ADIS DRUG EVALUATION

Drugs 2002; 62 (17): 2539-2567
0012-6667/02/0017-2539/$30.00/0

Fixed Combination Trandolapril/Verapamil Sustained-Release

A Review of its Use in Essential Hypertension

Richard B. R. Muijsers, Monique P. Curran and *Caroline M. Perry*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

G.L. Bakris, Rush Presbyterian St Lukes Medical Center, Chicago, Illinois, USA; ***D. Power***, Austin & Repatriation Medical Centre, Heidleberg, Victoria, Australia; ***E. Erdmann***, University of Cologne, Cologne, Germany; ***J.F. Hansen***, Bispebjerg University Hospital, Copenhagen, Denmark; ***F.H. Messerli***, Ochsner Clinic, New Orleans, Louisiana, USA; ***C.J. Pepine***, University of Florida College of Medicine, Gainsville, Florida, USA; ***M.L. Ruilope***, Hospital 12 de Octubre, Madrid, Spain; ***P.S. Sever***, St Mary's Hospital Medical School, London, England; ***R.P. Singh***, University of Colorado Health Sciences Center, Denver, Colorado, USA.

Data Selection

Sources: Medical literature published in any language since 1980 on trandolapril/verapamil SR, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'verapamil trandolapril' or 'trandolapril verapamil' and 'hypertension'. EMBASE search terms were 'verapamil trandolapril' or 'trandolapril verapamil' and 'hypertension'. AdisBase search terms were 'verapamil trandolapril' or 'trandolapril verapamil' and 'hypertension'. Searches were last updated 30 Oct 2002.

Selection: Studies in patients with hypertension who received trandolapril/verapamil SR. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Verapamil SR, trandolapril, hypertension, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

In well designed studies in patients with mild to moderate hypertension, combinations of the sustained-release (SR) formulation of the nondihydropyridine calcium channel antagonist verapamil 120 to 240 mg/day and the ACE inhibitor trandolapril 0.5 to 8 mg/day were significantly more effective in reducing sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline than placebo. In most randomised studies, combinations of verapamil SR 120 to 240 mg/day and trandolapril 0.5 to 8 mg/day were significantly more effective in lowering sitting DBP and SBP than the corresponding monotherapies administered at the same dosage. Trandolapril/verapamil SR 2/180 mg/day provided significantly more effective 24-hour ambulatory blood pressure (BP) control than of the corresponding monotherapies. Moreover, trandolapril/verapamil SR reduced BP in patients inadequately controlled with either of the corresponding monotherapies.

The antihypertensive efficacy of trandolapril/verapamil SR 2/180 mg/day was generally similar to that of other combinations of antihypertensive agents (metoprolol/hydrochlorothiazide, atenolol/chlorthalidone, lisinopril/hydrochlorothiazide, enalapril/hydrochlorothiazide) in patients with hypertension, including those with type 2 diabetes mellitus.

Trandolapril/verapamil SR reduced BP in patients with hypertension and type 2 diabetes or primary renal disease, Black patients and elderly patients. Trandolapril/verapamil SR was more effective than the individual components administered as monotherapy in reducing proteinuria in patients with type 2 diabetes or primary renal disease. Trandolapril/verapamil SR had a neutral or beneficial effect on metabolic parameters (glucose, insulin, lipids) in patients with hypertension, including those with type 2 diabetes.

Trandolapril/verapamil SR preserved left ventricular function in patients with heart failure. Fewer cardiac events occurred after therapy with trandolapril/verapamil SR than after trandolapril alone in post-myocardial infarction patients with congestive heart failure.

The incidence of adverse events in recipients of trandolapril/verapamil SR was similar to that of the individual components, and that of other combination therapies. In placebo-controlled trials conducted in the US, headache, upper respiratory tract infections, cough, constipation, atrioventricular block (first degree) and

dizziness were the most commonly reported adverse events in recipients of combinations of verapamil SR (120 to 240 mg/day) and trandolapril (0.5 to 8 mg/day).

