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ORIGINALS

Effect of valsartan on arterial blood pressure and renal function in patients with arterial hypertension and type 2 diabetes mellitus. Lavapal study

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SUMMARY

Arterial hypertension and diabetes mellitus give rise to a situation of high cardiovascular risk. The potential renoprotection from inhibition of the renin-angiotensin system is a valid option in this type of patient.

Objective: *Evaluate the effect of valsartan on blood pressure (BP) and renal function in albuminuric patients with type 2 diabetes and arterial hypertension.*

Patients and methods: *This was a prospective, observational study. Seventy-four diabetic patients with a blood pressure of ≥ 140/90 mmHg, with micro or macroalbuminuria and a) blood creatinine levels lower 1.5 mg/dl (group 1) or b) blood creatinine levels between 1.5 and 2 mg/dl (group 2), were studied and followed up for a 12-week period. Treatment was started with valsartan 80 mg/d, increasing to 160 mg/d, adding torasemide at a dose of 5 mg/d if the target blood pressure of 130/85 mmHg has not been achieved. The degree of BP reduction was analyzed comparatively using a mercury sphygmomanometer and a semi-automatic monitor, the Omron HEM 705 CP.*

Results: *All patients showed a significant reduction of the systolic (SBP) and diastolic (DBP) blood pressures ($p< 0.001$) over the study period, decreasing from 150.7 ± 12.8 to 130.8 ± 9.6 and from 94.7 ± 7.7 to 76.8 ± 6.3 mmHg, respectively. A significant reduction was observed only for diastolic blood pressure (101.4 ± 8.8 to 79.4 ± 5.6; $p < 0.001$) in the group 2 of patients. Lowest BP values were always obtained with the semiautomatic device. At the end of the study, 9.5% maintained valsartan 80 mg/d and 36.5% required the addition of a second or third drug to valsartan 160 mg in order to achieve the therapeutic target BP. A significant reduction was observed in the microalbuminuria (75.5 ± 9.5 to 54.7 ± 7.3 μg/min; $p < 0.001$) and macroalbuminuria ($n = 20$; 0.93 ± 0.4 to 0.68 ± 0.4 g/day; $p < 0.001$).*

Conclusion: *Valsartan significantly reduced SBP and DBP. Valsartan at 160 mg/d had a significantly greater effect in reducing micro and macroalbuminuria. No chan-*

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ges were observed in renal function, HbA1c or serum potassium. The rate of adverse events was very low.

Key words: ***Hypertension. Diabetes mellitus. Valsartan. Renoprotection.***

EFECTO DEL VALSARTÁN SOBRE LA PRESIÓN ARTERIAL Y FUNCIONAL RENAL EN PACIENTES CON HIPERTENSIÓN ARTERIAL Y DIABETES MELLITUS TIPO 2. ESTUDIO LAPAVAL

RESUMEN

La hipertensión arterial junto a la diabetes mellitus son importantes determinantes de la aparición y evolución de la nefropatía diabética, y a la vez situación de elevado riesgo cardiovascular. La renoprotección mediante el bloqueo del sistema renina-angiotensina es una alternativa válida para este tipo de pacientes.

Objetivo: *Evaluar el efecto de valsartán, un antagonista específico de los receptores tipo 1 de la angiotensina II sobre la presión arterial y función renal en pacientes diabéticos tipo 2 con albuminuria e hipertensión arterial.*

Pacientes y método: *Se trata de un estudio prospectivo observacional, llevado a cabo en dos hospitales con pacientes procedentes de las diferentes unidades de Atención Primaria. Se analizaron 74 pacientes diabéticos tipo 2 con cifras de presión arterial ≥ 140/90 mm Hg, con presencia de micro o macroalbuminuria y a) cifras de creatinina en sangre inferiores a 1,5 mg/dl (grupo 1) o b) cifras de creatinina en sangre entre 1,5 y 2 mg/dl (grupo 2), seguidos durante 12 semanas. El tratamiento se inició con valsartán 80 mg/día, incrementando a 160 mg/día y añadiendo posteriormente torasemida a dosis de 5 mg/día si no se lograban alcanzar las cifras diana de presión arterial. El grado de reducción de la presión arterial fue analizado comparativamente con un esfigmomanómetro de mercurio y un monitor semiautomático Omron HEM 705 CP.*

