Original Article

Effects of Manidipine/Delapril *versus* Olmesartan/Hydrochlorothiazide Combination Therapy in Elderly Hypertensive Patients with Type 2 Diabetes Mellitus

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The purpose of this study was to compare the combination treatments of manidipine/delapril and olmesartan/hydrochlorothiazide (HCTZ) in elderly diabetic hypertensives. After a 4-week placebo period, 158 hypertensive patients with type 2 diabetes (age range: 66 to 74 years) were randomized to receive combination treatment of 10 mg manidipine plus 30 mg delapril or 20 mg olmesartan plus 12.5 mg HCTZ for 48 weeks in a prospective, parallel arm trial. After 12 weeks, manidipine or HCTZ was doubled in non-responders (systolic blood pressure [SBP] ≥130 mmHg and/or diastolic blood pressure [DBP] ≥80 mmHg). Patients were checked at the end of the placebo period and every 12 weeks thereafter. At each visit, lying, sitting and standing BP as well as fasting glycemia, glycosylated hemoglobin (HbA1c), electrolytes, uric acid, total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG) were evaluated. Both combinations reduced sitting SBP (−27.7 and −28.3 mmHg, respectively; both $p<0.001$) and DBP (−15.1 and −14.8 mmHg, respectively; both $p<0.01$) with no difference between the two treatments. Standing DBP was more markedly reduced by olmesartan/HCTZ (−19.5 mmHg; $p<0.001$) than by manidipine/delapril (−14.7 mmHg; $p<0.05$ *vs.* olmesartan/HCTZ). No changes in metabolic parameters were observed with manidipine/delapril, whereas an increase in HbA1c (+0.7%; $p<0.05$), uric acid (+0.4 mg/dL; $p<0.05$) and TG (+41.3 mg/dL; $p<0.05$), and a decrease in serum potassium (−0.3 mmol/L; $p<0.05$) and HDL-C (−3.4 mg/dL; $p<0.05$) were found in the olmesartan/HCTZ group. In conclusion, both combinations were similarly effective in reducing BP in elderly hypertensive diabetic patients. However, manidipine/delapril offered some advantages in terms of the less-pronounced BP orthostatic changes and absence of metabolic adverse effects. (*Hypertens Res* 2008; 31: 43–50)

***Key Words*: delapril, manidipine, olmesartan, hydrochlorothiazide, diabetic hypertensives**

Introduction

The current recommendation by the ESH/ESC and the JNC 7 hypertension treatment guidelines is to lower and maintain the blood pressure (BP) levels below 130/80 mmHg in subjects with diabetes mellitus, a target which can also be attained in elderly patients if the BP is dropped gradually with slow drug titration (*1*, *2*). This recommendation is based on the results of large prospective studies showing that tighter BP control in diabetic patients was associated with a significant decrease in cardiovascular morbidity and mortality (*3*,

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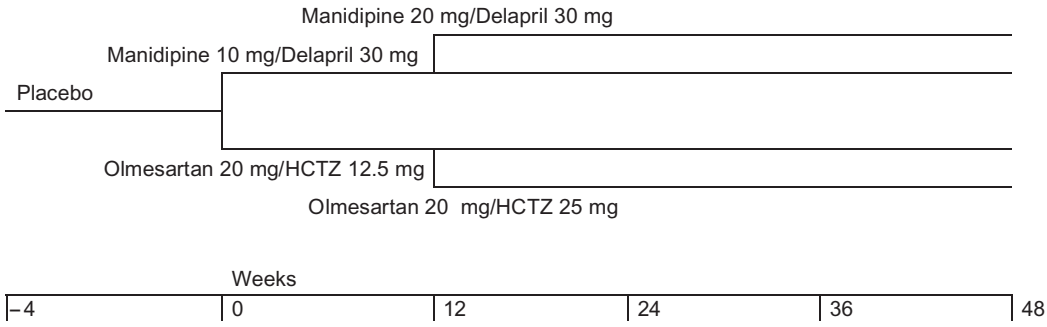

Fig. 1. *Study design.*

4). An ongoing trial is expected to provide further information and results (*5*).

Achieving these lower BP targets will require combination therapy in more than 60% of patients (*3*, *4*). The most logical combinations are those that include drugs that lower BP by different and complementary mechanisms (*1*, *2*, *6*). In choosing antihypertensive medications for diabetic patients, attention should be paid to not only the drugs' antihypertensive efficacy, but also their effects on postural decline in BP (given the propensity of diabetics to orthostatic hypotension), their metabolic profiles (which should be beneficial or at least neutral), and their influence on target organ damage. In this regard, inclusion of agents that target the renin-angiotensin system (RAS), such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), has been reported to exert particular benefits in reducing renal and cardiovascular risk in hypertensive patients with diabetes (*7–9*).

