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ORIGINAL ARTICLE

The treatment of severe hypertension with trandolapril, verapamil, and hydrochlorothiazide

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A multiple drug regimen consisting of trandolapril, verapamil and hydrochlorothiazide (HCTZ) were sequentially added in an open-label evaluation of patients with severe hypertension. Ninety patients (58 white and 32 black patients) were titrated on one or more drugs and followed for a 19-week maintenance period. Statistically significant ($P = 0.001$) mean (± s.d.) decreases in supine diastolic blood pressure (DBP) were 9.0 (±9.3) mm Hg for trandolapril, 13.9 (±11.0) mm Hg for the trandolapril + verapamil (TV) combination, and 19.0 (±12.3) mm Hg when hydrochlorothiazide was added to the combination. The decrease in BP observed on TV combination therapy plus HCTZ was significantly ($P = 0.001$) greater than the decrease observed for the TV combination, which was significantly ($P = 0.001$) greater than the decrease observed for trandolapril monotherapy. Clinical responder rates were 44.8%, 56% and 77.7% for trandolapril monotherapy, trandolapril + verapamil combination therapy and triple therapy, respectively. Black and white patients had similar response rates, but black patients appeared to benefit more from the addition of HCTZ; 20% of black patients achieved a post-treatment supine DBP <90 mm Hg compared to 12.8% of white patients. This study demonstrates that the addition of verapamil to trandolapril has an additive effect on BP that is maintained throughout the day.

Keywords: verapamil; trandolapril; hydrochlorothiazide; severe hypertension; blood pressure; black patients

Introduction

The physician today has a wide range of choices for the treatment of severe or resistant hypertension. The most frequently employed regimen has consisted of a diuretic, a sympatholytic agent, and a peripheral vasodilator.[1] But often this regimen does not reduce blood pressure (BP) to acceptable levels or leads to untoward side effects that result in discontinuation of the drug regimen by the patient. Thus, the ideal combination therapy should not only offer synergistic antihypertensive effects, but also an acceptable side effect profile. Recent publications have shown that when angiotensin-converting enzyme (ACE) inhibitors are combined with calcium channel blockers, the antihypertensive properties of the combination have been impressive.[1–3]

This paper reports the results of an evaluation of the safety and efficacy of the non-sulfhydryl ACE-inhibitor trandolapril in combination with the calcium antagonist verapamil in the treatment of patients with severe hypertension. Trandolapril is a prodrug which is rapidly hydrolyzed to its active diacid metabolite, trandolaprilat. Previous clinical trials have demonstrated that black hypertensives do not respond as well to ACE inhibitors as white hypertensives,[4–6] while racial responses to verapamil are similar.[7] Hence, results for black and white patients are reported separately.

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Patients and methods

Study design

This was an open-label, multicenter study to evaluate the safety and efficacy of trandolapril monotherapy (2 mg, 4 mg, or 8 mg) and trandolapril in combination with slow release verapamil (180 mg) in patients with severe hypertension. The study consisted of a 3- to 14-day single-blind, placebo run-in period, a 5-week, open-label dose-titration period, and a 19-week maintenance period. A diagram of the study design is presented as Figure 1.

Patient population

Patients could be enrolled in the study if they were between 21 and 70 years of age and had documented severe hypertension (supine diastolic BP: 115 to 135 mm Hg). Patients were excluded from enrollment if they had a cerebrovascular accident, convulsive disorder, or hypertensive encephalopathy within the previous year; experienced a myocardial infarction within 3 months of the study, or had severe cardiac abnormalities, ie, congestive heart failure (CHF), arrhythmias, conduction abjormalities, or atrioventricular (AV) block; had evidence of renal, hepatic,

