Effects of Verapamil Slow Release Plus Trandolapril Combination Therapy on Essential Hypertension

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ABSTRACT

Background: Fixed-dose combination antihypertensive therapy has been recommended for patients with essential hypertension who are unresponsive to monotherapy or as a first-line treatment.

Objective: We investigated the effects of a fixed-dose combination of the phenylalkylamine-type calcium channel blocker verapamil slow release (SR) plus the angiotensin-converting enzyme inhibitor trandolapril on blood pressure (BP), serum lipid profile, urinary albumin excretion (UAE), left ventricular mass (LVM), and LVM index (LVMI), as well as the adverse events associated with this treatment.

Methods: Patients aged 30 to 65 years with mild to moderate essential hypertension were included in the study. All of the patients received capsules containing combination treatment with verapamil SR 180 mg plus trandolapril 2 mg orally, daily for 12 weeks. Mean arterial pressure (MAP), systolic BP (SBP), diastolic BP (DBP), and heart rate (HR) were measured at baseline and at 4, 8, and 12 weeks of treatment. Serum lipid profile, UAE, LVM, LVMI, and body mass index (BMI) were determined at baseline and at the end of the study period. All patients underwent electrocardiography and echocardiography at baseline and week 12. The primary end point of the study was to achieve an SBP/DBP $\leq 140/\leq 90$ mm Hg (ie, normotensive) during week 12. All adverse events were assessed as mild, moderate, or severe at each visit. According to the response rate at week 12, patients were divided into 2 groups: those who became normotensive (*responders*) or those who remained hypertensive (SBP/DBP $> 140/> 90$ mm Hg; *nonresponders*).

Results: Forty-one patients (29 women, 12 men; mean [SD] age, 47.7 [7.8] years; mean [SD] BMI, 29.4 [3.5] kg/m²) were enrolled. The median duration of hypertension prior to enrollment was 5 months. Mean MAP, SBP, DBP, UAE, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C),

LDL-C/high-density lipoprotein cholesterol (HDL-C) ratio, LVM, LVMI, and BMI decreased significantly after 12 weeks of combination treatment; HR and triglyceride level did not change significantly. Treatment-related adverse events occurred in 31.7% of patients, and none were severe or caused any patient to withdraw from the study. The most common adverse events were cough, constipation, headache, and dryness in the throat. Microalbuminuria, which may be a marker of endothelial dysfunction, was found in 7 (17.1%) patients at baseline and regressed significantly after 12 weeks.

Conclusions: In this study population, the fixed-dose combination of verapamil–trandolapril was an effective and well-tolerated antihypertensive therapy. This combination significantly reduced MAP, BP, TC, LDL-C, LDL-C/HDL-C ratio, UAE, LVM, and LVMI. Also, microalbuminuria decreased after this treatment. Verapamil–trandolapril may be useful in preventing microalbuminuria and left ventricular hypertrophy in patients with essential hypertension. (*Curr Ther Res Clin Exp.* 2003;64:10–20) Copyright © 2003 Excerpta Medica, Inc.

Key words: essential hypertension, combination therapy, trandolapril, verapamil.

INTRODUCTION

Antihypertensive monotherapy has been shown to decrease blood pressure (BP) in only 50% of hypertensive patients, whereas increasing the dose has been shown to improve this figure to 70%.¹ When hypertensive patients are switched to another monotherapy, the response rate is similar (49.1%).² Therefore, patients with essential hypertension who do not respond to monotherapy are switched to combination therapy, which sometimes is used as first-line therapy.