Although the most effective combination antihypertensive strategy in these patients needs to be determined in large scale randomized trials, recent hypertension treatment guidelines suggest that a range of combinations including an ACE inhibitor or an ARB as initial therapy with calcium channel blockers (CCB) or diuretics as added drugs is worth considering (*1*, *2*). Thus one suitable combination may be that between delapril, an ACE inhibitor with high affinity for the C-terminal site of ACE (*10*), and manidipine, a second-generation dihydropyridine CCB with vascular selectivity and long-lasting activity (*11*, *12*), both of which have been proven effective in reducing BP in monotherapy with a good tolerability profile (*13–17*). Because of the complementary mechanism and long duration of action of these two drugs, their combination has been demonstrated to produce more marked reductions in BP values than monotherapy, with a persistence of the hypotensive effect over the 24-h dosing interval (*18*, *19*).

Among ARBs, olmesartan selectively inhibits Ang II binding to Ang II subtype 1 (AT1) receptors with high potency and affords satisfactory BP control in monotherapy with a good tolerability profile (*20–23*). Its combination with hydrochlorothiazide (HCTZ) has been shown to provide better 24-h BP control than monotherapy in patients with mild-to-moderate as well as in those with severe hypertension (*24*, *25*).

The aim of the present study was to compare the antihypertensive efficacy and tolerability of manidipine/delapril combination therapy and olmesartan/HCTZ combination therapy in the treatment of elderly hypertensive patients with type 2 diabetes mellitus. Given the propensity of this type of population to develop orthostatic hypotension (*26–28*), special attention was focused on postural BP changes.

Methods

This was a 12-month, prospective, randomized, open label, blinded-endpoint (PROBE) parallel group study, with 2 treatment arms. Male and female outpatients, aged 66–74 years, with essential hypertension (defined as sitting systolic BP [SBP] $\geq$130 and $<$180 mmHg and sitting diastolic BP [DBP] $\geq$80 and $<$100 mmHg after a 4-week, run-in placebo period) and associated type 2 diabetes mellitus (*29*, *30*) in stable metabolic control (absence of glycosuria, HbA1c $<$7% and no change in hypoglycemic drugs in the last 6 months) were considered for enrollment. Patients with secondary hypertension, serum creatinine $\geq$140 μmol/L, serum potassium $<$3.5 mEq/L, body mass index (BMI) $>$30 kg/m^2, a smoking habit, history of myocardial infarction or stroke within 6 months prior to the study, congestive heart failure, cancer or any severe disease likely to interfere with the conduction of the study were excluded, as were those with known contraindications or intolerance to HCTZ, ARBs, ACE inhibitors, or calcium antagonists. Patients with isolated systolic hypertension (ISH) were also excluded from the study due to the different pathogenetic mechanisms of this form of hypertension. The study was performed in accordance with the Declaration of Helsinki and its amendments and all patients gave their written informed consent to participate in the study at the time of enrollment.

The study design is summarized in Fig. 1. After a 4-week, run-in placebo period, during which antihypertensives but not oral antidiabetic drugs were discontinued, patients fulfilling the inclusion criteria were randomly treated with the combination of 10 mg manidipine plus 30 mg delapril or the combination of 20 mg olmesartan plus 12.5 mg HCTZ, both given once daily in the morning (at approximately 8 AM)