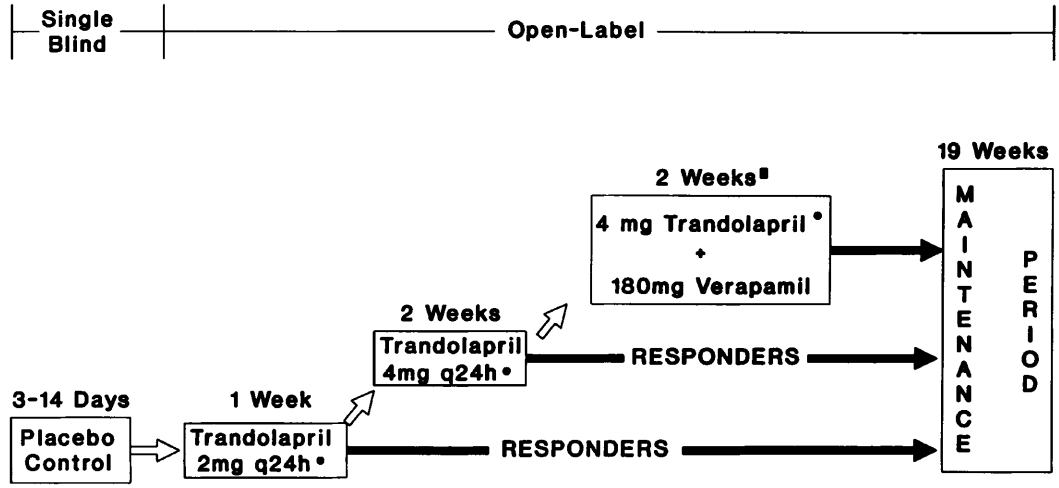

Figure 1 Diagram of study design. (•) Trandolapril dose doubled in black patients. (■) Hydrochlorothiazide could be added if supine DBP was not ⩽90 mm Hg after 2 weeks.

hematological, or other metabolic abnormalities that could interfere with study drug absorption, metabolism, or excretion; had a history of drug abuse or addiction. Patients were also excluded if they required the concomitant use of other antihypertensives, digitalis glycosides, antiarrhythmics, antidepressant drugs, central nervous system stimulants and depressants, chronic non-steroidal anti-inflammatory drugs and analgesics, as well as any medication that could elevate BP.

The protocol was approved by the appropriate institutional review committee and all patients gave written informed consent.

Study procedures

At the initial visit prior to entry into the study, BP was recorded in both arms. The arm with the highest sitting diastolic BP (DBP) was used for all subsequent measurements throughout the study. Patients who had been newly diagnosed or who had been previously treated for severe hypertension, discontinued all antihypertensive medications and entered into a single-blind, placebo run-in period of at least 3 days but no longer than 14 days duration. During the run-in period, patients were administered placebo once a day. At the end of the placebo run-in period, patients with documented severe hypertension advanced into a 5-week, open-label, dose-titration period. Qualifying DBP of between 115 and 135 mm Hg was determined as the mean of three consecutive supine DBP measurements taken 2 min apart. In order to be advanced into the dose-titration period, qualifying BP had to be documented on the last visit of the placebo run-in period. The first dose of trandolapril could be administered immediately after severe hypertension was documented at the time points indicated above. All subsequent doses were administered between 08.00 and 10.00 hours for the duration of the study.

Since it has been reported that black patients do not respond as well to ACE inhibitors as white patients, the black patients in this study were administered higher doses of trandolapril than the white patients.[6]

The titration period began with the administration of a low dose of trandolapril, 2 mg qAM in the case of the white patients and 4 mg qAM in the case of the black patients. If adequate control of BP was not achieved after 1 week, the dose of trandolapril was doubled for both white and black patients. BP was considered adequately controlled if supine DBP was ⩽90 mm Hg. If after 2 weeks at the high dose of trandolapril, the patient's BP was still not adequately controlled, 180 mg qAM of the calcium channel blocker verapamil was added. The daily dose of verapamil remained constant for the duration of the study. If a satisfactory response was not achieved after 2 weeks of combined trandolapril plus verapamil therapy, the investigator could add 12.5 mg to 25 mg of hydrochlorothiazide (HCTZ) or discontinue the patient from the study.

At the principal investigator's discretion, patients could be titrated more rapidly than indicated in the protocol to achieve faster BP control. Patients exhibiting a satisfactory response to either trandolapril or to trandolapril/verapamil combined therapy (with or without HCTZ) at the completion of the dose-titration period, continued to receive this therapy during the 19-week maintenance period.