Resultados: *En todos los pacientes objeto de estudio la presión arterial sistólica (PAS) y diastólica (PAD), pero no la presión de pulso, disminuyeron significativamente ($p < 0,001$) a lo largo del periodo analizado, pasando de 150,7 ± 12,8 a 130,8 ± 9,6 y de 94,7 ± 7,7 a 76,8 ± 6,3 mm Hg respectivamente. En el grupo 2 sólo se halló una reducción significativa de la presión arterial diastólica (101,4 ± 8,8 a 79,4 ± 5,6; $p < 0,001$). Los valores más bajos de presión arterial se obtuvieron siempre con el monitor semiautomático. Al final del estudio, el 9,5% de los pacientes se mantenía con valsartán 80 mg/día, al 48,6% de los pacientes se le dobló la dosis y el 36,5% de los pacientes necesitó la adición de un segundo o tercer fármaco al valsartán 160 mg/día para alcanzar la diana terapéutica de presión arterial. Hubo una reducción significativa de la microalbuminuria (75,5 ± 9,5 a 54,7 ± 7,3 μg/min; $p < 0,001$) y macroalbuminuria ($n = 20$; 0,93 ± 0,4 a 0,68 ± 0,4 g/d; $p < 0,001$) en todos los pacientes analizados respecto a sus valores basales.*

Conclusión: *El valsartán disminuye significativamente las cifras de PAS y PAD, alcanzándose en todos los casos el objetivo establecido, precisándo para ello los tres regímenes terapéuticos. El valsartán a dosis de 160 mg/día alcanzó un significativo y mayor efecto en la reducción de la micro y macroalbuminuria. No se encontraron modificaciones en las cifras de creatinina en sangre, aclaramiento de creatinina, HbA1c y potasio sérico. Los valores de HDL-colesterol aumentaron significativamente. La tasa de acontecimientos adversos fue mínima.*

Palabras clave: ***Hipertensión. Diabetes mellitus. Valsartán. Albuminuria.***

INTRODUCTION

Diabetes mellitus (DM), a true cardiovascular disease with a metabolic origin, is currently a disease with a prevalence that is alarmingly increasing worldwide as longevity, obesity and sedentary lifestyle of the population do so. Suffering from DM entails supporting a cardiovascular risk two to four times higher than that of the non-diabetic individual.

If arterial hypertension (AHT) is added to diabetes, which prevalence is twice than that in the non-diabetic population, the risk is increases two-fold for cardiac complications and four-fold for cerebrovascular attacks. Therefore, it can be stated that the combination of diabetes and AHT is truly explosive for the risk of suffering both macro- (cardiac, cerebral, and peripheral) and microvascular (ocular and renal) complications, making this pathological binomial the one that most morbimortality causes in the human being[1,2]. There is a large clinical evidence about the benefits from an appropriate treatment of AHT in diabetes. AHT control in these patients represents a greater decrease in the cardiovascular and renal risks than in the hypertensive non-diabetic population, making of diabetics a very grateful population to this therapeutic manouver[3-7].

While in type 1 DM (DM1) the incidence of AHT is closely related to diabetic nephropathy and is relatively rare without microalbuminuria (MAU). In type-2 (DM2), this relationship is not so clear-cut: AHT is present in 39% of the patients at the time of diagnosis and affects half of the diabetics before the occurrence of microalbuminuria, the percentage increasing to 85-95% during the clinical nephropathy phase.

Possibly diabetes is the disease that most accelerates atherosclerosis, as we can see in clinical practice with its striking vascular calcifications. This would affect the aortic stiffening explaining this way the profile of systolic AHT of the diabetic patient, its treatment refractoriness, the described frequency and severity of left ventricular hypertrophy, the non-dipper pattern of out-patient blood pressure monitoring (OBPM), and the generally early onset of AHT with no relation with renal disfunction.[1]

As it has been discussed, the clinical consequences of suffering from diabetes and AHT are so devastating that, from long time ago, there is an general consensus, reflected on institutional guidelines, recommending that pharmacological treatment should be implemented as early and aggressively as possible[4,8-11]. In spite of this, a high number of patients have inappropriately controlled arterial hypertension[12].

In both types of DM, the occurrence of proteinuria (macroalbuminuria) clinically detectable (urine albumin excretion > 200 µg/min) indicates the way to progression to chronic renal failure (CRF). This situation is preceded by the microalbuminuric phase. There are increasing data indicating that proteinuria reduction and normalization is a key therapeutic goal for renal protection[5-7] and possibly for cardioprotection[13]. In DM2, two recent studies with irbesartan and losartan[6] have demonstrated protection from renal function worsening in patients with established nephropathy, a protection that is independent from the anti-hypertensive effect. Renoprotection from angiotensin II receptor antagonists (ARA-II), which selectively block AT1 receptors, is mainly due to the reduction of micromacroalbuminuria and might be graded by the degree of renal function.