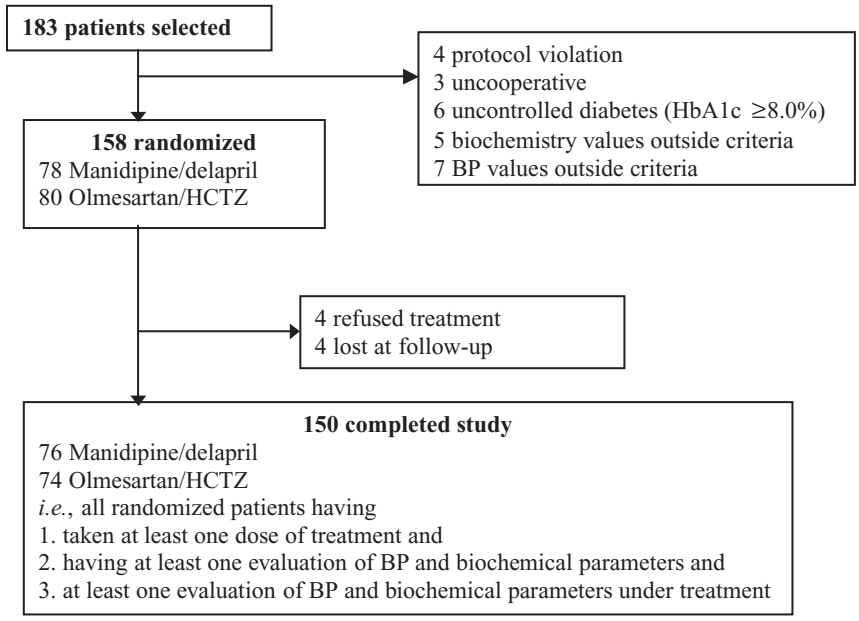

Fig. 2. *Flow chart of patient recruitment and disposition of patients entered into the study.*

Table 1. Baseline Characteristics of the Patients

Demographic and clinical characteristics	Manidipine/ delapril (n=81)	Olmesartan/ HCTZ (n=77)
Age, years	69.5±3.2	70.2±3.5
Male/female, *n*	39/42	38/39
BMI, kg/m^2	27.7±1.4	27.3±1.2
Weight, kg	77.3±7.2	77.0±6.8
Height, cm	167±3.5	168±3.7
HbA1c, %	6.6±0.5	6.8±0.4
Sitting SBP, mmHg	157.5±10.2	158.8±9.7
Sitting DBP, mmHg	94.1±8.7	93.8±8.2
Sitting HR, bpm	77.6±6.1	76.8±5.8
Diabetes duration, years	12.5±4.5	11.8±4.0
Hypertension duration, years	9.5±3.8	8.3±3.0
Previous antihypertensive treatment, *n* (%)	46 (61)	48 (64)

Data are expressed as mean±SD. HCTZ, hydrochlorothiazide; BMI, body mass index; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

for 48 weeks.

After 12 weeks a dose titration consisting of a doubling of manidipine (to 20 mg) or HCTZ (to 25 mg) was permitted in nonresponder patients (SBP ≥130 mmHg and/or DBP ≥80 mmHg). From the time of enrollment until the completion of the study, all participants maintained their usual diet and level of physical activity and avoided changes in body weight. No concomitant medication was allowed with the exception of oral hypoglycemic agents when required. Potassium supplementations were given to patients with serum potassium <3.5 mEq/L at check-ups performed every 12 weeks throughout the study period.

Patients were checked at the end of the placebo run-in period and every 12 weeks thereafter. At each visit, BP, heart rate (HR) and body weight were measured and adverse events were recorded. BP measurements were obtained from each patient (right arm) in the sitting position by physicians using a standard mercury sphygmomanometer (Erkameter 3000; ERKA, Bad Tolz, Germany) (Korotkoff I and V) with a cuff of appropriate size. BP was always measured in the morning before daily drug intake (*i.e.*, at trough, 22–24 h after dosing) and after the subject had rested 10 min in a quiet room. Three successive BP readings were obtained at 1-min intervals and averaged. To evaluate the orthostatic changes, BP was also evaluated after 10 min in a supine position and after 2 min in a standing position. HR was measured by pulse palpation for 30 s just before the sitting and lying BP measurements and immediately after the standing BP measurements. Patients' body weights were measured with light clothes and without shoes and BMI was calculated as the weight in kg divided by the height in m squared.

At each visit blood samples were drawn in the fasting state (in the morning after a 12-h overnight fast) for evaluation of the following laboratory parameters: fasting plasma glucose (FPG), HbA1c, uric acid, serum potassium, total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) and triglycerides (TG). We used plasma obtained by addition of Na_2-EDTA, 1 mg/mL, and centrifuged at 3,000 × g for 15 min at 4°C. Immediately after centrifugation, the plasma samples were

Table 2. Sitting, Lying and Standing Blood Pressure and Heart Rate during the Study with Both Treatments