Patient visits were scheduled every week during the 5-week dose-titration period, and at weeks 1, 3, 7, 9, 11, 15, and 19 of the 19-week maintenance period. At each visit, a physical examination was performed, vital signs and BP were measured, compliance was evaluated, and the patient was questioned about the occurrence of adverse reactions. The patient's cardiac status was monitored periodically throughout the study by 12-lead ECG. Routine clinical laboratory evaluations were also performed.

BP measurements were trough readings taken immediately prior to the day's administration of scheduled study drug dose. At each study visit, after having the patient rest in a supine position for a minimum of 10 min, systolic/diastolic BP and heart

rate were measured. Standing BP measurements were also made, but are not reported here.

Measures of efficacy

The primary measure of efficacy was mean change in trough supine DBP from baseline to post-treatment. Baseline was considered the last BP measurement taken prior to the first open-label dose. Post-treatment was the last trough BP measurement on a particular treatment.

In addition to evaluating the mean change in supine DBP, patients meeting the definition of 'responder' were tabulated. For the purpose of this study, a responder was defined as a patient whose post-treatment trough supine DBP was <90 mm Hg, or who had at least a 10 mm Hg decrease in supine DBP from baseline to post-treatment.

Statistical analysis

Summary statistics were tabulated for demographics and baseline supine BPs. Counts and percentages of patients with adverse events were tabulated. Mean changes from baseline to post-treatment supine BP were tested for significance at the two-tailed 0.05 level using paired *t*-tests.

Results

Patient characteristics

Ninety patients with severe hypertension were enrolled at 11 study centers. Sixty-three patients (70%) were male and 27 were female. Patients had a mean age of 51.0 ± 11.1 years (range: 24–71 years). Fifty-eight patients (64%) were white and 32 (36%) were black. Demographic and baseline characteristics are summarized by treatment: trandolapril monotherapy (T), trandolapril verapamil combination therapy (TV), and combination therapy with hydrochlorothiazide added (TV/HCTZ) in Table 1. The three treatment groups were comparable with regard to baseline characteristics. Black and white patients also had similar baseline characteristics with the exception of weight. The white patients were an average 12 pounds heavier than the black patients.

The patients had an average history of hypertension of 12 years and the average patient had previously received 2.4 (range: 0–7) antihypertensive drugs.

Seventy-five patients (83%) were titrated to combination therapy with trandolapril and verapamil during the study.

Seventy-one patients (79%) were titrated to combination therapy plus HCTZ by the completion of the study. Equal percentages of white and black patients, 62% and 63%, respectively, were titrated to the highest doses of TV combination therapy plus HCTZ.

Forty-one patients (46%) discontinued therapy before the end of the 19-week maintenance period: 11 during monotherapy (T), five during combination therapy (TV), and 25 during combination therapy plus hydrochlorothiazide (TV/HCTZ).

BP response

Eighty-seven of the 90 patients enrolled in the study were included in the analysis of BP. The three patients that were excluded did not have appropriate post-treatment trough BP measurements.

Trandolapril monotherapy significantly ($P < 0.01$) decreased supine DBP in this population of severely hypertensive patients (Table 2). The decrease (± s.d.) in DBP (–9.0 mm Hg, ±9.3) that was observed following trandolapril monotherapy was enhanced by the addition of verapamil, resulting in a decrease of 13.9 ± 11.0 mm Hg following administration of TV combination therapy ($P < 0.01$). Patients who went on to receive TV combination therapy plus HCTZ had an overall mean decrease in supine DBP of 19 ± 12.3 mm Hg ($P < 0.01$). Significant mean decreases in BP were observed for both black and white patients. However, white patients had a greater mean decrease in BP on trandolapril monotherapy compared to black patients. The effects on systolic BP (SBP) paralleled those of DBP.

The decrease in BP observed on TV combination therapy plus HCTZ was significantly ($P = 0.001$) greater than the decrease observed for the TV combination, which was significantly ($P = 0.001$) greater than the decrease observed for trandolapril monotherapy.

As can be seen in Table 2, the per cent of patients characterized as 'responders' increased by 11% when trandolapril was administered in combination with verapamil. The addition of HCTZ to the TV combination resulted in a 22% increase in responder rate to 77%.