The main goal of the study was to analyze the degree of reduction of blood pressure levels after treatment with the selective ARA II valsartan*[**]

Valsartan is Diovan from Novartis Pharmaceuticas UK Ltd, Frimley, United Kingdom in DM2 patients. Established secondary objectives were to evaluate the effect of blood pressure (BP) levels reduction on renal disease progression, assessed by modifications in urinary excretion of albumin and plasma creatinine levels, and to check for possible differences in blood pressure levels assessed by mercury sphingomanometer (ME) and semi-automatic monitor (SM).

PATIENTS AND METHODS

Patients

Patients aged 35 to 75 years were included in the study to evaluate the effect of valsartan on arterial blood pressure and on renal function (LAVAPAL study: Las Palmas-Valsartan). The selection phase was established from October 2002 and May 2003. Of the 78 patients examined, 74 patients (58,1% women) with type 2 diabetes mellitus (DM2) and arterial hypertension (BP ε 14/90 mmHg) with microalbuminuria > 0 or macroalbuminuria > 0.15 mg/dL and with: a) plasma creatinine (Cr) < 1.5 mg/dL (group 1); or b) plasma creatinine between 1.5-2.0 mg/dL (group 2) were studied and followed-up for 12 weeks. Exclusion criteria were type 1 diabetes, the occurrence of non-diabetic nephropathy, renal failure with creatinine levels > 2.0 mg/dL or creati-

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nine clearance < 45 mL/min/1.73 m^2, a diagnosis of secondary AHT, the need of more than three drugs to control blood pressure, personal history of previous intake of angiotensin converting enzyme inhibitors (ACEI) or AT1 receptor blockers (ARA II), within 5 weeks prior to study treatment assignment. Also excluded were patients with morbid obesity (BMI > 40) or regular intake of non-steroidal anti-inflammatory drugs (NSAIDS), possibility of being pregnant, a previous ischemic or hemorrhagic vascular episode or heart failure within 12 months prior to inclusion, liver disease or serum potassium < 3.5 mEq/L or > 6.0 mEq/L, and non-controlled diabetes (HbA1c > 10.0%). Patients could be early withdrawn from the study because of adverse events (AE), protocol violation, or patient's own decision. The study was favorably evaluated by the Ethics Committee of our Hospital. All included patients were informed and gave their consent.

Study design

Two centers participated in this study, including patients from the area of Primary Care Units (PCU) and hospitalization with three coordinators (JCRP, JNM, and CPT), with an active control of 12-weeks duration. Once the patients were selected, the clinical history taken and inclusion criteria checked, valsartan treatment was started at an 80 mg/d dose. Following established evidences, the goal for BP was 130/85 mmHg[14]. A follow-up was done at weeks 4, 8 and 12. If there was an insufficient BP control with initial treatment, the valsartan dose was doubled at the next visit. In case of necessary, torasemide 5 mg/d could be added from the 8^{th} week and on. Dietary sodium restriction was recommended and explained to all patients, which they had to accomplish. At the initial assessment, anthropometrical characteristics and previous antihypertensive treatment were determined, and blood was drawn for blood biochemistry including glucose, glycosilated hemoglobin (high resolution liquid chromatography-HPLC), creatinine, urea, uric acid, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides using the standard biochemical techniques in hospital laboratories. Twenty-four-hour urine was collected to determine proteinuria (turbidimetry with end-point kinetic reaction with benzetonium chloride) and microalbuminuria (immunoturbidimetry). These same parameters were newly obtained at the end of the 12-weeks treatment. Microalbuminuria (MAU) was measured in 24-hour urine samples and was confirmed in each visit. Electrocardiogram was optional, according to the investigators judgment. Blood pressure was measured according to usual considerations, the dominant arm with the patient sitting and after a 5 minutes resting interval using Korotkoff's phases I and V with the mercury sphingomanometer, and according to the indications with the automatic oscillometry method with the OMRON HEM 705CP (Omron Healthcare) monitor. Two BP determinations were done with a 2-minutes interval. The mean value was used for calculations. The pulse pressure value was obtained as the SBP and DBP difference.

Statistical analysis

Quantitative variables are expressed by centralization and dispersion parameters: arithmetic mean and standard deviation, except for microalbuminuria that is expressed as mean _ standard error of the mean. The normality hypothesis of these variables was checked by Kolmogorov-Smirnov Test for just one sample. Qualitative variables were analyzed with the absolute frequency of appearance of each one of categories, and with relative frequencies.