Combination therapy is of fundamental importance in hypertension because it has been shown to effectively reduce elevated BP in >80% of hypertensive patients.^{3,4} In fact, as many as 50% of patients with uncomplicated, mild to moderate (grade 1 or 2) essential hypertension require drugs for adequate BP control.⁴ Combining 2 antihypertensive agents may enhance their efficacy and reduce the incidence of adverse events because it is possible to use a low dose of each drug rather than a high dose of 1 drug.⁵

Because the different drugs have different mechanisms of action, vascular complications and end-organ damage may decrease with combination therapy.^{6,7} Among the various possible combinations of antihypertensive agents, the combination of an angiotensin-converting enzyme (ACE) inhibitor and a calcium channel blocker appears to be particularly attractive because these drugs have different effects on the cardiovascular system. Previous studies^{8–14} have suggested that the combination of a heart rate (HR)–lowering calcium channel blocker (verapamil slow release [SR]) and a long-acting ACE inhibitor (trandolapril) was more effective than was monotherapy in reducing

BP. Microalbuminuria may be a marker of diffuse vascular abnormalities predisposing to cardiovascular disease and/or hypertensive renal disease; the antiproteinuric efficacy of the verapamil–trandolapril combination therapy has been demonstrated.^{11,15} However, the effects of this fixed-dose combination therapy on microalbuminuria have not been sufficiently examined. In this study, we investigated the effects of a fixed-dose combination of verapamil SR and trandolapril on BP, HR, serum lipid profile, urinary albumin excretion (UAE), left ventricular mass (LVM), and LVM index (LVMI), as well as treatment-related adverse events.

PATIENTS AND METHODS

This study was conducted at Gazi University Hospital. Patients aged 30 to 65 years with grade 1 or 2 essential hypertension (according to the sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure¹⁶ classification) were included in the study. Patients with secondary hypertension, fasting plasma glucose level >100 mg/dL, serum creatinine level >2 mg/dL, chronic liver disease, severe hypertension, chronic heart failure, atrioventricular block, severe bradycardia, cardiomyopathy, or proteinuria (UAE >200 mg/L) were excluded. Institutional review board approval was obtained. All patients provided written informed consent to participate.

All patients received the fixed-dose combination treatment with capsules containing the phenylalkylamine calcium channel blocker verapamil SR 180 mg plus the ACE inhibitor trandolapril 2 mg given orally, daily for 12 weeks. A sodium-restricted (≤ 100 mmol/d) and lipid-restricted diet was prescribed to all patients. Dietary compliance was not assessed using food diaries but was discussed at each visit. Mean arterial pressure (MAP), systolic BP (SBP), diastolic BP (DBP), and HR were measured in the sitting position at baseline and at 4, 8, and 12 weeks of treatment. All patients underwent electrocardiographic (ECG) examinations at baseline and at week 12. All patients also underwent M-mode Doppler echocardiography (RT 6700 3.5-MHz transducer, General Electric Medical Systems, Waukesha, Wisconsin) on standard parasternal long axis, parasternal short axis, apical 2 spaces, and apical 4 spaces, by the same physician, at baseline and at week 12.

UAE was measured with nephelometric assay (Turbox®, Orion Diagnostica, Espoo, Finland), and microalbuminuria was defined as UAE 20 to 200 mg/L. Serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (Tg) were measured with an automatic analyzer (Aeroset®, Abbott Laboratories, Abbott Park, Illinois). LDL-C/HDL-C ratio was calculated. LVM was calculated according to the formula developed by Devereux and Reichek.¹⁷ LVMI was determined as follows:

$$\text{LVMI (g/m}^2\text{)} = \text{LVM (g)}/\text{body surface area (m}^2\text{)}$$

An LVM of 90 to 218 g and an LVMI $<131 \text{ g/m}^2$ (men) or $<110 \text{ g/m}^2$ (women) were considered normal. Serum lipid profile, UAE, LVM, LVMI, and body mass index (BMI) were determined at baseline and at the end of the treatment period.

For efficacy assessment, patients were divided into 2 groups based on whether they achieved normal BP (SBP/DBP $\leq 140/\leq 90$ mm Hg) after 12 weeks of treatment (*responders* [primary end point]) or remained hypertensive (SBP/DBP $>140/>90$ mm Hg; *nonresponders*).

Patients' tolerability was evaluated every 4 weeks. All adverse events were assessed as mild, moderate, or severe at each visit.