In conclusion, the fixed-dose combination of trandolapril/verapamil SR is an effective treatment for patients with hypertension, including those with type 2 diabetes. Trandolapril/verapamil SR tended to be more effective than monotherapy with either verapamil SR or trandolapril, and generally showed antihypertensive efficacy similar to that of other combination antihypertensive therapies. Current data support the use of trandolapril/verapamil SR as an alternative treatment when monotherapy with either agent is not effective. Data from large clinical trials currently being conducted will assist in fully defining the role of trandolapril/verapamil SR as a cardio- and renoprotective agent.

Pharmacodynamic Profile

Verapamil is a nondihydropyridine calcium channel antagonist that reduces blood pressure via the inhibition of the inward flow of calcium ions through the L-type channels. Verapamil appears to exert its antihypertensive effects without activating any counter-balancing mechanisms such as tachycardia, water or sodium retention or the stimulation of the renin-angiotensin-aldosterone system.

Trandolapril exerts its antihypertensive effects through inhibition of ACE. The decrease in angiotensin II levels leads to decreased vasopressor activity and decreased aldosterone secretion. Trandolapril also reduces the breakdown of bradykinin (a vasodilator).

The combination of trandolapril/verapamil sustained-release (SR) generally had no effect on heart rate in patients with hypertension; although a small, but significant, reduction in heart rate was reported in a randomised, double-blind study. In patients with hypertension, trandolapril/verapamil SR had a positive effect on aortic elastic properties (assessed according to pulse wave velocity) and decreased left ventricular (LV) mass. Trandolapril/verapamil SR improved LV ejection fraction in patients with angina pectoris (noncomparative study) and in patients with heart failure (comparative study). Fewer cardiac events occurred after trandolapril/verapamil SR than after monotherapy with trandolapril in post-myocardial infarction patients with congestive heart failure.

Trandolapril/verapamil SR had a neutral or beneficial effect on metabolic parameters (glucose, insulin, lipids) in patients with hypertension with or without type 2 diabetes mellitus. Trandolapril/verapamil SR reduced proteinuria in patients with hypertension and diabetic nephropathy and in patients with primary renal disease.

Pharmacokinetic Profile

In volunteers administered a single dose of trandolapril/verapamil SR (dose not stated), peak plasma concentrations (C_{max}) values of verapamil, trandolapril and trandolaprilat were reached after 4 to 15, 0.5 to 2 and 2 to 12 hours, respectively.

The pharmacokinetics of trandolapril and trandolaprilat were the same when trandolapril was administered as monotherapy or as a fixed combination with verapamil SR. The verapamil area under the concentration-time curve (AUC) and C_{max} increased by 65 and 54% when verapamil SR 240mg was administered in combination with trandolapril 4mg.

Trandolapril is rapidly converted in the liver to trandolaprilat, the biologically active diacid. The bioavailability of trandolapril is about 10% and that of trandolaprilat is about 70%. The bioavailability of trandolapril was not affected by the presence of food. The bioavailability of verapamil is low (10 to 20%), because of the rapid biotransformation of verapamil during hepatic first-past metabolism.

Plasma protein binding of verapamil is about 90%; that of trandolapril is about 80% and is independent of drug concentration. Trandolaprilat is highly bound to plasma protein in a concentration-dependent manner (94% at 0.04 μg/L).

Plasma concentrations of verapamil and trandolaprilat at steady-state (reached after approximately 1 week of once-daily trandolapril/verapamil SR) were up to 2-fold higher than those obtained with a single dose of trandolapril/verapamil SR.

The bioavailability and the time to C_{max} of verapamil were decreased by the presence of food. The bioavailabilities of verapamil and trandolapril were increased in elderly patients, relative to younger patients, administered trandolapril/verapamil SR.

Approximately 70% of verapamil is excreted as metabolites in the urine, and 15% in the faeces. After administration of a radioactive dose of trandolapril, approximately 33% of the radioactivity was recovered in the urine and 66% in the faeces. Elimination of trandolaprilat is triphasic, with an effective elimination half-life of about 10 hours and a prolonged terminal elimination half-life.