Checking for the degree of systolic and diastolic blood pressure and pulse reduction after valsartan treatment (80 and 160 mg/d, and valsartan 160 mg/d plus other drugs), as well as changes between basal and final analyzed biochemical parameters was done by the Student' t test for equal means with paired samples, or its non-parametric alternative, the Wilcoxon' s test when necessary. The statistical significance level was established at $p < 0.05$. Data analysis was based on intention-to-treat analysis, and was done with statistical software SPSS, 11.5 version.

RESULTS

The 74 included patients started valsartan (Diovan) treatment 80 mg/d at the first visit. Seventy patients completed the study. Withdrawal reasons were: AE, 1; withdrawal from the study, 1; lack of blood pressure control, 2.

Clinical and demographic characteristics of the patients were similar. All were Caucasian. Known disease duration for diabetes was at least one year. 21.6% of the patients were smokers, and 13.5% alcohol consumers, with 12.2% with ethanol consumption lower than 40 g/day. Seventy-three percent had dyslipidemia, 21.6% had cardiovascular disease, and 8.1% had some chronic disorder other

Table I. Characteristics of studied patients

	Basal	Final	p
Glucose (mg/dL)	146 ± 43.8	137 ± 30.7	0.035
HbA_1c (%)	7.5 ± 0.7	7.4 ± 0.73	0.102
Creatinine (mg/dL)	1.02 ± 0.24	1.01 ± 0.21	0.725
Potassium (mEq/L)	4.7 ± 0.51	4.8 ± 0.57	0.307
Cholesterol (mg/dL)	215.75 ± 24.6	206.3 ± 22.25	< 0.001
HDL (mg/dL)	48.56 ± 13.12	50.71 ± 13.2	0.011
Atherogenic index	4.7 ± 1.2	4.22 ± 0.85	< 0.001
Triglycerides (mg/dL)	164.7 ± 52.8	156.4 ± 41.2	0.06
Microalbuminuria (µg/min)**	75.54 ± 9.5	54.7 ± 7.3	0.012
Proteinuria (g/d)	0.9 ± 0.45	0.68 ± 0.4	< 0.001

Values are expressed as mean ± SD, except for microalbuminuria (mean ± SE)**

than diabetes. The main clinical and biochemical data at the beginning and at the end of the study, and their statistical analysis, are shown in Table I. With regards to anti-hypertensive drugs used before inclusion, 36.5% of the patients were taking some calcium-channel blocker, 23% some diuretic, 17.6% a beta-blocker agent, and 23% some angiotensin-converting enzyme inhibitor (ACEI), and another different drug in the remaining 4.1%. 28.3% of the population included in the study was on anti-aggregation treatment with aspirin, and 32.4% on statins, and 22.9% with fib rates or others. Only two patients had their diabetes controlled with diet and non-pharmacological management, the remaining were on insulin, oral anti-diabetics, or both.

Effect of valsartan treatment on blood pressure levels

In the patients study sample, diastolic (DBP) and systolic (SBP) arterial blood pressure, but not pulse pressure (PP), significantly decreased ($p < 0.001$) throughout the analysis period, varying from 150.7 ± 12.8 to 130.8 ± 9.6, and from 94.7 ± 7.7 to 76.8 ± 6.6 mmHg, respectively. This change was already noticeable from the second visit. In all cases, the BP goal was achieved, the three therapeutic regimens being necessary. A significant decrease of SBP and DBP is achieved with valsartan 80 mg, 13.3 _ 9.5 and 14.3 ± 8.8 mmHg, $p = 0.02$; with valsartan 160 mg, 19.7 ± 8 and 17.6 ± 7.2 mmHg, $p < 0.001$; and with valsartan 160 mg plus other drugs, 22 ± 14.7 and 19.1 ± 5.4 mmHg, $p < 0.001$. BP changes with each treatment regimen are shown in Figure 1. Only 9.5% of the patients that started on treatment with valsartan 80 mg/d were kept at the same dose until the end of the study; 48.6% of the patients had their dose doubled; and 36.5% required the addition of a second o third drug to valsartan 160 mg/d to reach the therapeutic BP target.

