Trandolapril: a newer angiotensin-converting enzyme inhibitor.

Guay DR

Author information

Abstract

BACKGROUND:
Trandolapril is a newer angiotensin-converting enzyme (ACE) inhibitor that is approved by the US Food and Drug Administration for the treatment of hypertension and for use in stable patients who have evidence of left ventricular (LV) systolic dysfunction or symptoms of chronic heart failure within the first 2 days after an acute myocardial infarction (AMI). The fixed-dose combination of trandolapril and verapamil extended release (ER) is approved for the treatment of hypertension only.

OBJECTIVE:
The purpose of this article was to review the pharmacology, pharmacokinetics, clinical efficacy, and safety profile of trandolapril as monotherapy and in fixed-dose combination with verapamil ER.

METHODS:
Relevant studies were identified through a MEDLINE/PubMed search of the English-language literature published between January 1983 and August 2002 and a review of the bibliographies of identified articles.

RESULTS:
Trandolapril has a sufficient duration of inhibition of plasma ACE activity to allow once-daily dosing. It is converted by esterases to the active trandolaprilat metabolite, with mean terminal disposition half-lives of < 1 and approximately 75 hours for the prodrug and metabolite, respectively. In comparative trials in the management of hypertension, trandolapril 1 to 4 mg/d was statistically indistinguishable from or superior to captopril 100 mg/d, enalapril 10 or 20 mg/d, hydrochlorothiazide (HCTZ) 25 mg/d, nifedipine ER 30 or 40 mg/d, nitrrendipine 20 mg/d, perindopril 4 mg/d, and verapamil ER 120 to 240 mg/d. In the Trandolapril Cardiac Evaluation, trandolapril also significantly reduced all-cause mortality, cardiovascular mortality, sudden death, and progression to severe chronic heart failure in patients with evidence of LV systolic dysfunction after AMI. In comparative trials in the management of hypertension, the combination of trandolapril 1 or 2 mg/d and verapamil ER 180 mg/d was statistically indistinguishable from or superior to the combinations of atenolol 50 or 100 mg/d plus chlorthalidone 12.5 or 25 mg/d, captopril 50 mg/d plus HCTZ 25 mg/d, lisinopril 20 mg/d plus HCTZ 12.5 mg/d, and metoprolol 100 mg/d plus HCTZ 12.5 mg/d. The most common adverse effects of trandolapril monotherapy in clinical trials of < or = 1 year's duration included cough, dizziness, and diarrhea (frequency < or = 1.9%). The most common adverse effects of trandolapril/verapamil ER therapy in clinical trials of < or = 1 year's duration included first-degree atrioventricular block, bradycardia, constipation, cough, diarrhea, dizziness, fatigue, and dyspnea (frequency < or = 4.6%). Based on the literature search, there are no published pharmacoeconomic evaluations of trandolapril alone or combined with verapamil ER in the US health care setting.

CONCLUSIONS:
Based on the literature, trandolapril is a well-tolerated and effective antihypertensive agent, whether used alone or in combination with verapamil ER. These products may be valuable in patients with LV systolic dysfunction after AMI, although the combination product is approved for the management of hypertension only.

PMID:

Meyer BH¹, Pauly NC.

Abstract

This multicenter international trial recruited 205 patients from 16 investigators. After a 4-week, single-blind placebo run-in, patients were randomized to receive 16 weeks of trandolapril 2 mg/day (68 patients), hydrochlorothiazide (HCTZ) 25 mg/day (68 patients), or the combination (69 patients). Morning predosing supine diastolic blood pressure (DBP) was the primary efficacy measurement. Intention-to-treat analysis showed significant decreases in all three groups in mean (+/- SEM) supine DBP throughout the study, with no significant differences at week 16 between trandolapril (-10.6 +/- 1.3 mm Hg) and HCTZ (-10.9 +/- 1.3 mm Hg). The combination gave a significantly greater reduction than either drug alone (-15.1 +/- 1.13 mm Hg). Blood pressure was normalized in the combination group in 67% of patients, a significantly higher proportion than either trandolapril (63%) or HCTZ (60%; p = 0.04). Each treatment was well tolerated. The incidence of adverse events was similar in all three groups. Trandolapril 2 mg once daily is an effective antihypertensive agent, comparable to HCTZ. Furthermore, the combination of the two drugs was shown to enhance the antihypertensive effect of the two compounds alone.
Efficacy and safety of a new long-acting drug combination, trandolapril/verapamil as compared to monotherapy in primary hypertension. Swedish TARKA trialists.