In patients with hypertension administered trandolapril/verapamil SR, the presence of fatty liver disease did not alter the pharmacokinetics of verapamil. However, trandolaprilat C_{max} and AUC_{24h} values were elevated.

The pharmacokinetics of trandolapril were unchanged in patients with renal impairment; however, renal trandolaprilat clearance decreased with increasing renal insufficiency.

Therapeutic Use

In randomised, double-blind studies, combination therapy with once-daily trandolapril 0.5 to 8mg and once-daily verapamil SR 120 to 240mg was significantly more effective in lowering sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) than placebo in patients with mild to moderate hypertension. The number of responders to treatment with trandolapril/verapamil SR 2/180, 2/240 and 4/240 mg/day was significantly higher than that with placebo. In most randomised studies, combinations of trandolapril 1 to 4 mg/day and verapamil SR 120 to 240 mg/day were significantly more effective in lowering sitting DBP and SBP than the corresponding monotherapies administered at the same dosage. The mean reduction in 24-hour ambulatory blood pressure (BP) was significantly greater with combination trandolapril/verapamil SR 2/180 mg/day than with either of the monotherapies administered at the same dosage. Moreover, trandolapril/verapamil SR was effective in reducing BP in patients unresponsive to either of the agents administered as monotherapy.

Trandolapril/verapamil SR was effective in reducing BP in special populations of patients with hypertension, including those with type 2 diabetes or primary renal disease, and black or elderly patients.

Reductions in BP were generally similar in recipients of trandolapril/verapamil SR 2/180 mg/day to those in recipients of other antihypertensive combinations (metoprolol/hydrochlorothiazide, atenolol/chlorthalidone, lisinopril/hydrochlorothiazide, enalapril/hydrochlorothiazide) in patients with hypertension, including those with type 2 diabetes.

Tolerability

Trandolapril/verapamil SR is generally well tolerated and the adverse event profile corresponds to that of the monocomponents. In placebo-controlled trials, the incidence of adverse events was 28, 34, 27 and 26% in recipients of trandolapril/verapamil SR 2/180 mg/day, trandolapril 0.5 to 8 mg/day, verapamil SR 120 to 240 mg/day and placebo, respectively. In placebo-controlled trials conducted in the US, headache, upper respiratory tract infections, cough, constipation, atrio-

ventricular block (first degree) and dizziness were the most commonly reported adverse events in recipients of combinations of trandolapril (0.5 to 8 mg/day) and verapamil SR (120 to 240 mg/day). The incidence of prolongation of the PQ interval was similar in recipients of trandolapril/verapamil SR, the monotherapy components or placebo.

There were no significant differences in the incidence of adverse events in recipients of trandolapril/verapamil SR (34%), atenolol/chlorthalidone (32%), lisinopril/hydrochlorothiazide (29%), or placebo (21%) during a well designed, trial in patients with hypertension.

Dosage and Administration

In the US, the fixed combination of trandolapril/verapamil SR is approved for the treatment of hypertension, but not for initial therapy. The recommended usual dosage of verapamil SR is 120 to 480 mg/day administered as a single dose or as two divided doses. The recommended usual dosage of trandolapril is 1 to 4 mg/day administered as a single dose or as two divided doses. Clinical trials of trandolapril/verapamil SR have only investigated once-daily dosing. The fixed combination of trandolapril/verapamil SR is available as 2/180, 1/240, 2/240 and 4/240mg tablets.

In European countries, the fixed combination of trandolapril/verapamil SR is available as 2/180mg capsules. The usual dosage is one capsule, taken once-daily in the morning.

Trandolapril/verapamil SR should be administered with food.

The safety and efficacy of trandolapril/verapamil SR has not been established in patients aged under 18 years. Trandolapril/verapamil SR is contraindicated in patients who are hypersensitive to an ACE inhibitor or verapamil. Trandolapril/verapamil SR is also contraindicated in patients with severe LV dysfunction, hypotension (SBP <90mm Hg) or cardiogenic shock, in patients with sick sinus syndrome (except those with an artificial ventricular pacemaker), second or third degree atrioventricular block (except those with an artificial ventricular pacemaker), in patients with atrial flutter or atrial fibrillations and an accessory bypass tract, and in patients with a history of ACE inhibitor-related angioedema. Trandolapril/verapamil SR should be administered with caution to patients with renal or hepatic impairment.