Statistical Analysis

Results are expressed as mean (SD) for normally distributed values and as median for values that are not normally distributed. Paired Student *t* test or Wilcoxon signed rank test was used to compare values at baseline with those at the end of the study period. Unpaired Student *t* test or Mann-Whitney *U* test was applied to compare differences between groups. Changes in repeated values over time were compared with repeated-measures analysis of variance. Correlations between parameters were tested using Spearman's rank sum test. Statistical significance was set at $P < 0.05$.

RESULTS

Forty-one patients (29 women, 12 men; mean [SD] age, 47.7 [7.8] years; mean [SD] BMI, 29.4 [3.5] kg/m^2) were enrolled in the study. The median duration of hypertension prior to enrollment was 5 months.

Prior to entering the study, 9 (22%) patients had used ≥ 1 antihypertensive drug, 10 (24.4%) patients had used no antihypertensive drugs, and 22 (53.7%) patients had used antihypertensive drugs irregularly. Left ventricular hypertrophy was identified in 15 (36.6%) patients.

At weeks 4, 8, and 12, verapamil–trandolapril combination treatment had significantly reduced mean MAP, SBP, and DBP ($P < 0.001$ for all vs baseline); HR did not change significantly (Table I). The mean decrease in SBP/DBP was 28.9/22.7 mm Hg. DBP was normalized (<90 mm Hg) in 26 (63.4%) patients after

Table I. Blood pressure and heart rate (HR) at baseline and weeks 4, 8, and 12 of treatment with verapamil–trandolapril combination. (Values are expressed as mean [SD].)

Variable	Baseline	Week 4	Week 8	Week 12
MAP, mm Hg	122.7 (10.9)	102.1 (9.0)*	100.3 (7.5)*	97.9 (8.9)*
SBP, mm Hg	158.3 (21.3)	132.9 (12.7)*	131.0 (10.8)*	129.4 (11.6)*
DBP, mm Hg	104.9 (7.2)	86.7 (8.9)*	85.0 (7.7)*	82.2 (8.8)*
HR, bpm	79.9 (8.7)	79.8 (9.7)	79.5 (11.6)	76.5 (7.8)

MAP = mean arterial pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure.

* $P < 0.001$ versus baseline.

4 weeks, in 32 (78.0%) patients after 8 weeks, and in 33 (80.5%) patients after 12 weeks of treatment. The remaining 8 (19.5%) patients did not respond to treatment, and either the dosage was increased or another medication was added to the treatment regimen.

Mean serum lipid levels, UAE, LVM, LVMI, and BMI at baseline and after 12 weeks of antihypertensive treatment are shown in Table II. At week 12, mean TC ($P = 0.020$), LDL-C ($P = 0.002$), LDL-C/HDL-C ratio ($P = 0.006$), median UAE ($P < 0.001$), and mean LVM ($P = 0.007$) and LVMI ($P = 0.010$) were decreased significantly. At the end of the treatment period, mean BMI also had significantly decreased ($P = 0.003$). Mean LVM and LVMI were reduced by 9.7% and 9.8%, respectively. On echocardiography, ejection fraction and fractional shortening were within normal limits at baseline and did not change significantly after treatment. The mean end-diastolic diameter of the left ventricle and the thickness of the interventricular septum did not change significantly between baseline and the end of the study. The mean (SD) posterior wall thickness was reduced from 1.1 (0.13) mm to 0.99 (0.13) mm ($P = 0.001$). Therefore, the main factor in reducing LVM was thinning of the posterior wall. At the beginning of the study, 23 (56.1%) patients had normal LVM and 18 (43.9%) patients had abnormal LVM. In the latter group, mean LVM was reduced significantly after treatment ($P < 0.001$; Table II). Before treatment, mean (SD) LVMI in men was slightly higher than in women (108.9 [34.5] g/m² vs 97.3 [28.5] g/m², respectively), but this difference did not reach statistical significance. After treatment, mean LVMI in men decreased significantly from baseline ($P = 0.013$) (Figure).

