SYSTEMIC HYPERTENSION

Comparison of Effects of Felodipine Versus Hydrochlorothiazide on Arterial Diameter and Pulse-Wave Velocity in Essential Hypertension

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In a double-blind cross-over study, the arterial changes produced by hydrochlorothiazide were compared with those observed after the calcium antagonist felodipine in 16 patients with mild to moderate systemic hypertension. Diameter changes at the site of the common carotid and brachial arteries were investigated using pulsed Doppler velocimetry, and pulse-wave velocities of the aortic, brachial and femorotibial areas were measured using standard noninvasive techniques. Whereas hydrochlorothiazide and felodipine similarly decreased blood pressure, hydrochlorothiazide did not change pulse-wave velocity, and the diameters of the brachial and common carotid arteries. Felodipine significantly decreased pulse-wave velocity, and increased brachial arterial diameter and compliance, with no change in carotid arterial diameter. Evidence was found that although felodipine had specific effects on the arterial system of hypertensive subjects, hydrochlorothiazide did not produce any sizable arterial change. These differential effects may influence specifically the heart afterload, with important consequences for diuretics that are known to cause minimal changes in cardiac structure and function.

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Antihypertensive drug treatment has heterogeneous effects on the arterial tree of the cardiovascular system.[1] Whereas the incidence of cerebrovascular accidents is significantly reduced, there are fewer changes in the incidence of ischemic coronary disease. One possible explanation is that antihypertensive agents have heterogeneous effects on the mechanical properties of the large arteries. Whereas converting enzyme inhibitors, calcium antagonists and some drugs blocking the autonomic nervous system are known to improve the viscoelastic properties of the arterial wall, minor changes are observed after administration of propanolol and dihydralazine.[2] In this regard, no controlled study was performed with diuretics, which are the most common antihypertensive agents. However, epidemiologic studies have shown that for the same age and mean arterial pressure, subjects with increased sodium intake had a more marked increase in pulse-wave velocity (PWV), a classical marker of arterial rigidity, than did those with low sodium intake.[3,4] However, in hypertensive subjects, a cross-over double-blind study has shown that reduced sodium intake is associated with an increased arterial diameter at the site of the brachial (but not the common carotid) artery.[5]

The present study evaluates the arterial effects of hydrochlorothiazide[6] versus felodipine[7,8] in hypertensive patients using a double-blind cross-over design.

METHODS

Patients: Sixteen patients (11 men and 5 women) with essential hypertension completed this study. Mean age ± 1 SD was 53 ± 12 years (range 33 to 76). Mean weight was 76 ± 15 kg, and mean height 168 ± 8 cm. Diastolic pressure measured by mercury sphygmomanometer was constantly >95 mm Hg after a 21-day placebo period. All subjects had mild to moderate hypertension according to World Health Organization criteria (diastolic blood pressure <115 mm Hg by mercury sphygmomanometer, Korotkoff phase V). Extensive clinical and biological investigations were performed according to previously described procedures,[5] indicating that patients had essential hypertension without cardiac, neurologic or renal involvement, arteriosclerosis obliterans of the lower limbs, or diabetes mellitus. Written informed consent was obtained from patients. The study was approved by the ethical committee of Broussais Hospital.

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TABLE I Casual Supine Blood Pressure (BP) Measurements Before and After Each Treatment: Mercury Sphygmomanometer

Supine	Baseline	Felodipine	Hydrochlorothiazide	p Value (intergroup comparison)*
Systolic BP (mm Hg)	166 ± 15	142 ± 16	150 ± 15	<0.02
Diastolic BP (mm Hg)	102 ± 5	88 ± 8	91 ± 8	NS
Mean BP (mm Hg)	123 ± 7	106 ± 11	110 ± 10	<0.02
Heart rate (beats/min)	71 ± 10	72 ± 10	68 ± 10	<0.02

*Felodipine versus hydrochlorothiazide.