Karlberg BE, Andrup M, Odén A.

Abstract

OBJECTIVE:
To evaluate the clinical efficacy and safety of a new antihypertensive drug combination of trandolapril/verapamil compared to monotherapy with verapamil or trandolapril, in patients with mild to moderate primary hypertension.

DESIGN:
A multicentre, prospective, randomized, double-blind, controlled cross-over study with specific statistical considerations.

SETTINGS:
Eighteen primary health care centres and out-patient hospital clinics in Sweden.

PATIENTS:
Two hundred and twenty-six outpatients with uncomplicated primary hypertension with a baseline sitting diastolic blood pressure (BP) between 95 and 115 mmHg.

INTERVENTIONS:
After a 4-week placebo period, patients were randomized to treatment for 8 weeks with trandolapril/verapamil (2 mg/180 mg) or each drug alone (verapamil 240 mg, trandolapril 2 mg) for 8 weeks.

MAIN OUTCOME MEASURES:
Treatment responses (blood pressure (BP) fall and rate pressure product) to the three regimens with statistical comparison and also in relation to plasma concentrations of active renin (AR). Adverse events and safety were also evaluated.

RESULTS:
The mean BP fall was significantly greater with the combination (20/15 mmHg), p < 0.00054, as compared to both trandolapril (14/11 mmHg) or verapamil (13/11) mmHg. The difference between verapamil and trandolapril was not significant. Rate pressure product decreased significantly more on the combination, p < 0.001, than on trandolapril or verapamil alone. Treatment response to trandolapril was positively correlated to initial AR (r = 0.30-0.43). All treatments were well tolerated and safe.

CONCLUSIONS:
The new fixed drug combination trandolapril/verapamil was superior to monotherapy with either of these drugs alone regarding reduction of both BP and rate pressure product. This combination can be safely and effectively used for the treatment of mild to moderate primary hypertension.

PMID:
10855738

[PubMed - indexed for MEDLINE]
Trandolapril, but not verapamil nor their association, restores the physiological renal hemodynamic response to adrenergic activation in essential hypertension.

Author(s): Lambertucci L, Di Serio C, Castellani S, Torrini M, Lotti E, Cristofari C, Masotti G, Marchionni N, Ungar A

Affiliation(s): Unit of Geriatric Medicine and Cardiology, Department of Clinical Care Medicine and Surgery, University of Florence and Azienda Ospedaliero Universitaria Careggi, Florence, Italy.