Although black and white patients had similar response rates, black patients appeared to benefit more when HCTZ was added to TV combination therapy. The percentage of patients who achieved a

Table 1 Demographic and baseline characteristics

Treatment	*No. of pts*	*Sex*		*Race*		*Age*[a] *(years)*	*Supine blood pressure*[a] *(mm Hg)*	
		M	*F*	*White*	*Black*		*Systolic*	*Diastolic*
T	90	63	27	58	32	51.0 ± 11.1	182.3 ± 19.1	119.8 ± 5.5
TV	78	54	24	51	27	51.2 ± 10.7	181.8 ± 17.7	119.6 ± 5.1
TV/HCTZ	73	51	22	48	25	51.8 ± 10.4	182.2 ± 17.7	119.7 ± 5.3

T = trandolapril; TV = trandolapril/verapamil; HCTZ = hydrochlorothiazide. [a]Mean ± standard deviation.

Table 2 Mean (± s.d.) supine blood pressure (mm Hg)

Treatment	*White*	*Black*	*All patients*
T			
No.	57	30	87
Diastolic BP[a]	−10.5 ± 9.5*	−6.2 ± 8.3*	−9.0 ± 9.3*
Systolic BP[a]	−7.5 ± 15.7*	−1.2 ± 12.9	−5.3 ± 15.0*
Clinical Resp Rate[b]	49.1%	36.6%	44.8%
TV			
No.	49	26	75
Diastolic BP[a]	−14.3 ± 10.9*†	−13.1 ± 11.4*‡	−13.9 ± 11.0*‡
Systolic BP[a]	−14.6 ± 16.7*‡	−14.5 ± 17.1*‡	−14.6 ± 16.7*‡
Clinical Resp Rate[b]	57.1%	53.8%	56.0%
TV/HCTZ			
No.	47	25	72
Diastolic BP[a]	−18.6 ± 11.5*¶	−20.0 ± 13.9*¶	−19.0 ± 12.3*¶
Systolic BP[a]	−26.1 ± 18.7*¶	−28.7 ± 21.4*¶	−27.0 ± 19.6*¶
Clinical Resp Rate[b]	74.4%	84.0%	77.7%

[a]Diastolic/systolic BP data represent change from baseline.
[b]Reduction in diastolic BP of ⩾10 mm Hg or <90 mm Hg. T = trandolapril; TV = trandolapril/verapamil; HCTZ = hydrochlorothiazide. *P = 0.001 compared to baseline; †P<0.01, ‡P = 0.001 compared to monotherapy; ¶P = 0.001 compared to TV combination therapy.

post-treatment DBP <90 mm Hg reached a maximum of 12.8% for white patients compared to 20% for black patients on TV combination therapy plus HCTZ.

Heart rate as determined by supine pulse measurements was not affected by the addition of verapamil to trandolapril.

Adverse reactions

Thirty-six of 90 patients (40%) who received trandolapril alone, 27 of 78 patients (35%) who received trandolapril in combination with verapamil, and 35 of 73 patients (48%) who received combination therapy plus HCTZ experienced adverse reactions during the open label phase of the study. The most frequently reported adverse reactions are presented in Table 3.

Two patients had hypotension reported as an adverse reaction after receiving TV combination therapy (8/180 mg). Both patients went on to complete the protocol, one after a reduction in trandolapril dose to 4 mg.

Nine patients discontinued treatment because of adverse reactions: five on monotherapy (headache, nausea, fatigue, excessive perspiration, vomiting, headache, dizziness, dyspnea, neuro-orthopedic symptoms, chest pressure), two on combination therapy (parasthesia face/scalp, cough), and two patients on combination therapy plus HCTZ (chest pain, impotence).

Table 3 Most frequently reported (>5%) adverse reactions

Adverse reaction	*T*	*TV*	*TV/HCTZ*
Headache	20.0%	5.1%	9.6%
Dizziness	3.3%	3.8%	8.2%
Cough	2.2%	5.1%	6.8%
Fatigue	3.3%	3.8%	5.5%
Edema	0.0%	2.6%	5.5%
URT Congest	2.2%	2.6%	5.5%
Joint Pain	0.0%	0.0%	5.5%

T = trandolapril; TV = trandolapril/verapamil; HCTZ = hydrochlorothiazide; URT = upper respiratory tract.