Variable	Manidipine/delapril ($n=76$)		Olmesartan/HCTZ ($n=74$)	
	Placebo	Treatment	Placebo	Treatment
Sitting SBP, mmHg	157.5±10.2	128.8±7.0†	158.8±9.7	129.5±3.9†
Sitting DBP, mmHg	94.1±8.7	79.1±5.3†	93.8±8.2	78.6±3.1†
Lying SBP, mmHg	161.5±11.1	132.2±4.8†	162.2±10.7	134.4±5.1†
Lying DBP, mmHg	93.6±8.9	79.7±3.0†	92.9±8.8	80.4±3.5†
Standing SBP, mmHg	156.3±9.7*	127.1±5.2*,†	156.8±9.2*	126.4±3.8*,†
Standing DBP, mmHg	94.2±9.1	79.5±3.9†	94.6±9.4	74.1±2.6*,†,§
Sitting HR, bpm	77.6±6.1	78.6±5.5	76.8±5.8	79.9±6.2
Lying HR, bpm	76.2±5.8	77.3±6.1	75.8±6.3	78.1±7.1
Standing HR, bpm	80.1±7.9*	80.9±7.2*	79.4±7.7*	82.2±6.8*

Data are mean±SD. HCTZ, hydrochlorothiazide; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. $^{\dagger}p<0.001$ *vs*. placebo; $^{\S}p<0.05$ *vs*. manidipine/delapril; *$p<0.05$ *vs*. lying.

frozen and stored at −80°C for ≤3 months. All measurements were performed in a central laboratory. Plasma glucose was assayed using a glucose-oxidase method (GOD/PAP; Roche Diagnostics, Mannheim, Germany) with intra- and inter-assay coefficients of variation (CsV) <2% (*31*). HbA1c was measured using high-performance liquid chromatography (DIAMAT; Bio-Rad Laboratories Inc., Hercules, USA; normal value, 4.2%–6.2%), with intra- and inter-assay CsV of <2% (*32*). TC and TG levels were determined using fully enzymatic techniques (*33*, *34*) on a clinical chemistry analyzer (Hitachi 737; Hitachi, Tokyo, Japan); HDL-C was measured after precipitation of plasma apolipoprotein B (apo B)–containing lipoproteins with phosphotungstic acid (*35*). LDL-C levels were calculated using the Friedewald formula (*36*).

At each visit treatment tolerability was assessed in terms of adverse events spontaneously reported by the patients, elicited by a careful interview, or observed by the investigators and changes in laboratory parameters. Treatment compliance was assessed by counting the number of pills remaining at each visit. The primary outcome was BP response defined as a reduction in SBP <130 mmHg and DBP <80 mmHg and/or reduction of SBP ≥20 mmHg and/or reduction of DBP ≥10 mmHg as measured in the sitting position after 48 weeks. Secondary outcome criteria were possible metabolic changes in both groups.

Statistical Analysis

An intention-to-treat analysis was performed in patients who had received at least one dose of study medication and had a subsequent efficacy observation. Data are expressed as the means±SD. The homogeneity check of patient distribution between the two treatment groups was performed using the χ^2 test. The results were analyzed statistically using analysis of variance and Student's *t*-test (paired/unpaired for intra/inter-group comparisons). All tests were two-tailed and values of $p<0.05$ were considered to indicate statistical significance.

Results

As shown in Fig. 2, a total of 183 patients were recruited between September 2004 and June 2005. At the end of the 4-week run-in period, 158 patients (86.3%) were randomized to receive manidipine/delapril combination treatment ($n=78$) or olmesartan/HCTZ combination treatment ($n=80$). Their main demographic and clinical characteristics are shown in Table 1. The two treatment groups were comparable in terms of age, sex, BMI, weight, height, HbA1c, baseline sitting BP and HR, and duration of diabetes and hypertension. Eight patients withdrew after randomization (4 refused treatment and 4 were lost at follow-up); their characteristics were similar to those of patients finally included in the study. A total 150 patients, 76 in the manidipine/delapril group and 74 in the olmesartan/HCTZ group, completed the study. At 12 weeks, 44% of patients in the manidipine/delapril group and 49% of patients in the olmesartan/HCTZ group required dose titration consisting of a doubling of manidipine or HCTZ due to insufficient BP control.

The BP and HR results are shown in Table 2. Both manidipine/delapril and olmesartan/HCTZ significantly reduced sitting SBP (−27.7 mmHg and −28.3 mmHg respectively; both $p<0.001$ *vs*. placebo) and DBP (−15.1 mmHg and −14.8 mmHg, respectively; $p<0.001$ *vs*. placebo), with no significant difference between the two treatments. Similar results were obtained for lying SBP/DBP values, which were reduced by both manidipine/delapril (−29.3/−13.5 mmHg; $p<0.001$ *vs*. placebo) and olmesartan/HCTZ (−27.8/−12.5 mmHg; $p<0.001$ *vs*. placebo), with no significant difference between the two treatments. By contrast, standing DBP values were more markedly reduced by olmesartan/HCTZ therapy (−19.5 mmHg; $p<0.001$ *vs*. placebo) than by manidipine/delapril therapy (−14.7 mmHg; $p<0.05$ *vs*. olmesartan/HCTZ). As shown in Fig. 3, the mean postural changes in both SBP and DBP were more pronounced in the olmesartan/HCTZ group than in the manidipine/delapril group.