1. Introduction

Essential hypertension, defined as resting diastolic blood pressure (DBP) ≥90mm Hg and/or systolic BP (SBP) ≥140mm Hg,[1] is a disease of unknown aetiology. Chronically elevated blood pressure (BP) is associated with an increased risk of cardiovascular morbidity and mortality, and with end-stage renal failure.[2]

Although single-agent drug therapy remains the recommended initial treatment for hypertension,[1-3] patients are commonly unable to achieve BP goals with monotherapy.[4] Consequently, combination therapy, employing different classes of antihypertensives simultaneously, has been used. Moreover, combination therapy, particularly when low doses or drugs from different classes are involved, may have additive or synergistic effects on BP and minimise dose-dependent adverse events.[2]

One such combination involves trandolapril, an ACE inhibitor with a long duration of action, and a sustained-release (SR) formulation of verapamil, a nondihydropyridine calcium channel antagonist. Both trandolapril[5,6] and verapamil[7,8] are well established treatment options for patients with hyper-

tension and have been previously reviewed in *Drugs*.

This review provides an overview of the use of trandolapril/verapamil SR in the treatment of patients with predominantly mild to moderate hypertension. Although a fixed combination tablet is available, this review also includes studies in which the combination was administered as separate tablets or capsules. Trandolapril/verapamil SR has been briefly reviewed previously in *Drugs*.[9]

2. Pharmacodynamic Profile

Available data concerning the pharmacodynamic effects of trandolapril and verapamil SR when coadministered are reasonably limited (see section 2.3). Consequently, this review also provides a brief summary of the pharmacodynamic properties of each individual agent (section 2.1 and section 2.2) as previously reviewed in *Drugs*.[5-8] In addition, data from more recently published studies have also been added.[10-13] The main pharmacodynamic properties of trandolapril and verapamil are summarised in table I.

2.1 Trandolapril

Trandolapril exerts its antihypertensive effects through inhibition of ACE, preventing the conversion of angiotensin I to angiotensin II.[18] The decrease in angiotensin II levels results in decreased vasopressor activity, decreased aldosterone secretion and provides negative feedback for renin secretion. Since ACE is structurally identical to kinase II, one of the enzymes responsible for the transformation of bradykinin into inactive peptides, trandolapril can also degrade bradykinin, a potent vasodilator.[5,6,16,19,20]

Trandolapril markedly reduced both SBP and DBP throughout a 24-hour post-dose period, while generally having no effect on heart rate, stroke volume or cardiac output.[5,6] Trandolapril 2 to 4 mg/day for 1 year significantly improved diastolic function and reduced left ventricular (LV) hypertrophy in patients with hypertension and LV hypertrophy.[5,6] Trandolapril generally had no effect on metabolic parameters (including lipid and glucose levels and insulin sensitivity).[5,6,10,12]

2.2 Verapamil

Verapamil is a nondihydropyridine (phenylalkylamine) calcium channel antagonist that inhibits the inward flow of calcium ions through the L-type calcium channels.[7,8,19-21] This causes a dilatation in peripheral and coronary blood vessels, and results in decreased blood pressure. Verapamil

Table I. Overview of the pharmacodynamic properties of verapamil and trandolapril in patients with essential hypertension

