated. Other hemodynamic measurements included cardiac index (CI), left ventricular (LV) ejection fraction (EF), and total peripheral resistance (TPR) measured by the first-pass radionuclide angiography technique. At the end of N or HCT administration significant descreases ($p < 0.001$) in SBP, DBP, and MBP vs. baseline values were observed in both hypertensive groups. In the N group a significant decrease ($p < 0.01$) in TPR and RVR, and significant increases ($p < 0.05$) in CI, ERPF, and ERBF were observed. In the HCT group a significant decrease ($p < 0.05$) in RVR was found without significant changes in other hemodynamic parameters. No important side effects were observed with either therapy. In conclusion, nitrendipine was effective in reducing blood pressure in mild to moderate hypertensive patients and exerted favorable effects on cardiac and renal function.**

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Key Words. **calcium channel blockers, nitrendipine, essential arterial hypertension, cardiac function, renal function**

Calcium channel antagonists are effective antihypertensive agents with potent smooth-muscle relaxing properties, which could account for their efficacy in lowering total peripheral resistance in hypertensive patients. Calcium channel antagonists have a definitive place in the treatment of arterial hypertension, but they vary their tissue selectivity and pharmacokinetics, so it is necessary to evaluate the hemodynamic changes induced by each one individually or separately [1–3].

Nitrendipine is a selective, long-acting dihydropyridine calcium antagonist with an important systemic vasodilatatory effect [4]. Its effectiveness in lowering blood pressure has been well documented in animals and humans in acute and prolonged studies. It appears to be well tolerated and can improve left ventricular function [5–7]. Although the systemic effects of nitrendipine are generally well known, its renal effects are only now being characterized [8].

A potential role for calcium antagonists in preserving or preventing the pathophysiological progression of hypertensive renal disease or in attenuating the progression of chronic renal disease has been recently suggested [9,10]. In fact a fundamental concept implicit in the evaluation of any antihypertensive drugs is related to its effects on renal function, because a decrease in renal perfusion pressure induces several compensatory reactions that tend to limit any blood pressure-lowering effect [10,11].

In this study antihypertensive effectiveness, the safety of nitrendipine, and its effects on central and renal hemodynamics were evaluated in patients with mild to moderate hypertension. Our final goal was to ascertain whether the reduction in blood pressure in-

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duced by nitrendipine administration was associated with maintained renal function.

Patients and Methods

Patients

Forty-three consecutive hypertensive outpatients attending the antihypertensive center of the Internal Medicine Department at the University of Palermo, Italy were enrolled, but only 26 patients (16 women and 10 men; mean age 45.4 ± 3.9 years), 15 with mild and 11 with moderate established essential hypertension, were studied. 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 patients were totally unselected as far as preliminary investigations were completed. They included routine biochemical tests (including creatinine clearance and oral glucose tolerance tests), chest X-ray, standard and 24-hour EKG monitoring, M- and B-mode echocardiography, and fundus oculi examination.

Exclusion criteria included accelerated hypertension, cardiovascular diseases (defined as myocardial infarction, chest pain, heart block, valvular diseases, cardiac enlargement, and heart failure), renal diseases, and renal failure (serum creatinine > 1.4 mg/dl), insulin-dependent or -independent diabetes mellitus, electrolyte imbalances, moderate or severe Keith-Wagener hypertensive retinopathy, alcoholism, or psychiatric problems. The patients with concomitant left ventricular hypertrophy defined according to echocardiographic criteria [12] 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 Sicilian Regional Ethical Committee.

After a 14-day run-in period with placebo, patients with persistent diastolic blood pressure higher than 90 mmHg were randomly assigned to a double-blind 8-week controlled trial of nitrendipine (N) 20 mg once a day (13 pts) or hydrochlorothiazide (HTC) 25 mg once a day (13 pts). The drugs were supplied by Bayropharm S.r.l. Both hypertensive groups were maintained on a normal sodium diet (150 mEq/day). In view of this all the patients were advised to follow a computerized and no-added-salt diet. The good adhesion to dietetic regimen was controlled through periodical and randomized examination of urinary excretion of sodium.

Clinical characteristics, central and renal hemodynamic investigations, and laboratory tests were performed at the end of the run-in period (D0) and 24 hours after the last N or HCT dose (D57). Clinical measurements included heart rate (HR), which was derived from the electrocardiographic trace, and systolic (SBP) and diastolic (DBP) blood pressure (BP), which were measured in triplicate using a mercury sphygmomanometer after 5 minutes in the supine position. Korotkoff phase V was used for DBP. BP and HR were also measured on days 14, 28, 42, and 56. Mean blood pressure (MBP) was calculated as the sum of DBP plus one third of the pulse pressure.