Table II. Laboratory values and left ventricular mass (LVM) in all study patients (N = 41) before and after 12 weeks of treatment with verapamil–trandolapril combination. (All values are expressed as mean [SD] except triglycerides [Tg] and urinary albumin excretion [UAE].)

Variable	Baseline	Week 12	P
TC, mg/dL	217.7 (51.5)	207.6 (43.6)	0.020
LDL-C, mg/dL	138.3 (40.3)	124.9 (39.8)	0.002
HDL-C, mg/dL	44.3 (11.2)	46.9 (15.4)	NS
LDL-C/HDL-C ratio	3.3 (1.2)	2.9 (1.1)	0.006
Median Tg, mg/dL	150.0	147.0	NS
Range	74.0–649.0	65.0–1297.0	
Median UAE, mg/L	11.0	6.0	<0.001
Range	0.6–92.0	0.6–30.0	
LVM, g	219.4 (61.7)	198.2 (55.2)	0.007
Normal (n = 23)	184.8 (26.1)	186.1 (34.5)	NS
Abnormal (n = 18)	263.6 (66.3)	213.7 (72)	<0.001
LVMI, g/m ²	105.5 (32.9)	95.2 (25.3)	0.010
BMI, kg/m ²	29.4 (3.5)	29.0 (3.6)	0.003

TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; LVMI = left ventricular mass index; BMI = body mass index.

Figure. Mean left ventricular mass index (LVMI) in women ($n = 29$) and men ($n = 12$) at baseline and after 12 weeks of treatment with verapamil–trandolapril combination therapy. * $P = 0.013$ versus baseline.

Mean SBP, DBP, serum Tg level, and BMI in nonresponders were significantly higher than in responders at week 12 ($P < 0.05$ for all) (Table III). Furthermore, mean SBP and BMI in nonresponders were higher than in responders at baseline ($P < 0.05$ for both). These factors may be responsible for insufficient response to antihypertensive treatment in nonresponders.

In the 7 (17.1%) patients who had microalbuminuria at the beginning of the study, mean MAP ($P = 0.018$), SBP ($P = 0.041$), DBP ($P = 0.018$), UAE ($P = 0.018$), and BMI ($P = 0.043$) were significantly reduced at the end of the treatment period (Table IV). However, no significant differences in mean serum lipid levels (except Tg [$P = 0.041$]), LVM, or LVMI were noted. No correlation was found between microalbuminuria and age, sex, duration of hypertension, MAP, LDL-C level, LVM, LVMI, or BMI.

Thirteen patients (31.7%) reported mild or moderate treatment-related adverse events: 5 (12.2%) patients had cough, 3 (7.3%) constipation, 3 (7.3%) both cough and constipation, 1 (2.4%) headache, and 1 (2.4%) dryness in the throat. None of these patients withdrew; however, in 1 patient with cough, the severity of the cough steadily increased throughout the study, and this patient discontinued treatment at the end of the study.

DISCUSSION

Although hypertension can be controlled with monotherapy in ~50% of patients, this rate increases to 80% with combination therapies using >2 drugs.^{3,4} The

Table III. Study measurements in patients who had normal blood pressure ($\leq 140/\leq 90$ mm Hg; responders) compared with those who remained hypertensive (systolic blood pressure [SBP]/diastolic blood pressure [DBP] $>140/>90$ mm Hg; nonresponders) before and after 12 weeks of treatment with verapamil–trandolapril combination. (All values are expressed as mean [SD] except triglycerides [Tg] and urinary albumin excretion [UAE].)