An additional 32 patients discontinued the study before completion. Twenty-one patients discontinued due to an unsatisfactory therapeutic response, seven patients discontinued due to failure to follow the appointment schedule, two patients refused further therapy, and two patients moved out of the area.

Clinical laboratory parameters, including glucose, potassium, and cholesterol, were not adversely affected by any study medication or combination treatment.

Discussion

Trandolapril monotherapy, administered once daily, produced statistically significant decreases in supine DBP in this population of severely hypertensive patients. The response of the black hypertensives to trandolapril is consistent with previously published reports that indicate that black patients respond less well to ACE inhibitors than white patients, an effect that may be dose-related.[6,8]

Once a day dosing with trandolapril in combination with verapamil produced significant decreases in supine DBP beyond the decreases produced by trandolapril alone. The combination was equally effective in lowering BP in black and white hypertensive patients. Both black and white patients achieved further significant reductions in supine DBP when HCTZ was added to TV combination therapy, however, black patients appeared to benefit more than white patients. With the addition of HCTZ, the response rate for black patients was 84% compared to 74% for white patients. It is of interest to note that the percentages of black patients and white patients requiring 25 mg HCTZ was similar. Of the 32 black patients studied, 20 (63%) required 25 mg HCTZ compared to 34 of 58 (59%) white patients.

Our study is consistent with reports that indicate that there is little or no racial difference in BP

response when ACE inhibitors are combined with diuretics. In studies in patients with mild to moderate hypertension, the administration of captopril resulted in a greater decrease in BP in white patients compared to black patients. However, after HCTZ was added, the response was similar for both groups.[8,9]

The overall rate of normotension (DBP <90 mm Hg) of 15.3% observed in our study is not unexpected for severely hypertensive patients with a mean baseline DBP of 119.8 mm Hg. In a study of 97 severely hypertensive patients (DBP $\geqslant 115$ to 130 mm Hg) comparing b.i.d. quinapril to b.i.d. captopril, the percentage of patients achieving diastolic $\leqslant 90$ mm Hg after 2 weeks of monotherapy followed by 4 weeks of combined therapy with HCTZ was 22% for quinapril and 11% for captopril.[10]

Overall, the results of our study are in agreement with other published reports demonstrating an additive antihypertensive effect when a calcium channel blocker is administered in combination with an ACE inhibitor. A study of 184 patients with mild to moderate hypertension demonstrated that once a day dosing with verapamil in combination with enalapril was significantly more effective in reducing BP than either drug alone.[3] In another study in 132 patients with mild to moderate hypertension, the combination of diltiazem b.i.d. and captopril b.i.d. resulted in significant decreases in BP beyond the decreases observed for either monotherapy.[11] Results of hypertension studies combining the dihydropyridine calcium channel blocker nifedipine with captopril demonstrated an additive effect when the two agents were administered together.[1,2] However, those studies also demonstrated that it was necessary to administer the combination, three, and sometimes four times a day to maintain adequate control of BP in patients with severe or resistant hypertension. In our study, once daily dosing with trandolapril in combination with verapamil resulted in an additive decrease in both systolic and diastolic BP, achieving a 56% response rate regardless of race. Similar results were obtained from a study comparing a once-a-day regimen of amlodipine and benazepril alone and in combination.[12] A recent abstract by Mancia *et al*,[13] reported that a once-a-day combination of trandolapril and verapamil was more effective and balanced over 24 h than either drug alone. Utilizing 24-h ambulatory BP monitoring, the investigators found that the TV combination had a better trough-to-peak ratio than either monotherapy.

Our study clearly demonstrates that the addition of the calcium channel blocker verapamil to trandolapril has an additive effect on BP that is maintained throughout the day as determined by trough BP. Once-a-day administration of the TV combination therapy safely and effectively lowered supine DBP in black and white patients with severe or resistant hypertension.

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