Publication type: Randomized Controlled Trial

The purpose of this study was to evaluate the effects of antihypertensive drugs on renal hemodynamics in hypertensive patients during an adrenergic activation by mental stress (MS), which induces renal vasoconstriction in healthy subjects. Renal hemodynamics was assessed twice in 30 middle-aged essential hypertensive patients (57+/-6 years) after 15 days of pharmacological wash-out and after 15 days of treatment with Trandolapril (T, 4 mg, n=10), Verapamil (V, 240 mg, n=10), or both (T 2 mg+V 180 mg, n=10). Each experiment consisted of 4 30-min periods (baseline, MS, recovery I and II). Renal hemodynamics was evaluated with effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) from plasminogen activator inhibitor and inulin clearance, respectively. MS increased blood pressure (BP) to a similar extent before and after each treatment. Before treatment, the increasing BP was not associated with any modification of ERPF in the 3 groups. Renal vascular resistances (RVR) markedly increased during MS (+23% in the T group, +21.6% in the V group, and +32.9% in the T+V group); GFR remained constant during the whole experiment. After treatment, ERPF decreased significantly during MS in the T group (-15%, P<0.05) and in the V group (-11.7%, p<0.01); in the T+V group, ERPF modifications were not statistically significant (P=0.07). In the T group, ERPF reverted to baseline values at the end of the stimulus, whereas in the V group, renal vasoconstriction was more prolonged. Only in hypertensive patients treated with 4 mg of T, RVR reverted to baseline during the recovery I, whereas in the V group, RVR remained elevated for the whole experiment. No modifications of GFR were observed in all groups. The kidney of hypertensive patients cannot react to a sympathetic stimulus with the physiological vasoconstriction. A short-term antihypertensive treatment with 4 mg of T restores the physiological renal response to adrenergic activation. Copyright (c) 2011 Mosby, Inc. All rights reserved.
Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes patients with microalbuminuria: the BENEDICT-B randomized trial.


Affiliation(s): Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases Aldo e Cele Dacco, Villa Camozzi, Ranica, Italy.


Publication type: Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't

OBJECTIVES: To address whether nondihydropyridine calcium-channel blocker added-on angiotensin-converting-enzyme inhibitor therapy ameliorates albuminuria and cardiovascular outcomes in type 2 diabetes patients. DESIGN: The Bergamo Nephrologic Diabetes Complications Trial-B was a multicentre, prospective, double-blind, parallel-group trial comparing renal and cardiovascular outcomes in 281 hypertensive type 2 diabetes patients with microalbuminuria randomized to at least 2-year VeraTran (verapamil/trandolapril 180 mg/2 mg daily) or trandolapril (2 mg daily, identical image) treatment. Main outcome was persistent macroalbuminuria (albuminuria >200 microg/min in two consecutive visits). Treatment targets were SBP/DBP less than 120/80 mmHg and HbA1C less than 7%. RESULTS: Over a median follow-up of 4.5 years, 18 patients (13%) on VeraTran vs. 15 (10.5%) on trandolapril [unadjusted hazard ratio (95% confidence interval [CI]) 1.07 (0.54-2.12), P = 0.852] progressed to macroalbuminuria, respectively; 62 (44.9%) vs. 71 (49.7%) [0.80 (0.57-1.12), P = 0.198] regressed to normoalbuminuria (urinary albumin excretion <20 microg/min), and 20 (14.5%) vs. 21 (14.7%) [hazard ratio 0.93 (0.50-1.72), P = 0.816] had major cardiovascular events. BP and metabolic control were similar between groups. Patients with cardiovascular events were significantly less [13 (9.8%) vs. 28 (18.9%), hazard ratio: 0.37 (0.19-0.71), P = 0.003] among those regressing to normoalbuminuria than those without regression. Difference was independent of treatment allocation and was significant also after adjusting for baseline characteristics [0.40 (0.20-0.79), P = 0.009], follow-up SBP [0.40 (0.20-0.80), P = 0.010] or DBP [0.36 (0.18-0.73), P = 0.004] BP or HbA1C [0.43 (0.21-0.88), P = 0.021]. CONCLUSION: In hypertensive type 2 diabetes patients with microalbuminuria, verapamil added-on trandolapril did not improve renal or cardiovascular outcomes. Independent of verapamil, trandolapril normalized albuminuria in half of patients and this translated into significant cardioprotection.
Efficacy and tolerability of trandolapril in mild to moderate hypertension-a double blind comparative clinical trial with enalapril in Indian population.


Affiliation(s): Department of Pharmacology, Kasturba Medical College, Manipal.