Methods

Renal hemodynamics

Renal hemodynamics were evaluated by radionuclide study according to methods described by Schlegel et al. and Gates et al. [13,14]. The methods utilized for the measurement 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, respectively, present in the kidneys 1–3 minutes after administration according to the following procedure. All the patients were well hydrated orally (10 ml/kg, 1–2 hours before the study). An 18-gauge cannula was placed into a right or left antecubital vein and 3 mCi of Tc-99m DTPA (freshly prepared from a constant source), followed at 15-minute intervals by 250 μCi of I-131-labeled sodium iodohippurate, were injected. The injected dose was measured by counting the syringe on the gamma camera under standardized geometry (at 20 cm). Renal data acquisition was also performed with the computerized, large-field scintillation camera (General Electric) with a high-resolution 1.5-in. parallel-hole collimator, with the patient in a supine position over the camera. The data were recorded in the computer memory every 15 seconds over 10 minutes for Tc-99m DTPA and 20 minutes for I-131 hippuran. Data acquisition was initiated at the moment of injection, and the data were analyzed at the end of the study, after outlining each kidney in a region of interest. In practice, 3–4 minutes is sufficient for each measurement, as described by Schlegel et al. [13]. To calculate the 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; the relative and fractional uptake were related to the clearance value by the empiric regression equations previously reported [13,14].

Using radionuclide techniques, effective renal plasma flow (ERPF; ml/min), effective renal blood flow [ERBF = ERPF/(1 − Ht); 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 × 80/ERBF (dynes × sec × cm^{-5}). The accuracy and reliability of this technique in the evaluation of global renal function or unilateral kidney function have been validated by Chakati et al. [15], and this technique is currently utilized in our laboratory [16].

In addition, the noninvasive radionuclide technique gives a certain advantage in comparison with the traditional method utilized in evaluating the ERPF or GFR. In fact, the isotopic methods provide an estimate of GFR or ERPF without blood or urine sampling. These methods allow the determination of these measurements separately for each kidney and derive values for global renal function [15]. In contrast, the standard techniques usually require continuous intravenous administration of adequate substances, as well as inulin or PAH with multiple blood and urine analysis. Furthermore, these techniques do not allow measurements of unilateral renal function without invasive ureteral catheterization [15].

Central hemodynamics

Central hemodynamics were determined by first-pass radionuclide angiocardiography according to a validated method currently utilized in our laboratory [17]. First-pass radionuclide angiocardiography represents a useful method for central hemodynamic determination. It is known that this technique is well correlated with contrast ventriculography [18]. For reliable assessments it is necessary to provide adequate standardization of the procedure, in particular, ensuring a homogenous radioactive bolus and a rapid injection of the tracer [17,18].

Using first-pass radionuclide angiography, cardiac index (CI; ml/min/mq) and left ventricular ejection fraction (LVEF; %) were calculated. The total peripheral resistance (TPR) was also measured by the formula: TPR = MBP × 80 × 1332/CI (dynes × sec × cm^{-5} × mEq).

Statistical analysis

The data were expressed as mean ± standard error of the mean (SEM). Statistical analysis was carried out using one-way analysis of variance (ANOVA) and a t test for paired data.

Results

The results are summarized in Tables 1–3. There was no statistically significant difference between the two treatment groups in the baseline characteristics (Table 1 and 2).

Nitrendipine group

After nitrendipine treatment a statistically significant ($p < 0.01$) decrease vs. baseline values was observed for SBP, DBP, and MBP (Table 1). Blood pressure normalization (DBP ≤ 90 mmHg) occurred in 10 of the 13 hypertensive patients. Nitrendipine administration induced a significant increase ($p < 0.05$) in CI, ERPF, and ERBF and a significant decrease ($p < 0.01$) in TPR and RVR; mild but not significant increases in LVEF and GFR were found, but no significant change in FF (Table 2).

No clinically important modification occurred in the biochemical tests (Table 3). Only transient and mild side effects were reported in three patients: dizziness (one case) and flushing (three cases).

Hydrochlorothiazide group

After hydrochlorothiazide treatment, a slight but significant ($p < 0.05$) weight loss and a significant ($p < 0.01$) decrease in SBP, DBP, and MBP were observed (Table 1). Blood pressure normalization (DBP ≤ 90 mmHg) occurred in 8 of 13 hypertensive patients.