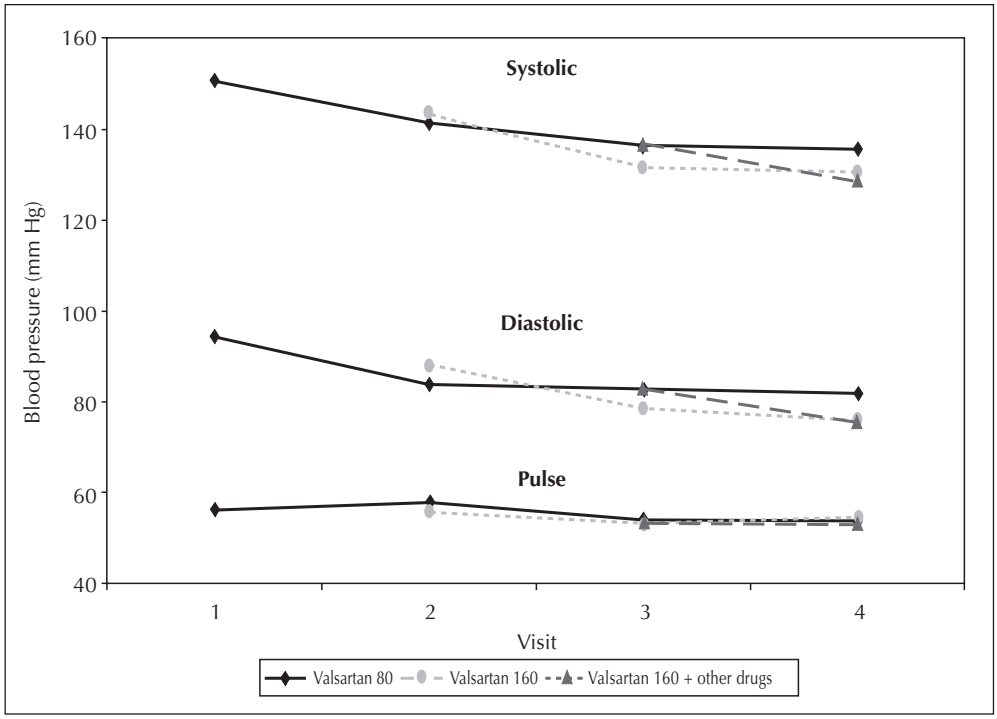

Fig. 1.—Progression of arterial blood pressure levels in all patients throughout the study, according to therapeutic regimen

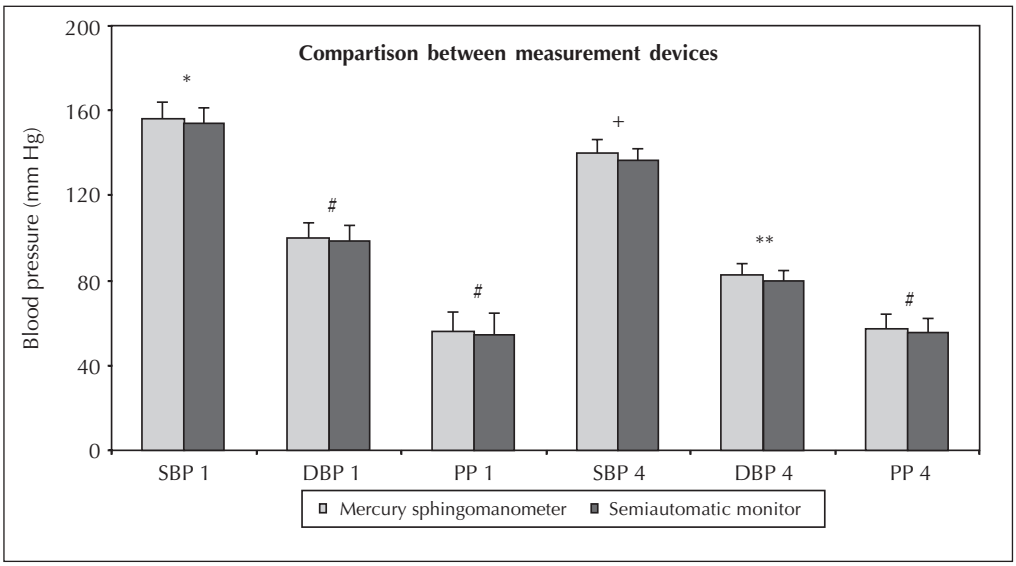

*Fig. 2.—Systolic (SBP) and diastolic (DBP) arterial blood pressure, and pulse pressure (PP) levels at firts (1) and last (4) visits, according to measurement device used. *p = 0.002; #p = NS; +p [0.001; **p = 0.008.*

Blood pressure levels variation according to the measuring device

When evaluating BP levels obtained by mercury sphingomanometer (ME) and semi-automatic monitor (SM), we did find significant differences in SBP readings at the first and fourth visits, and in DBP readings at the fourth visit (Figure 2). The lowest values are always obtained with SM, which would mean the tendency to round up with the monitor and to overestimation with the ME.