Patients participated in a 12-week, randomized, double-blind, cross-over study. After the placebo-period, patients were randomized into 2 groups. Subjects in group A received tablets containing 25 to 50 mg of hydrochlorothiazide daily for 6 weeks. Subjects in group B received indentical tablets containing 5 to 10 mg of felodipine daily for 6 weeks. At the end of this period, the treatment was changed, with patients in group A receiving felodipine, and those in group B receiving hydrochlorothiazide for 6 weeks. Each sequence of 6 weeks was divided in 2 periods of 3 weeks, at the end of which the dosage of each compound was doubled if diastolic blood pressure was >95 mm Hg. Finally, at the end of the trial, 11 subjects received 10 mg of felodipine, and 5 received 5 mg; 13 subjects received 50 mg of hydrochlorothiazide, and 3 received 25 mg. Hemodynamic determinations were performed at the end of the placebo washout period, and at the end of the first (6th week) and second (12th week) active treatment periods.

Hemodynamic determinations: The study was performed at controlled room temperature of 20 ± 2.5°C with the patient in the recumbent position and after 15 minutes of rest. Hemodynamic measurements were obtained before and 3 hours after the last drug administration (6th and 12th weeks), according to the well-known pharmacokinetic and pharmacodynamic effects of the drugs.[6–8] Arterial blood pressure was measured automatically every 3 minutes in the left arm with an oscillometric blood pressure recorder (Dinamap, Model 845 P, Critikon, Tampa, Florida).[5] Hemodynamic measurements were obtained in the right common carotid and right brachial arteries.

Carotid and forearm hemodynamic values were obtained with a bidimensional pulsed Doppler system (Alvar Electronics, Montreuil, France),[9] the probe of which was fixed with a stereotactic device over the course of the artery, as previously described and validated.[9,10] In brief, arterial diameter and blood flow velocity are measured separately, using a bidimensional recording of the Doppler signals, and a range-gated time system of reception. The resolution of the method for diameter measurements is 0.34 mm, a finding that has been validated in vitro.[9] Reproducibility for the arterial diameter is ≤5%, and for blood flow velocity between 10 and 15%.[9,10] Blood flow is calculated as the product of blood velocity and cross-sectional area deduced from the arterial diameter by using a cylindrical representation of the artery. Arterial blood flow is expressed in ml/min. Local vascular resistance is calculated as the ratio between simultaneous mean blood pressure (measured from Dinamap apparatus) and flow.

For the determination of PWV, 5 different Doppler flow recordings were obtained at 5 sites[10,11]: the base of the neck over the common carotid artery, over the right femoral artery, over the right posterior tibial artery, over the right brachial artery in the axilla, and the right radial artery at the wrist. Flow was measured with a directional continu Doppler unit (SEGA M842, 10 MHz) with handheld probes. As previously described, the time delay was measured between the feet of the flow waves recorded at these different points, and the distance traveled by the pulse was measured between the different recording sites over the body surface with a tape measure.[10,11] Arterial PWV was calculated as the ratio between distance and transit time. The reproducibility of the measurements were published in detail previously.[10,11]

Brachial artery compliance was evaluated using a propagative model,[10,11] according to the Bramwell-Hill equation: $PWV^2 = (VdP/pdV)$, where p is blood density, and dV and dP are changes in volume (V) and pressure (P), respectively. As described previously,[11] when a thin arterial wall is assumed, compliance of the brachial artery (expressed per unit of length) may be calculated as: $dV/dP = 3.14\ r^2/p\ PWV^2$.

Statistical evaluation: Statistical analysis was performed with the NESS® statistical software (Kaysville, Utah). Baseline values of groups A and B were compared with 2-way analysis of variance, and did not show any difference. Modifications of the different hemodynamic and biological parameters were compared with 3-way (patient, treatment and sequence) analysis of variance[12]; this test did not indicate any difference in the 2 sequences of treatment. A p value <0.05 was considered significant.