Moreover, a statistically significant ($p < 0.05$) decrease vs. baseline values for RVR was found without a significant change in CI, EF, TPR, ERPF, ERBF, GFR, and FF (Table 2). No clinically important modification occurred in the biochemical tests (Table 3),

Table 1. *Clinical characteristics (mean value ± SEM) of two hypertensive groups before and after nitrendipine or hydrochlorothiazide*

	Nitrendipine (20 mg/day) n = 13		Hydrochlorothiazide (25 mg/day) n = 13	
	Baseline	Treatment	Baseline	Teratment
Age (years)	46.6 ± 4.2		42.5 ± 3.3	
Body weight (kg)	80.7 ± 3.8	78.5 ± 3.4	78.2 ± 3.7	73.0 ± 3.8[a]
Height (m)	1.68 ± 0.03		1.71 ± 0.02	
BMI (kg/m^2)	28.3 ± 0.6	27.5 ± 0.6	26.7 ± 0.7	25.8 ± 0.5
BSA (mq)	1.90 ± 0.06	1.88 ± 0.05	1.89 ± 0.05	1.80 ± 0.05
HR (b/m)	77.0 ± 1.50	80.7 ± 1.20	78.0 ± 1.8	76.7 ± 1.4
SBP (mmHg)	160.6 ± 4.8	148.1 ± 2.5[b]	163.3 ± 1.8	149.7 ± 1.9[b]
DBP (mmHg)	101.8 ± 4.1	90.0 ± 1.3[b]	99.6 ± 1.3	88.9 ± 1.4[b]
MBP (mmHg)	121.8 ± 4.2	109.3 ± 1.6[b]	120.8 ± 1.2	108.9 ± 1.6[b]

BMI = body mass index; BSA = body surface area; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure.

[a] $p < 0.05$ vs. baseline.

[b] $p < 0.01$ vs. baseline.

Table 2. Central and renal hemodynamic characteristics (mean value ± SEM) in hypertensive patients before and after nitrendipine or hydrochlorothiazide administration

	Nitrendipine (20 mg/day) n = 13		Hydrochlorothiazide (25 mg/day) n = 13	
	Baseline	Treatment	Baseline	Treatment
CI (ml/mq/m)	3,396 ± 439	3,950 ± 410[a]	3,271 ± 511	3,203 ± 407
LVEF (%)	62.5 ± 1.67	65.0 ± 1.50	63.0 ± 2.0	62.8 ± 1.9
TPR (dyne·sec·cm^{-5}·mq)	2,850 ± 252	2,171 ± 275[b]	2,954 ± 192	2,877 ± 185
ERPF (ml/m)	511 ± 41	592 ± 53[a]	544 ± 37	537 ± 51
ERBF (ml/m)	922 ± 71	1,072 ± 84[a]	1,007 ± 90	958 ± 77
GFR (ml/m)	103.1 ± 5.0	108.5 ± 6.2	105.2 ± 6.0	104.7 ± 5.5
FF (%)	20.1 ± 0.1	19.6 ± 0.1	19.3 ± 0.2	19.7 ± 0.1
RVR (dyne·sec·cm^{-5})	10,560 ± 777	8,096 ± 673[b]	9,596 ± 492	8,820 ± 417*

CI = cardiac index; LVEF = left ventricular ejection fraction; TPR = total peripheral resistance; ERPF = effective renal plasma flow; ERBF = effective renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction; RVR = renal vascular resistance.
[a] $p < 0.05$ vs. baseline.
[b] $p < 0.01$ vs. baseline.

Table 3. Biochemical tests (mean value ± SEM) in hypertensive patients before and after nitrendipine or hydrochlorothiazide administration