Blood pressure levels control according to plasma creatinine

A significant SBP (150.8 ± 13.1 to 130 ± 9.2 mmHg, $p < 0.001$), DBP (94.2 ± 7.5 to 76.6 ± 6.3 mmHg, $p < 0.001$) and PP (56.6 ± 10.9 to 53.4 ± 6.5 mmHg, $p = 0.023$) decrease was obtained throughout the 12-week treatment period in only group 1 of patients (n = 65). In group 2, a significant decrease was obtained only for DBP (101.4 _ 8.8 to 79.4 ± 5.6; $p < 0.001$).

Effect of valsartan treatment on renal disease progression

A significant reduction was observed in microalbumin excretion rate (75.5 ± 9.5 to 54.7 ± 7.3 µg/min; $p < 0.001$) and macroalbuminuria (n = 20; 0.93 ± 0.4 to 0.68 ± 0.4 g/day; $p < 0.001$) in all patients as compared to baseline values. MAU or macroalbuminuria reduction gradient in both studied groups according to plasma creatinine levels is shown in figure 3. The effect of this drug on MAU values was: valsartan 160 mg/d, 30.2 ± 7.7 µg/min, $p < 0.001$; valsartan 160 mg plus other drugs, 9 ± 19.8 µg/min, $p = 0.136$; and on macroalbuminuria values: valsartan 160 mg, 0.3 ± 0.11 g/day, $p = 0.001$; and valsartan 160 mg plus other drugs, 0.2 ± 0.16 g/day, $p = 0.003$, then showing a greater and significant effect in MAU and macroalbuminuria levels reduction with the administration of valsartan 160 mg (fig. 4).

With the used doses, there were no changes in blood creatinine levels. When patients were categorized according to their creatinine levels, the reduction in MAU and macroalbuminuria levels was only significant in group 1, 20 ± 8.1 µg/min, $p < 0.001$, and 0.25 g/d, $p < 0.001$, respectively.

At the end of the study, there were no significant differences in serum HbA1c or potassium levels as compared to baseline. Total cholesterol and glucose levels, and atherogenic index significantly decrease, with the subsequent increase in HDL-cholesterol levels.

DISCUSSION

This study shows that valsartan treatment with 80-160 mg/day doses, as monotherapy or in combination with other anti-hypertensive drugs, is effective and well tolerated by patients with type II diabetes mellitus and arterial hypertension. Valsartan also induced a significant reduction of micro- and macroalbuminuria in those patients with creatinine levels lower than 1.5 mg/dL.

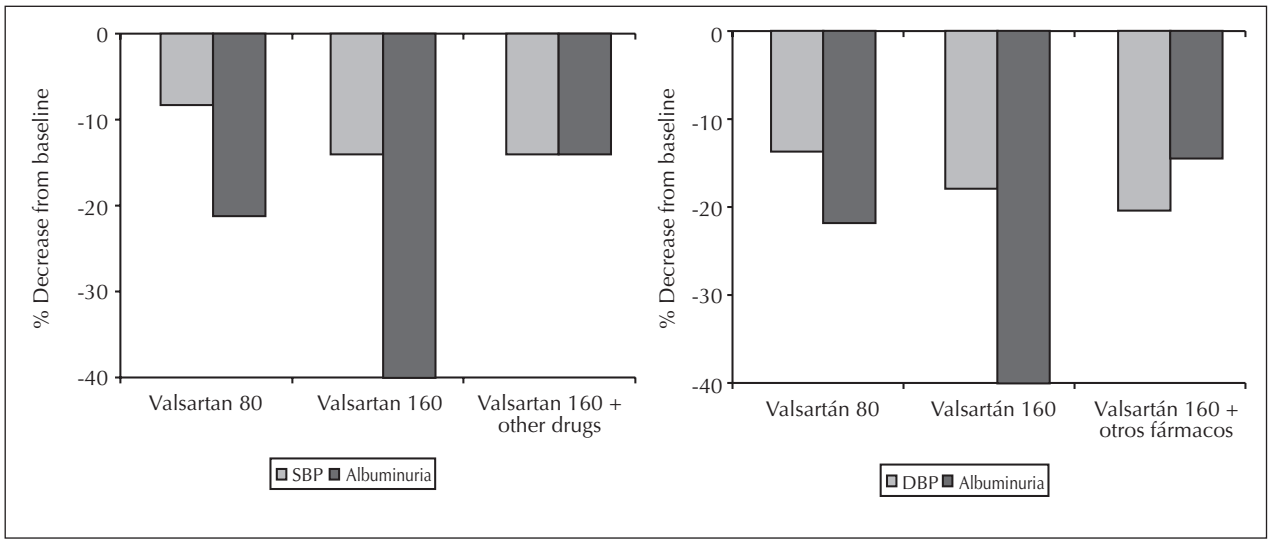

Fig. 3.—Percentage or reduction of systolic arterial blood pressure (SBP), diastolic blood pressure (DBP), and albuminuria as compared to baseline in patients with blood creatinine < 1.5 mg/dL (Group 1).