Variable	Responders (n = 33)		Nonresponders (n = 8)	
	Baseline	Week 12	Baseline	Week 12
MAP, mm Hg	121.4 (11.0)	95.8 (8.1)	128.9 (8.2)	108.1(3.8)*
SBP, mm Hg	155.1 (20.7)	126.3 (9.7)	173.8 (18.2)*	144.5 (7.3)*
DBP, mm Hg	104.6 (7.4)	80.6 (8.4)	106.4 (6.3)	89.7 (6.9)*
HR, bpm	79.9 (8.7)	77.3 (8.1)	80.3 (9.6)	72.9 (5.1)
TC, mg/dL	211.2 (48.8)	205.5 (44.0)	249.3 (56.4)	217.8 (42.8)
LDL-C, mg/dL	134.6 (39.6)	124.9 (39.4)	156.4 (41.7)	124.9 (44.8)
HDL-C, mg/dL	44.4 (11.6)	47.3 (16.3)	44.3 (9.5)	44.7 (10.8)
LDL-C/HDL-C ratio	3.2 (1.3)	2.9 (1.1)	3.6 (1.1)	3.0 (1.4)
Median Tg, mg/dL	135.0	134.5	209.0	300.0*
Range	74.0–649.0	65.0–1297.0	110.0–313.0	120.0–366.0
Median UAE, mg/L	11.0	6.0	8.0	6.0
Range	0.6–92.0	0.6–30.0	2.5–18.0	0.6–16.0
LVM, g	221.6 (66.8)	198.1 (58.2)	208.6 (26.7)	198.6 (41.0)
LVMI, g/m ²	106.8 (34.6)	95.6 (26.3)	99.4 (24.1)	93.1 (21.3)
BMI, kg/m ²	28.7 (3.2)	28.2 (3.2)	32.9 (3.0)*	33.0 (3.2)*

MAP = mean arterial pressure; HR = heart rate; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; LVM = left ventricular mass; LVMI = left ventricular mass index; BMI = body mass index.

* $P < 0.05$ versus same time point among responders.

response rate at the end of this study was comparable (80.5% of patients). The decrease in HR with verapamil SR was not statistically significant.

The incidence of microalbuminuria in patients with essential hypertension has been reported to be 8% to 40%.^{18–20} In our study, it was 17.1% (7 patients). Combination treatment significantly decreased UAE both in microalbuminuric and normoalbuminuric patients. In microalbuminuric patients, SBP, DBP, MAP, UAE, and BMI were significantly reduced at the end of the treatment period, but no significant differences in either LVM, LVMI, or serum lipid levels, except for Tg, were noted. We found no correlation between microalbuminuria and MAP. Thus, the antiproteinuric response of verapamil–trandolapril combination treatment seems to be independent of effective BP reduction. However, the number of microalbuminuric patients in our study was not sufficient to identify a relationship between these parameters. In a previous study,²¹ the reduction of UAE with ACE inhibitor therapy appeared to be mediated by a reduction of intraglomerular pressure that was independent of systemic BP reduction and the nonhemodynamic intrarenal effects of the therapy. Hemmelder et al¹⁵ have

Table IV. Study measurements before and after 12 weeks of treatment with verapamil–trandolapril combination in patients who had microalbuminuria at the beginning of the study (n = 7). (All values are expressed as mean [SD] except triglycerides [Tg] and urinary albumin excretion [UAE].)

Variable	Baseline	Week 12
MAP, mm Hg	121.3 (14)	96.5 (10.6)*
SBP, mm Hg	154.3 (25.1)	125.5 (12) [†]
DBP, mm Hg	104.8 (9)	81.9 (10.5)*
HR, bpm	78.0 (7.3)	74.6 (11.8)
TC, mg/dL	220.4 (78.9)	220.4 (59.4)
LDL-C, mg/dL	135.9 (63.7)	127.7 (46.4)
HDL-C, mg/dL	42.7 (9.8)	40.4 (7.7)
LDL-C/HDL-C ratio	3.1 (0.9)	3.3 (1.5)
Median Tg, mg/dL	189.0	319.0 [‡]
Range	84.0–649.0	122.0–1297.0
Median UAE, mg/L	20.0	13.0*
Range	20.0–92.0	0.6–30.0
LVM, g	242.8 (121.3)	217.2 (96.9)
LVMI, g/m ²	113.0 (48.7)	103.1 (36.5)
BMI, kg/m ²	30.4 (3.6)	29.8 (3.8) [‡]

MAP = mean arterial pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; LVM = left ventricular mass; LVMI = left ventricular mass index; BMI = body mass index.