Publication type: Comparative Study; Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't

Several large scale clinical trials have demonstrated that angiotensin converting enzyme inhibitors offer cardiovascular and renal protection independent of their effects on systolic BP. Trandolapril is a new angiotensin converting enzyme inhibitor approved for the treatment of hypertension. The potential advantages of this drug are long duration of action and better tolerability. The objective of the study was to compare the efficacy and tolerability of trandolapril with that of enalapril in mild to moderate hypertension in Indian population. In this double blind, multicentric, parallel comparative clinical study, 120 patients with mild to moderate hypertension were randomly assigned to receive trandolapril 2 mg or enalapril 5 mg once daily for 8 weeks. The attainment of sitting diastolic blood pressure <90 mmHg at the end of 8th week was considered as primary outcome measure and attainment of diastolic blood pressure <90 mmHg or reduction of at least 10 mmHg diastolic blood pressure compared to baseline at any visit was considered as secondary outcome measures. 98.4% patients treated with trandolapril and 92.6% patients treated with enalapril fulfilled the primary outcome measure. 54, 72 and 62% patients on trandolapril and 52, 61 & 64% patients on enalapril fulfilled secondary outcome measure at the end of 2nd, 4th and 8th week respectively. Also trandolapril was better tolerated than enalapril with no significant abnormality in lab parameters.
INVEST: INternational VErapamil SR Trandolapril STudy

Information source: University of Florida
Information obtained from ClinicalTrials.gov on June 20, 2008
Link to the current ClinicalTrials.gov record.

Condition(s) targeted: Hypertension; Coronary Artery Disease

Intervention: Verapamil SR/Trandolapril/Hydrochlorothiazide (HCTZ) (Drug); Atenolol/HCTZ/Trandolapril (Drug)

Phase: Phase 4

Status: Completed

Sponsored by: University of Florida

Official(s) and/or principal investigator(s):
Carl J Pepine, MD, Principal Investigator, Affiliation: University of Florida

Summary

Because blood pressure affects the heart, blood vessels, kidneys, and the entire body, it is important to keep it as normal as possible. There are several different ways to control blood pressure and to prevent or limit the development of heart disease due to high blood pressure. The purpose of this study is to compare two treatments to see how well they work and the difference in their side effects. One treatment includes the use of a calcium antagonist drug (Isoptin sustained release [SR] or Verapamil SR). The other treatment excludes the calcium antagonist and may include a non-calcium antagonist drug called a beta blocker (Tenormin or Atenolol). Both treatments may also include medication called angiotensin converting enzyme (ACE) inhibitors and water pills. None of the drugs in this study are experimental, they are all approved by the Food and Drug Administration (FDA).

Clinical Details

Official title: INternational VErapamil SR Trandolapril STudy

Study design: Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study

Primary outcome: First occurrence of death or nonfatal myocardial infarction (MI) or nonfatal stroke

Secondary outcome:

Death
Nonfatal MI
Nonfatal stroke
Newly diagnosed diabetes
BP control

Cancer

Gastrointestinal (GI) bleeding

Alzheimer's Disease

Parkinson's Disease

Cardiovascular (CV) hospitalizations

Quality of life

Compliance

**Detailed description:** INVEST is an investigator initiated international, prospective, randomized study comparing two pharmacotherapy strategies to control hypertension in ambulatory patients with coronary artery disease (CAD). One strategy, the calcium antagonist care strategy, centers on a calcium antagonist (verapamil SR) followed by addition of an ACE inhibitor (trandolapril) and then diuretic (hydrochlorothiazide) as needed to achieve target blood pressures (BP). The other strategy, the non-calcium antagonist care strategy, uses a beta-blocker (atenolol) followed by addition of low-dose diuretic and then an ACE inhibitor (trandolapril) as needed to reach target BP. In either strategy additional drugs can be added provided the calcium antagonist is retained in the calcium antagonist care strategy and calcium antagonists are omitted in the non-calcium antagonist care strategy.