Trandolapril (trandolaprilat[a])	Verapamil
Reduces blood pressure via the inhibition of the angiotensin-converting enzyme. The decrease in angiotensin II levels leads to decreased vasopressor activity, decreased aldosterone secretion and increased plasma renin[5,6]	Reduces blood pressure via the inhibition of the inward flow of calcium ions across the cell membrane of cardiac and vascular smooth muscle cells[7,8]
Reduces the breakdown of bradykinin (a vasodilator)[5,6]	Inhibits sympathetic nervous cell activation[13]
Has a neutral or moderating effect on heart rate without affecting cardiac output or stroke volume[5,6]	Has a neutral or a moderating effect on heart rate without altering cardiac output[7,8,14]
Reduces left ventricular hypertrophy[5,6]	Reduces left ventricular hypertrophy[15]
Reduces sodium and water retention and leads to a small increase in serum potassium (via inhibition of aldosterone production)[5,6,16]	Does not induce water or sodium retention[7,8]
Neutral effect on lipid metabolism[5,6] and improves[11] or has a neutral effect on[10,12] insulin sensitivity	Neutral effect on glucose and lipid metabolism[7,8]
Improves elastic properties of large arteries - increases arterial compliance and brachial artery diameter, and decreases forearm vascular resistance and carotid-femoral pulse wave velocity[5,6]	
	Does not alter serum calcium levels[17]

a Trandolapril is a prodrug which is de-esterified to form trandolaprilat.

appears to exert its antihypertensive effect without activating any counter-balancing mechanisms such as tachycardia, water or sodium retention, or stimulation of the renin-angiotensin-aldosterone system.[8]

Verapamil may have benefits over the dihydropyridine calcium antagonists in terms of activation of the sympathetic nervous system.[13,22] The effects of Verapamil and Amlodipine on autonomic function in Patients with Hypertension at Rest and during Exercise (VAMPHYRE) study randomised 145 patients with DBP ≥95mm Hg to verapamil SR 240 mg/day or amlodipine 5 mg/day for 8 weeks. In this double-blind study, the 24-hour low-frequency/high-frequency ratio was higher after amlodipine than after verapamil SR (4.66 *vs* 4.10; p = 0.001, intention-to-treat analysis). Plasma norepinephrine levels (1.59 *vs* 1.32 nmol/L; p < 0.0001) were higher after amlodipine than verapamil SR treatment. These results suggest amlodipine, but not verapamil SR, induced a shift towards sympathetic predominance. The increase in baroreflex sensitivity was significantly higher with verapamil SR (27%; p = 0.01) than with amlodipine (21%), suggesting more effective restoration of short-term autonomic control of BP by verapamil SR.[13]

2.3 Trandolapril/Verapamil Sustained-Release (SR)

2.3.1 Cardiovascular Effects

Heart Rate

Treatment with trandolapril/verapamil SR did not generally affect heart rate in patients with mild to moderate essential hypertension. There was no change in heart rate in several randomised, double-blind studies (see section 4 for study details).[23-25] Nonetheless, small but statistically significant reductions from baseline in mean 24-hour heart rates were recorded in one study in 234 patients receiving verapamil SR 180mg once daily (4.5 beats/min; p < 0.01) or trandolapril/verapamil SR 1/180mg once daily (3.9 beats/min; p < 0.01) for 8 weeks, but not in recipients of trandolapril 1mg once daily or placebo for 8 weeks.[26]

Total Peripheral Resistance

In a 6-month, double-blind, randomised study in patients with hypertension (DBP ≥90 and <115mm Hg), trandolapril/verapamil SR 1/180mg once daily (n = 26) reduced total peripheral resistance by 14% (from 1596 to 1370 m/s/cm^{-5}).[25] This reduction was not statistically significant, but was considered clinically relevant by the researchers. Treatment with metoprolol/hydrochlorothiazide 100/12.5mg once daily (n = 25) did not affect this variable (1646 m/s/cm^{-5} at baseline and 1629 m/s/cm^{-5} after treatment).[25]

Arterial Structure and Function

Treatment with trandolapril/verapamil SR positively affected aortic elastic properties (assessed according to pulse wave velocity [PWV]) in patients with mild to moderate hypertension in randomised, double-blind studies.[25,27,28]

After six months' treatment, trandolapril/verapamil SR 1/180 mg/day significantly (p < 0.05) reduced PWV during isometric exercise (4 minute value) by 9% versus baseline in 26 patients with hypertension (DBP ≥90 and <115mm Hg).[25] Treatment-induced reductions from baseline in PWV in 25 patients treated with metoprolol/hydrochlorothiazide 100/12.5 mg/day were small and nonsignificant. Reductions in PWV at rest did not reach significance in either of the treatment groups.[25]