RESULTS

Table I shows that whereas felodipine and hydrochlorothiazide decrease diastolic blood pressure equally, systolic and mean arterial pressure were slightly lower with felodipine ($p < 0.02$).

Table II indicates that whereas neither felodipine nor hydrochlorothiazide changed carotid arterial hemodynamics, significant changes were observed at the site of the brachial artery. Specifically, by comparison with hydrochlorothiazide, felodipine decreased resistance ($p < 0.05$), and increased diameter ($p < 0.05$) and compliance (p

TABLE II Changes in Arterial Hemodynamic Parameters

	Baseline	Felodipine	Hydrochlorothiazide	p Value (intergroup comparison)*
Brachial Artery				
Diameter (cm)	0.437 ± 0.060	0.449 ± 0.060	0.431 ± 0.050	<0.05
Blood flow velocity ($cm \cdot s^{-1}$)	4 ± 2	5 ± 2	4 ± 2	NS
Blood flow ($ml \cdot min^{-1}$)	109 ± 55	136 ± 58	117 ± 50	NS
Vascular resistance ($dynes \cdot s \cdot cm^{-4}$)	104 ± 40	72 ± 30	92 ± 46	<0.05
Arterial compliance ($dynes \cdot cm^{-4} \cdot 10^{-7}$)	1.1 ± 0.5	1.7 ± 0.8	1.2 ± 0.6	<0.005
Carotid Artery				
Diameter (cm)	0.628 ± 0.060	0.627 ± 0.050	0.596 ± 0.060	NS
Blood flow velocity ($cm \cdot s^{-1}$)	16 ± 3	17 ± 4	16 ± 3	NS
Blood flow ($ml \cdot min^{-1}$)	625 ± 147	667 ± 143	585 ± 100	NS
Vascular resistance ($dynes \cdot s \cdot cm^{-4}$)	16 ± 5	15 ± 5	17 ± 4	NS

*Felodipine versus hydrochlorothiazide.

TABLE III Changes in Pulse-Wave Velocities

Pulse-Wave Velocity (m/s)	Baseline	Felodipine	Hydrochlorothiazide	p Value (intergroup comparison)*
Carotid–femoral	11 ± 2	9 ± 2	10 ± 2	<0.005
Femorotibial	13 ± 2	11 ± 2	12 ± 2	<0.005
Carotidoradial	12 ± 2	10 ± 2	11 ± 2	<0.005

*Felodipine versus hydrochlorothiazide.

<0.005). Brachial artery hemodynamics after hydrochlorothiazide were similar to those of baseline values.

Table III indicates the changes in PWV. Whereas no change was observed after hydrochlorothiazide, a significant decrease was observed after felodipine ($p < 0.005$) in the 3 arterial sites studied.

No difference was observed in biological parameters, with the exception of plasma potassium (4.1 ± 0.1 with felodipine, and 3.7 ± 0.02 with hydrochlorothiazide) ($p < 0.02$).

DISCUSSION

In the present, double-blind, cross-over study, felodipine and hydrochlorothiazide did not change arterial hemodynamics at the site of the carotid artery (which is an elastic artery), but caused different changes in PWV and arterial hemodynamics at the site of the brachial artery (which is a muscular artery). Whereas hydrochlorothiazide did not change PWV and brachial artery hemodynamics, felodipine decreased vascular resistance and increased compliance of the brachial artery, and decreased PWV in the brachial, femoral and aortic areas. However, these findings should be interpreted carefully, because blood pressure changes were relatively smaller after hydrochlorothiazide than after felodipine and since the pulsed Doppler techniques have some limits regarding resolution and reproducibility (see Methods).[9,10,13]