**P* = 0.018 versus baseline.

[†]*P* = 0.041 versus baseline.

[‡]*P* = 0.043 versus baseline.

suggested that, in contrast to the antiproteinuric effect of trandolapril, the anti-proteinuric response to verapamil therapy is dependent on BP reduction in nondiabetic renal disease. However, a fixed-dose combination of verapamil and trandolapril provided additional antiproteinuric efficacy. In addition, this combination at half-doses resulted in decreases in BP and UAE that were similar to the decrease achieved with a single treatment of a full dose of trandolapril.

It is not known whether the presence of microalbuminuria in patients with essential hypertension is a marker of renal damage or cardiovascular risk^{22,23}; however, it is well known that microalbuminuria can be reversed with BP control. On the other hand, in a study by Bakris et al,¹¹ the combination of verapamil–trandolapril reduced UAE to a greater extent than did either agent alone, and this occurred at a lower dose of each drug and was independent of further reductions in MAP. The additive effects of verapamil–trandolapril on microalbuminuria, independent of BP reduction, have been associated with their effects on glomerular size selectivity, which is a barrier for large molecular weights.

Left ventricular hypertrophy, which is one of the results of uncontrolled hypertension, is an important risk factor for cardiac morbidity and mortality. Both ACE inhibitors and calcium channel blockers reduce left ventricular hypertrophy. ACE inhibitors act in 2 ways—(1) by decreasing systolic workload of the heart and afterload by lowering the systemic BP and (2) by preventing the proliferative action of angiotensin II. The nondihydropyridine class of calcium channel blockers reduces LVM more effectively than does the dihydropyridine class.²⁴ In our study, in which we combined these 2 agents, mean LVM and LVMI were reduced 9.7% and 9.8%, respectively, and the main factor in the reduction of LVM was thinning of the posterior wall. The ejection fraction and fractional shortening were within normal limits, and combination therapy did not significantly change these findings. In other words, combination therapy had a neutral effect on these 2 variables. Aepfelbacher et al²⁵ also found that combination therapy with verapamil–trandolapril (180 and 2 mg/d, or 360 and 4 mg/d) in patients with mild to moderate hypertension reduced the mean (SD) LVM from 275 (104) g to 250 (95) g (regression ratio, 10%).

Dyslipidemia is another independent risk factor for cardiovascular disease,^{16,26} especially high LDL-C level and the LDL-C/HDL-C ratio. In hypertensive patients who are at risk for cardiovascular disease, different classes of antihypertensive drugs affect serum lipid levels differently. ACE inhibitors have a neutral effect, whereas calcium channel blockers decrease LDL-C level. In our study, the fixed-dose combination of verapamil–trandolapril decreased the serum TC and LDL-C levels and LDL-C/HDL-C ratio significantly. However, a sodium- and lipid-restricted diet was prescribed for the patients, and the mean BMI of these patients had decreased significantly by the end of the study. For these reasons, the lipid-lowering effect observed only with combination therapy is difficult to explain. The effectiveness of decreased BMI and strict dietary control in the patients during the study period cannot be denied.

The incidence of adverse events of fixed-dose verapamil–trandolapril combination therapy has ranged from 17% to 46%.²⁷ Constipation, cough, asthenia, headache, nausea, and first-degree atrioventricular block can develop with this therapy.²⁷ In our study, the incidence of adverse events was 31.7%, and all adverse events were assessed as mild to moderate.

None of the adverse events were considered serious or required additional medical treatment. None of the patients withdrew during the study period. Only 1 patient complained of moderate cough, which began at week 8, but this patient continued treatment voluntarily until the end of the study. Therefore, the study medication was well tolerated.

CONCLUSIONS

In this study population, the fixed-dose combination of verapamil–trandolapril was an effective and well-tolerated antihypertensive treatment. This combination significantly reduced MAP, BP, TC, LDL-C, LDL-C/HDL-C ratio, UAE, LVM,

and LVMI. Verapamil–trandolapril may be a useful treatment to prevent microalbuminuria and left ventricular hypertrophy in patients with essential hypertension.

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