Arterial hypertension (AHT) is twice frequent in DM individuals than non-diabetic ones[1], being essential AHT the main presenting form of this AHT. Between 35-75% of cardiovascular and renal complications of diabetic patients are attributable to AHT.[1] AHT treatment in type 2 DM provides important and dramatic benefits. A target goal of DBP ≤ 80 mmHg seems optimal, and although target SBP goals have not been strictly evaluated, levels of 135 or less mmHg seem reasonable[8,9]. In a literature review from recent years, we can observe that studies such as SHEP[15], SYST-EUR[11], HOPE[16], RENAAL[5], IPDM[7], HOT[17], UKPDS[4] and ABCD[18], clearly show that an adequate blood pressure control in type 2 DM produces a substantial decrease of the cardiovascular risk and death. Similarly, the risk for microvascular disease, such as decrease of visual acuity and end-stage chronic renal failure, is also reduced[4,5,7,11,15-18] The choice of the initial anti-hypertensive agent

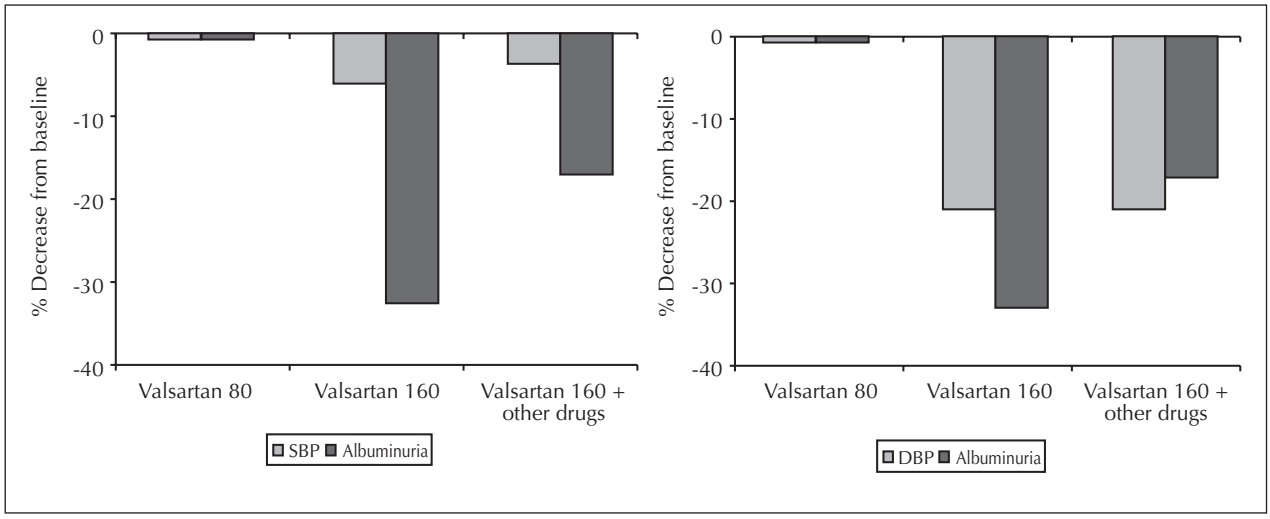

Fig. 4.—Percentage of reduction of systolic arterial blood pressure (SBP), diastolic blood pressure (DBP), and albuminuria as compared to baseline in patients with blood creatinine between 1.5-2.0 mg/dL (Group 2).

in diabetic patients is difficult to establish due to the existing literature controversies, favoring the type and characteristics of the treated population than an evidence-based reasoning. What it do seem to be clear is the need for using more than one drug. From the existent evidence, angiotensin II receptor antagonists are the drugs of first choice[6] without the deleterious metabolic effects of thiazides, also frequently recommended for their low cost. Valsartan, a powerful and well tolerated, highly selective AT1 receptor antagonist, has anti-hypertensive properties and a good tolerability profile[19]. With the administration of 80 mg/day a plasma peak level may be already observed within 2 hours, with a half-life of 7 hours. Valsartan 80-160 mg/day was able to achieve the target goal of SBP and DBP in 58.1% of the patients, whereas 36.5% needed a second or third anti-hypertensive drug, achieving a 13.21% and 18.9% reduction of SBP and DBP, respectively. These figures are slightly higher than those in other series that include type 2 DM patients with arterial hypertension. This blood pressure reduction was not accompanied by changes in creatinine or serum potassium values from baseline, by contrast to observations in other studies regarding the renin-angiotensin-aldosterone system (RAS) blockade in individuals with type 2 DM[20]. Until now, it was known that an optimal control of glucose levels would reduce microvascular complications from diabetes; however, data from the latest studies, among which UKPDS,[4] showed that strict glycemic control reduced retinopathy progression and the need for photocoagulation, but within 10 years of follow-up, retinopathy, renal function and mortality were not significantly improved[21]. By contrast, AHT control was clearly effective in reducing cardiovascular risk and mortality during a 4-6 years period[22], suggesting that AHT control in the DM patient is paramount to reduce microvascular complications[4].