Likewise, treatment with trandolapril/verapamil SR 2/180 mg/day for 6 months significantly reduced PWV from baseline by 14% (p < 0.05) in one study (n = 69),[28] and by 27% in another (n = 41: data presented as an abstract, significance vs baseline not stated).[27] PWV was reduced by 24% in recipients of atenolol/chlorthalidone 100/25 mg/day,[27] but this reduction was not significantly different from that in recipients of trandolapril/verapamil SR. Post-ischaemic maximal forearm blood flow also improved to a greater extent in recipients of trandolapril/verapamil SR than in recipients of atenolol/chlorthalidone (18 *vs* 8%; p = 0.002).[27]

Left Ventricular Structure and Function

LV hypertrophy is an independent risk factor for cardiac and cerebral morbidity in patients with hypertension, and it has been speculated that its regression during antihypertensive therapy may reduce the risk of complications including myocardial infarction, stroke and heart failure.[29] Trandolapril/verapamil SR had beneficial effects on LV structure in patients with hypertension, according to data from one randomised, double-blind[28] and two noncomparative [30,31] trials.

In a study in 14 patients with mild to moderate hypertension, trandolapril/verapamil SR 2/180mg once or twice daily or 4/240mg once daily for 12 weeks decreased LV septal wall thickness by 8% ($p = 0.007$) and posterior wall thickness by 8% ($p = 0.009$).[30] These changes resulted in decreases in LV mass (9%; $p = 0.007$), and were accompanied by small, but significant, increases (12%; $p = 0.05$) in systolic function (assessed according to midwall fractional fibre shortening).[30]

Similarly, trandolapril/verapamil SR 2/180mg once daily reduced LV mass by 6% ($p = 0.01$ vs baseline) in 138 patients with mild-to-severe hypertension treated for 6 weeks[31] and the LV mass index by 8% ($p < 0.01$ vs baseline) in 23 patients with mild to moderate hypertension treated for 6 months.[28]

In a noncomparative study in 14 patients with angina pectoris and an LV ejection fraction of <40%, trandolapril/verapamil SR (2/180mg once daily for 2 weeks then 2/180mg twice daily for 10 weeks) increased LV ejection fraction from 28 to 35% ($p = 0.03$) and LV wall motion index from 1.0 to 1.2 ($p = 0.03$).[32] Moreover, exercise duration (6.9 to 7.7 minutes; $p = 0.01$) and the ratio of exercise to resting rate-pressure product (2.2 to 2.5; $p = 0.02$) also increased. Nitroglycerin use and the number of angina pectoris attacks were reduced ($p < 0.02$).[32]

Patients with Heart Failure

Preliminary evidence from a randomised, double-blind study (data presented in an abstract) suggests trandolapril/verapamil SR preserves LV function in patients with heart failure.[33] In 84 patients with New York Heart Association (NYHA) class I and II heart failure (LV ejection fraction of 35 to 50%; 69% in NYHA class I and 31% in NYHA class II), trandolapril/verapamil SR 2/180 mg/day for two weeks improved the mean LV ejection fraction from 45.3 to 48.3% (significance not stated). There was no change in pulmonary capillary wedge pressure or cardiac index. Further studies are required to determine if this effect is maintained when treatment is given for a longer period of time.

Post-Myocardial Infarction Patients with Congestive Heart Failure

Cardiac events occurred less frequently after trandolapril/verapamil SR (0.5/120mg twice daily for 1 month then 1/180mg twice daily for 2 months) than after monotherapy with trandolapril (0.5mg twice daily for 1 month then 1mg twice daily for 2 months) in a double-blind, randomised trial in 100 patients with congestive heart failure after an acute myocardial infarction.[34,35] All patients received diuretics throughout the study and the use of aspirin, long-acting nitrates and digoxin was also permitted.[34] The combined cardiac event rate (death, reinfarction, unstable angina or readmission due to worsening congestive heart failure) was significantly lower in trandolapril/verapamil SR than trandolapril recipients (14 *vs* 35%; $p = 0.015$). Reinfarction was also significantly less frequent in trandolapril/verapamil SR recipients than in patients treated with trandolapril (2 *vs* 14%; $p < 0.03$).[34,35]

2.3.2 Effects on Metabolic Profile

Trandolapril/verapamil SR had a neutral or a beneficial effect on metabolic parameters (glucose, insulin, lipids) in patients with hypertension with [36,37] or without[27,38] type 2 diabetes mellitus.