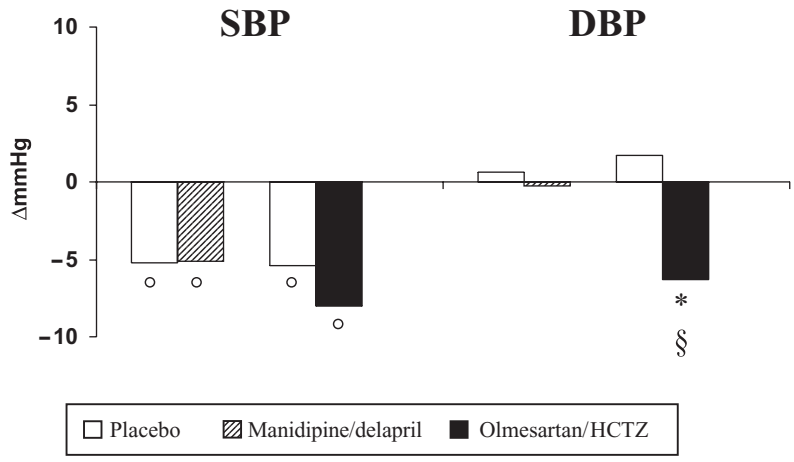

Fig. 3. *Effect of the manidipine/delapril combination and olmesartan/HCTZ combination on blood pressure orthostatic changes. SBP, systolic blood pressure; DBP, diastolic blood pressure. °$p < 0.05$ vs. lying; *$p < 0.01$ vs. lying; §$p < 0.01$ vs. manidipine/delapril.*

Table 3. Metabolic Parameters before and after Therapy

Variable	Manidipine/delapril (n=76)		Olmesartan/HCTZ (n=74)	
	Placebo	Treatment	Placebo	Treatment
Potassium, mmol/L	4.1±0.3	4.2±0.4	4.0±0.5	3.7±0.3*,§
Uric acid, mg/dL	5.7±1.2	5.8±1.3	5.7±1.1	6.0±1.4*
FPG, mg/dL	137.3±9.5	133.6±8.0	132.5±9.1	135.2±8.4
HbA1c, %	6.6±0.5	6.8±0.6	6.8±0.4	7.5±0.8*,§
Total cholesterol, mg/dL	194.5±14.4	190.2±13.0	191.6±14.0	196.6±14.9
HDL-C, mg/dL	42.5±4.0	43.2±3.8	44.0±4.2	40.6±3.3*,§
LDL-C, mg/dL	130.6±10.5	122.8±8.1	127.2±9.6	128.0±9.4
Triglycerides, mg/dL	111.7±29.8	122.3±32.4	102.5±22.6	143.8±36.1*

Data are mean±SD. HCTZ, hydrochlorothiazide; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol. *$p<0.05$ *vs*. placebo; §$p<0.05$ *vs*. manidipine/delapril.

Sitting and lying HR values were unaffected by either treatment (Table 2), while standing HR significantly increased ($p<0.05$) both in the placebo and treatment periods, with no significant difference between the two treatments.

The laboratory parameter results are reported in Table 3. A significant increase in HbA1c was observed in the olmesartan/HCTZ group (+0.7%; $p< 0.05$ *vs*. baseline), while no HbA1c change was observed in the manidipine/delapril group, with the difference between the two groups being statistically significant ($p<0.05$). Potassium levels were significantly decreased in the olmesartan/HCTZ group (−0.3 mmol/L; $p<0.05$ *vs*. baseline) but did not change in the manidipine/delapril group, and the difference between the two treatments was statistically significant ($p<0.05$). A significant increase in uric acid was observed in the olmesartan/HCTZ group (+0.4 mg/dL; $p<0.05$ *vs*. baseline), while no change occurred in the manidipine/delapril group. TC and LDL-C were not significantly affected by either treatment, while TG significantly increased (+41.3 mg/dL; $p<0.05$ *vs*. baseline) and HDL-C significantly decreased (−3.4 mg/dL; $p<0.05$ *vs*. baseline, and $p<0.05$ *vs*. manidipine/delapril) in the patients treated with olmesartan/HCTZ.