After hydrochlorothiazide, brachial artery diameter did not change significantly. However, modifications of <0.34 mm are within the resolution limits of the Doppler method. Thus, the possibility that the decrease in blood pressure produced by hydrochlorothiazide caused a slight reduction in brachial artery diameter due to the decrease in the distending pressure should not be completely excluded. However, this possibility does not appear to be probable, because the same trend should be expected at the site of the common carotid artery, which has a more elastic behavior than does the brachial artery and therefore is more sensitive to blood pressure changes. Finally the finding of unchanged brachial artery diameter after hydrochlorothiazide is in accordance with a shift of pressure-diameter curve toward lower values of blood pressure, suggesting that the diuretic compound caused intrinsic modifications of the arterial wall independent of changes in blood pressure. There are several arguments in favor of this interpretation. First, sodium may act directly on arterial smooth muscle tone through different mechanisms involving sodium-potassium pumps, calcium exchange, activation of the sympathetic nervous system, and action of natriuretic factors.[14–18] Second, experimental studies in rats indicate

that increased sodium intake modifies the arterial wall and produces significant structural changes.[19] Third, decreased sodium intake in hypertensive subjects causes an increase in diameter at the site of the brachial artery.[5] Finally, geometric changes of the brachial artery may occur after long-term administration of diuretic compounds. For example, after canreonate, ouabain causes a significant brachial artery constriction that is not observed in the absence of treatment.[20]

The absence of change in PWV after hydrochlorothiazide contrasts with the significant decrease observed with felodipine. Several mechanisms may be proposed to explain the absence of change in arterial distensibility. First, the decrease in blood pressure produced by hydrochlorothiazide was relatively small, and it is possible that a larger blood pressure reduction may produce a more substantial passive change in distensibility.[21] Second, the potassium depletion produced by diuretics may induce specific effects on the tone of brachial artery smooth muscle.[14] However, we showed previously that diuretic compounds did not change brachial artery diameter and distensibility, regardless of whether they cause hypo- or hyperkaliemia.[22] Finally, the counterregulatory mechanisms originating from the sympathetic and the renin-angiotensin systems after diuretic treatment[6] may interfere with the brachial artery changes. For example, the vasodilating properties of salt and water depletion may be masked by the brachial artery constriction mediated by norepinephrine or angiotensin.[2,23] In this regard, it is important to observe that the diuretic compound indapamide, which causes less counterregulatory mechanisms than does hydrochlorothiazide,[24] has been shown to increase compliance in clinical situations[24] and in experimental studies of rats.[25,26]

Whereas hydrochlorothiazide produced no sizable arterial change in hypertensive subjects, felodipine increased brachial artery diameter and compliance, and significantly decreased aortic, femoral and brachial PWV. Because felodipine increased brachial artery diameter despite the blood pressure reduction, the finding reveals a specific effect of felodipine on the arterial wall, as previously observed with diltiazem and dihydropiridine derivatives.[2,27] Since the drug did not increase blood flow velocity, it does not appear probable that the increase in brachial artery diameter was due to a flow-dependent mechanism.[10,28] It appears more likely that felodipine produced a direct arterial smooth muscle relaxation, as previously shown in clinical and experimental studies.[2,27,29] Finally, the substantial decrease in carotid-femoral PWV observed after felodipine contrasts with the absence of change observed after hydrochlorothiazide and may explain the more marked decrease in systolic blood pressure.

It was reported previously that antihypertensive drugs causing reversion of cardiac hypertrophy, such as converting enzyme inhibitors and calcium antagonists, simultaneously produce an increase in aortic compliance and distensibility.[30] However, the vasodilating drug dihydralazine has been shown to cause no change in cardiac hypertrophy, and furthermore, no change in aortic compliance and distensibility.[2,30,31] In the present study, it is shown that hydrochlorothiazide, which is known to cause minor changes in cardiac hypertrophy,[32] also has no effect on aortic compliance and distensibility. Therefore, it is suggested that the changes in the viscoelastic properties of the arterial wall may modulate the effect of the blood pressure changes on the structure of the heart after antihypertensive drug treatment.

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