Patients with Uncomplicated Hypertension

In two randomised studies,[27,38] treatment with trandolapril/verapamil SR 2/180 mg/day did not adversely affect lipid or glucose metabolism in patients with mild to moderate hypertension.

During a 16-week, nonblind, crossover trial in 100 patients with mild to moderate hypertension,

glucose levels increased from 5.17 mmol/L at baseline to 5.33 mmol/L after treatment with captopril/hydrochlorothiazide 50/25mg once daily, but did not increase with trandolapril/verapamil SR (5.17 *vs* 5.13 mmol/L); the between-group difference was significant ($p = 0.001$).[38] There were no significant differences between the groups with respect to the effect of treatment on low density lipoprotein (LDL) cholesterol, total cholesterol or triglyceride levels. However, high density lipoprotein (HDL) cholesterol levels, were significantly higher after trandolapril/verapamil SR than captopril/hydrochlorothiazide treatment (1.39 *vs* 1.35 mmol/L; $p < 0.03$).

Similar results were obtained during a 24-week double-blind study in 41 patients with mild to moderate hypertension (published as an abstract).[27] Glucose levels increased and HDL cholesterol levels decreased with atenolol/ chlorthalidone 100/25 mg/day, but these parameters did not change with trandolapril/verapamil SR 2/180 mg/day; the between-group difference was significant ($p = 0.004$ and $p < 0.05$). Potassium levels decreased with atenolol/ chlorthalidone, but showed no change with trandolapril/verapamil SR treatment ($p = 0.0007$ for the between-group difference).

Patients with Hypertension and Type 2 Diabetes

Glycosylated haemoglobin (HbA_{1c}) level is an important determinant of mortality risk in patients with diabetes as demonstrated in a large prospective trial in 4662 men.[39] This study demonstrated that a 1% increase in HbA_{1c} was associated with a 28% ($p = 0.002$) increase in all cause mortality after adjustment for age, SBP, serum cholesterol, body mass index, cigarette smoking habit, and a history of myocardial infarction or stroke.[39]

HbA_{1c} levels were maintained over 6[37] or 3[36] months in recipients of trandolapril/verapamil SR in two randomised, double-blind studies in 103[37] and 24[36] patients with hypertension and type 2 diabetes. In contrast, HbA_{1c} levels were not maintained in recipients of enalapril/hydrochlorothiazide[37] or atenolol/chlorthalidone[36] in these studies. In both studies, patients maintained the same oral antihyperglycaemic medication during the study as that used prior to entry into the study.

For example, in the larger study, HbA_{1c} values showed little change during treatment with trandolapril/verapamil SR 2/180 mg/day over a 6-month period (HbA_{1c} 5.91% at baseline vs 5.94% at treatment end).[37] In contrast, HbA_{1c} levels increased from 5.96 to 6.41% in patients treated with enalapril/hydrochlorothiazide 20/12.5 mg/day; the between-group difference was significant ($p = 0.04$). Mean blood glucose levels decreased by 16.8% in trandolapril/verapamil SR recipients and 0.8% in enalapril/hydrochlorothiazide recipients; however, the between-group difference was not significant. Lipid levels did not change in any group during treatment; there were no significant between-group differences.[37]