When we consider mean blood pressure values obtained with the mercury sphingomanometer and with the semi-automatic monitor, although with little differences, there are, however, statistically significant differences for SBP and DBP in most of the measurements per visit. We can consider that agreement between both methods is good for SBP, DBP, and PP, taking into account that differences between both devices readings is less than 5 mmHg. This little differences may be due to the use of digits 0 and 5, and so to an observer bias, as it has been communicated in other studies.[23] In our study, it is shown that BP levels are better controlled in the group of patients with blood creatinine levels < 1.5 mg/dL, likely due to a lesser degree of renal damage, and therefore, a lower use of anti-hypertensive drugs. If the patient already has macro- or microalbuminuria, or renal failure, we may achieve slowing or halting the rate of progression of diabetic nephropathy, slowing or preventing inclusion into dialysis.

In our case, AHT seems to have no relation with obesity, since the body mass index of our patients was within the overweight range. Besides, we should consider that AHT in our patients was controlled with just one drug in 58.1% of the cases.

The possibility of decreasing microalbuminuria with the administration of an ARA-II agent was firmly established in the IRMA-II study.[7] In that study, done with irbesartan, a 38% reduction from baseline in MAU levels was achieved, and therefore a 70% reduction of the risk for progression to macroalbuminuria (irbesartan at a 300 mg dose) in hypertensive patients with type 2 diabetes mellitus. These data are close to those found in our study, where a 27% reduction of MAU and macroalbuminuria is achieved, with the reduction in SBP showing the greatest benefit and that extends to the whole range of DBP, as it was already known. This reduction was clearly significant only in those subjects with valsartan treatment at a 160 mg, with blood creatinine levels < 1.5 mg/dL. According to Cochrane Library citing, the inhibition of angiotensin II activity by an ARA-II or ACEI agent may slow or stop urinary albumin excretion, even independently of blood pressure changes[24]. In our study, it is difficult to differentiate whether this effect is dependent or not of blood pressure changes, since the latter was reduced in the three therapeutic regimens, and due to the study design, only analytical determinations were done. By chance, these patients had normal renal function (Cr < 1.1 mg/dL, with calculated creatinine clearance > 100 mL/min). Two studies[5,6] analyzing similar populations but with different creatinine levels of 1.90[5] and 1.69[6] mg/dL, and micro- and macroalbuminuria, show efficacy from other ARA-II agents (losartan and irbesartan, respectively). In our study, group 2 did not reach the necessary sample size in order to find significant differences in the rates of albuminuria reduction (test power of 17.4%), in spite of the subsequent reduction of blood pressure levels.

Another issue to be considered in our study was the good tolerability of the drug, with just one case (1.4%) of withdrawal from an AE consisting in cephalalgia and dizziness.

There was a discreet but significant improvement in glucose, total cholesterol, and HDL-cholesterol blood levels from baseline. It is difficult to know whether this changes are due to pharmacological treatment or to a closer physician control of the pa-

tient. From our results, it may be suggested that valsartan has good tolerability profile and anti-hypertensive efficacy, it reduces albumin and proteins excretion rate, inducing a renoprotective effect en type 2 diabetic patients with arterial hypertension.

STUDY LIMITATIONS

We have found in our study a series of limitations essentially referred to the difficulty in recruiting patients with creatinine values between 1.5-2.0 mg/dL. Patient selection was kept in a so narrow range of creatinine levels to avoid possible pharmacological complications. This has led to include together macro- and microalbuminuria in the statistical study, in some of the analyses performed. In a study with such a design, it was equally complex to reflect sodium intake by means of serial determination of sodium urinary excretion. In spite of that, patients were told about the importance of keeping a low sodium intake throughout the study. The group of valsartan plus other drugs includes patients that were on diuretics and/or beta-blockers and/or alpha-blockers and/or vasodilators, besides valsartan.

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