The study is organized into 15 international regions with about 1,500 study investigators randomizing approximately 22,000 patients who will be treated for at least two years. The primary response variable is the occurrence of adverse outcome, defined as any of the following events: all cause mortality, nonfatal MI or nonfatal stroke. A number of secondary response variables, including newly diagnosed diabetes will also be evaluated.

The primary objective of this trial is to examine the hypothesis that the risk for adverse outcomes (all cause mortality, nonfatal MI or nonfatal stroke) in hypertensive patients with CAD is at least equivalent during treatment of hypertension with a calcium antagonist strategy when compared with a non-calcium antagonist strategy.

Unique features of INVEST are, in addition to its size and international scope, its design to mimic standard clinical practice and its all electronic online data entry, drug distribution system, study management system, and electronic physician compensation. This system will permit the entire trial to be conducted via the Internet. This design is believed to be a forerunner of clinical trials research for the future.

**Eligibility**

Minimum age: 50 Years. Maximum age: N/A. Gender(s): Both.

**Criteria:**

Inclusion Criteria:

- Male or female

- Age 50 to no upper limit

- Hypertension documented according to the 6th report of the Joint National Committee on
Detection and Evaluation of the treatment of high BP (JNC VI) and the need for drug therapy
(previously documented hypertension in patients currently taking antihypertensive agents is
acceptable)

- Documented CAD (e. g., classic angina pectoris (stable angina pectoris; Heberden angina
pectoris), myocardial infarction three or more months ago, abnormal coronary angiography, or
concordant abnormalities on two different types of stress tests)

- Willingness to sign informed consent

Exclusion Criteria:

- Unstable angina, angioplasty, coronary artery bypass graft surgery (CABG) or stroke
within one month. Patients taking beta blockers after myocardial infarction are excluded if study
enrollment is planned within 12 months of myocardial infarction. No time limitation if not taking beta-
blocker.

- Use of a ß-blocker within past two weeks

- Patients without a pacemaker and any of the following:

  - Sinus bradycardia (< 50 beats/min.)
  
  - Sick sinus syndrome

  - Atrioventricular (AV)-block of more than 1st degree

  - Documented contraindication to verapamil; documented contraindication to both atenolol
and hydrochlorothiazide

  - Atrial fibrillation/flutter with Wolff-Parkinson-White (WPW)-Syndrome

  - Severe heart failure (New York Heart Association [NYHA] IV).

  - Concomitant illnesses (e. g., severe renal failure [Serum creatinine ≥4. 0 mg/dl],
severe hepatic failure or known cirrhosis, etc.) which may affect outcome variables or where life
expectancy is two years or less or which are likely to require frequent hospitalizations and/or treatment
adjustments.

  - Patients with psychiatric, cognitive, or social (e. g., alcoholism, etc.) conditions
that would interfere with giving consent or cooperating or remaining available for follow-up for two
years.

Locations and Contacts
University of Florida, Gainesville, Florida 32610-0277, United States

Additional Information

Starting date: September 1997
Ending date: February 2003
Last updated: July 26, 2006
Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes patients with microalbuminuria: the BENEDICT-B randomized trial.


Affiliation(s): Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases Aldo e Cele Dacco, Villa Camozzi, Ranica, Italy.