	Nitrendipine (20 mg/day) n = 13		Hydrochlorothiazide (20 mg/day) n = 13	
	Baseline	Treatment	Baseline	Treatment
Glycemia (mg/dl)	90.2 ± 10.1	91.8 ± 9.5	88.4 ± 6.4	91.3 ± 5.8
BUN (mg/dl)	33.8 ± 1.9	35.5 ± 1.3	32.3 ± 1.2	38.3 ± 1.1
Creatinine (mg/dl)	1.0 ± 0.06	1.0 ± 0.05	0.9 ± 0.04	1.1 ± 0.05
Sodium (mEq/l)	144.1 ± 0.1	142.0 ± 0.07	140.1 ± 0.05	138.2 ± 0.06
Potassium (mEq/l)	4.42 ± 0.06	4.27 ± 0.08	4.61 ± 0.04	4.16 ± 0.03
Uric acid (mg/dl)	5.1 ± 0.5	5.2 ± 0.3	5.0 ± 0.5	5.7 ± 0.6
Cholesterol (mg/dl)	205 ± 8.5	200 ± 9.0	201 ± 8.4	213 ± 8.3
HDL cholesterol (mg/dl)	52.4 ± 2.8	53.6 ± 2.6	54.3 ± 2.4	53.2 ± 2.6
Triglyceride (mg/dl)	169 ± 7.1	160 ± 6.3	160 ± 6.2	171 ± 6.5
GOT (IU/l)	16.2 ± 1.8	16.0 ± 1.3	17.2 ± 1.4	16.9 ± 1.5
GPT (IU/l)	20.1 ± 2.1	19.6 ± 0.9	19.7 ± 1.2	20.3 ± 1.1
Bilirubin (mg/dl)	0.7 ± 0.03	0.8 ± 0.08	0.7 ± 0.06	0.75 ± 0.08

None of the differences are significant.

except for a transient hypokaliema, which occurred after 5 days of HCT treatment and was corrected with oral K^+ administration (8 mEq once a day for 3 days). Side effects were few and transient: Two patients complained of asthenia and three of dizziness.

Discussion and Conclusions

This study demonstrated that nitrendipine was effective in reducing blood pressure in mild to moderate hypertensive patients, as reported by other authors [1–8], and its antihypertensive efficacy was comparable to HCT. In our study nitrendipine (20 mg daily) normalized blood pressure (DBP ≤ 90 mmHg) in 77% of treated hypertensive patients without significant side effects. No case of tachycardia occurred in an analysis of individual cases. Moreover, nitrendipine treatment produced vasodilation with a significant decrease in systemic and renal vascular resistance, improvement in renal blood and plasma flow, and favorable effects on cardiac function. The favorable effects of short-term nitrendipine administration on renal hemodynamics have been reported for other calcium antagonists as well [9,10,19].

In contrast, antihypertensive treatment with many other drugs leads to a reduction in renal perfusion due to the fall in systemic arterial pressure [20]. Renal

circulatory effects of various antihypertensive agents may differ significantly, and some agents can even impair renal function through a fall in renal blood flow [21,22].

This represents a very important finding related to the development of end-stage renal disease in hypertensive patients who are inadequately treated [23]. No sufficient data are available on repeated measurements of ERPF or GFR during prolonged treatment of mild to moderate hypertension in subjects with normal or near-normal renal function. However, the up-to-date clinical data suggest that the reduction in blood pressure induced by some calcium antagonists as well as nitrendipine could prevent renal failure in hypertensive patients [10,24]. The mechanism of this protection is still to be further investigated, but there are indications that increased intraglomerular pressure or hyperfiltration are contributing factors to the progression of hypertensive nephrosclerosis in rats and that this can be retarded by lowering the intraglomerular pressure [11,25,26]. Whether increased glomerular hyperfiltration represents the first stage of hypertensive nephropathy will have to be confirmed by prospective trials in hypertensive patients.

Hypertensive patients studied by this group were characterized by normal renal function, despite a mild baseline reduction of renal hemodynamic measurements (decrease in ERPF and ERBF), according to the normal values of our laboratory. It has also been suggested that those essential hypertensive patients who have the impaired renal hemodynamics and renal excretory function show the greatest renal response to calcium antagonists [19].

The short-term effects of nitrendipine monotherapy, i.e., a significant increase in both ERPF and ERBF associated with an unchanged and normal GFR and filtration fraction are similar to those previously reported for nifedipine or amlodipine [9,10,24]. This leads one to speculate that nitrendipine may be able to protect renal function in treated hypertensives.

In fact, it has been recently suggested that if calcium antagonists predominantly decrease preglomerular (afferent) arteriolar resistance without decreasing postglomerular (efferent) arteriolar resistance, glomerular capillary pressure may increase, potentially accelerating hemodynamic glomerular injury [25,26].

Our results are consistent with the hypothesis that the improvement of renal function induced by nitrendipine administration is due to a reduction in both afferent and efferent glomerular arteriolar resistances. It is a very attractive concept but has yet to be proved that the calcium antagonists can provide long-term renal protection. In view of these long-term clinical studies, it will be necessary to determine if the short-term renal response to nitrendipine monotherapy is sustained or has the potential to modify the clinical course of hypertensive renal disease.

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