No serious adverse events were recorded during the trial. Three patients (3.9%) complained of side effects in the manidipine/delapril group (2 of ankle edema and 1 of dry cough), while 4 patients (5.4%) complained of side effects in the olmesartan/HCTZ group (3 of fainting and dizziness and 1 of headache and nausea). All reactions were mild. No patient was removed from the trial due to adverse events.

Discussion

The results of this study showed that in elderly patients with hypertension and associated type 2 diabetes mellitus, treatment with both manidipine/delapril combination therapy and olmesartan/HCTZ combination therapy produced a signifi-

cant reduction in BP values, allowing the patients to achieve their BP targets. This confirms that combination therapy is effective for achieving a more intensive BP control, which is needed to protect these high-risk patients from target organ damages.

Although equally effective in reducing BP levels, the two combinations differed in their influence on postural BP changes and metabolic parameters. Elderly hypertensive patients with diabetes are particularly prone to orthostatic hypotension, which may be very debilitating and is associated with increased morbidity and mortality (*37*). This phenomenon occurs in 14–30% of the general population over the age of 65 years (*27*, *38*) and in 12–28% of all patients with diabetes mellitus (*26*, *39*). Diabetic autonomic neuropathy is the most common underlying mechanism in this condition (*26*), but impaired baroreflex sensitivity, hyporeninemia and intravascular hypovolemia also contribute to the abnormal postural decline in BP (*28*, *40*, *41*). In the present study no patient presented orthostatic hypotension (defined as a decrease in BP of at least 20 mmHg systolic or 10 mmHg diastolic within 3 min of standing up) (*42*). However, the olmesartan/HCTZ combination produced a significant decrease in standing DBP values, which by contrast were unaffected by the manidipine/delapril combination. This altered response to postural changes, which might enhance the risk of orthostatic hypotension in elderly hypertensive diabetics, might be due to the diuretic-induced sodium loss, which could reduce the vasoconstrictor arteriolar response to sympathetic stimulation (*43*, *44*).

The thiazide diuretic was probably also the main cause of the metabolic changes observed with olmesartan/HCTZ treatment, notably an increase in HbA1c, uric acid and TG and a decrease in serum potassium and HDL-C. Diuretics administered as monotherapy are well known to produce hypokalemia, elevated serum levels of uric acid and lipids, and enhanced blood glucose levels (*45–48*). Potassium depletion may play a role in glucose intolerance by inhibiting the conversion of pro-insulin to insulin (*44*). The reduction in doses of thiazides that has taken place over the last several years has had a significant impact in reducing diuretic metabolic complications (*49*, *50*). Moreover, these undesirable adverse effects of thiazides may be lessened by combination with ARBs (*51*, *52*). Because of the tendency of ARBs to elevate serum potassium levels, hypokalemia is expected to be less of a problem with combination therapy, particularly if low doses of diuretics are used (*51*, *52*). Also, the tendency to produce hyperglycemia may be offset by the protective effect of ARBs, which have been observed to decrease the incidence of new-onset diabetes mellitus (*53*). In the present study, 49% of patients in the olmesartan/HCTZ group requested a dose titration (consisting of a doubling of HCTZ to 25 mg) due to insufficient BP control, which might have limited the protective effect of the ARB. Although the clinical relevance of diuretic-induced metabolic side effects is still debated, the choice of antihypertensive drugs, particularly in high-risk patients such as those with diabetes, should favor agents that do not worsen the global cardiovascular risk profile. No significant changes in metabolic parameters were observed in the patients treated with manidipine/delapril, which confirms previous observations (*54*, *55*).

Both manidipine/delapril and olmesartan/HCTZ were well-tolerated, and treatment compliance was good. Only 3.9% of patients in the manidipine/delapril group and 5.4% in the olmesartan/HCTZ group complained of adverse events, which were classified as non-serious and never required treatment discontinuation. The good tolerability of both treatments is reassuring, as clinicians are often concerned about lowering BP in older patients, while compliance with treatment is a crucial element in determining the success of antihypertensive therapy.

Conclusions

In conclusion, for the treatment of elderly hypertensive patients with type 2 diabetes, the combinations of manidipine/delapril and olmesartan/HCTZ were similarly effective in reducing BP levels with a good tolerability profile. However, in these high-risk patients, the combination of manidipine/delapril offered some advantages in terms of the less-pronounced BP postural changes and absence of metabolic adverse effects.

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