Publication type: Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't

OBJECTIVES: To address whether nondihydropyridine calcium-channel blocker added-on angiotensin-converting-enzyme inhibitor therapy ameliorates albuminuria and cardiovascular outcomes in type 2 diabetes patients. DESIGN: The Bergamo Nephrologic Diabetes Complications Trial-B was a multicentre, prospective, double-blind, parallel-group trial comparing renal and cardiovascular outcomes in 281 hypertensive type 2 diabetes patients with microalbuminuria randomized to at least 2-year VeraTran (verapamil/trandolapril 180 mg/2 mg daily) or trandolapril (2 mg daily, identical image) treatment. Main outcome was persistent macroalbuminuria (albuminuria >200 microg/min in two consecutive visits). Treatment targets were SBP/DBP less than 120/80 mmHg and HbA1C less than 7%. RESULTS: Over a median follow-up of 4.5 years, 18 patients (13%) on VeraTran vs. 15 (10.5%) on trandolapril [unadjusted hazard ratio (95% confidence interval [CI]) 1.07 (0.54-2.12), P = 0.852] progressed to macroalbuminuria, respectively; 62 (44.9%) vs. 71 (49.7%) [0.80 (0.57-1.12), P = 0.198] regressed to normoalbuminuria (urinary albumin excretion <20 microg/min), and 20 (14.5%) vs. 21 (14.7%) [hazard ratio 0.93 (0.50-1.72), P = 0.816] had major cardiovascular events. BP and metabolic control were similar between groups. Patients with cardiovascular events were significantly less [13 (9.8%) vs. 28 (18.9%), hazard ratio: 0.37 (0.19-0.71), P = 0.003] among those regressing to normoalbuminuria than those without regression. Difference was independent of treatment allocation and was significant also after adjusting for baseline characteristics [0.40 (0.20-0.79), P = 0.009], follow-up SBP [0.40 (0.20-0.80), P = 0.010] or DBP [0.36 (0.18-0.73), P = 0.004] BP or HbA1C [0.43 (0.21-0.88), P = 0.021]. CONCLUSION: In hypertensive type 2 diabetes patients with microalbuminuria, verapamil added-on trandolapril did not improve renal or cardiovascular outcomes. Independent of verapamil, trandolapril normalized albuminuria in half of patients and this translated into significant cardioprotection.
The duration of action of antihypertensive drugs may be assessed by several methods using ambulatory blood pressure monitoring (ABPM). The aim of this double-blind, randomized study was to compare the time-effect profile of once daily Trandolapril (Tra) 2 mg vs. Quinapril (Qui) 20 mg in 92 patients with mild-to-moderate hypertension. All patients received placebo during a 30-day run-in period followed by 2 months of active therapy and 1-day medication omission. ABPM was conducted on each period. 24 h antihypertensive coverage was assessed by trough:peak ratio (T/P) and smoothness index (SI) methods. Residual lowering of blood pressure after single-blind, 1 day medication omission was investigated as the SBP/DBP 48-h trough effect. There were no statistically significant differences between treatment groups in the mean SBP/DBP peak or trough effect. Individual T/P were not normally distributed and had very large variations explained by BP random- and activity-related fluctuations. Group T/P were 0.85 for Tra and 0.62 for Qui. The SI values were normally distributed and not statistically different between the two treatment groups. After dose omission, Qui was ineffective at 48-h trough while Tra retained a significant effect (SBP/DBP = -3.4/-4.3 mmHg) and this difference was even greater in ABPM-responders. Comparison of the trough:peak ratios and smoothness indexes of Tra and Qui failed to show any statistically significant difference on 24-h antihypertensive coverage. Nevertheless, residual lowering of blood pressure at 48-h trough suggests that Tra had a longer duration of action than Qui.

Treatment with verapamil and trandolapril in patients with congestive heart failure and angina pectoris or myocardial infarction. The DAVIT Study Group. Danish Verapamil Infarction Trial.

Hansen JF, Hagerup L, Sigurd B, Pedersen F, Mellemgaard K, Bjergaard OP.

Abstract
In a double-blind, randomized trial in a consecutive group of postinfarct patients in treatment with diuretic agents for congestive heart failure, the 3 month rate of cardiac events (i.e., death, repeat infarction, unstable angina pectoris, or repeat admission because of heart failure) was 14% in patients treated with verapamil and trandolapril and 35% in patients treated with trandolapril (p = 0.01). In another study of patients with angina pectoris and left ventricular ejection fraction less than 40%, trandolapril plus verapamil improved exercise duration and left ventricular ejection fraction. These findings indicate that combined treatment with verapamil and trandolapril may be beneficial in patients with congestive heart failure.

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