Similarly, in the 3-month study, there were no significant changes from baseline in plasma HbA_{1c}, fasting plasma glucose or insulin levels, or the insulin sensitivity index in recipients of trandolapril/verapamil SR (mean dosage 1.6/180 mg/day).[36] However, in patients treated with atenolol/chlorthalidone (mean dosage 71/18 mg/day), there was a reduction in the insulin sensitivity index compared with baseline (0.8 *vs* 0.3×10^{-4} min/μU/ml; $p < 0.05$). Changes in insulin sensitivity, plasma glucose levels and area under the glucose curve differed significantly between the atenolol/chlorthalidone and trandolapril/verapamil SR groups ($p < 0.05$ for all comparisons). Lipid indices did not change during trandolapril/verapamil SR treatment. In contrast, serum total triglyceride levels increased ($p < 0.03$) and HDL cholesterol levels decreased ($p < 0.02$) in atenolol/ chlorthalidone recipients.[36]

2.3.3 Effects on Renal Function

Trandolapril/verapamil SR was effective in reducing proteinuria in patients with hypertension and type 2 diabetes with or without overt nephropathy[36,37,40,41] and in patients with hypertension and primary renal disease.[42]

Patients with Type 2 Diabetes and Nephropathy

In randomised studies in patients with hypertension and type 2 diabetes and nephropathy, signifi-

cant reductions in albuminuria occurred in recipients of trandolapril/verapamil SR[36,37,40,41] and enalapril/hydrochlorothiazide,[37] but not in those receiving atenolol/chlorthalidone.[36]

In a 1-year nonblind trial in 37 patients with hypertension, type 2 diabetes and nephropathy (proteinuria >300 mg/day), the fixed combination of trandolapril/verapamil SR (mean dosage 2.9/219 mg/day) was more effective in reducing proteinuria than monotherapy with either verapamil SR (mean dosage 315 mg/day) or trandolapril (mean dosage 5.5 mg/day).[40] The reduction in proteinuria was greater in trandolapril/verapamil SR (62%; $p < 0.05$) than in verapamil SR (27%) or trandolapril (33%) recipients. There were no significant differences between the groups in the changes in glomerular filtration rate, or urinary sodium excretion. SBP/DBP was lowered to a similar extent in all treatment groups.[40]

Similarly, treatment with trandolapril/verapamil SR 2/180 mg/day for 6 months significantly reduced urine albumin levels (54%; $p < 0.001$ *vs* baseline) in patients (n = 30) with hypertension, type 2 diabetes and nephropathy (proteinuria >300 mg/day) who were nonresponders after previous treatment with an ACE inhibitor for at least 6 months.[41] There was no significant change in creatinine clearance in these patients.

Patients with hypertension and type 2 diabetes (n = 24) were randomised to trandolapril/verapamil SR (mean dosage 1.6/180 mg/day) or atenolol/chlorthalidone (71/18 mg/day) in a 12-week double-blind study.[36] Patients had varying levels of albuminuria at baseline (twelve were normoalbuminuric [<30 mg/day], eight had microalbuminuria [30 to 300 mg/day] and four had overt proteinuria [>300 mg/day]). The median reduction in albuminuria was significant during trandolapril/verapamil SR treatment (33%; $p < 0.025$), but not with atenolol/chlorthalidone treatment (11%).[36]

There was no significant difference in the antiproteinuric effect of trandolapril/verapamil SR (2/180 mg/day) and enalapril/hydrochlorothiazide (20/12.5 mg/day) in a 6-month, randomised, double-blind study in 103 patients with hypertension, type 2 diabetes and microalbuminuria (≤300 mg/day) or macroalbuminuria (>300 mg/day).[37] Globally, there was a significant ($p < 0.001$) reduction from baseline in albuminuria after treatment, with no significant difference between trandolapril/verapamil SR (601.5 to 339.8 mg/day) or enalapril/hydrochlorothiazide (409.9 to 161.5 mg/day) recipients. In patients with microalbuminuria at baseline or in patients with overt proteinuria at baseline, there was no significant difference between the treatment groups in the reduction of albuminuria.[37]

Patients with Primary Renal Disease

The effect of trandolapril/verapamil SR on proteinuria was also investigated in 119 patients with hypertension and primary renal disease (proteinuria >1 g/day) in a double-blind study.[42] Patients were initially randomised to trandolapril/verapamil SR 2/180 mg/day, trandolapril 2 mg/day, verapamil SR 240 mg/day or atenolol 50 mg/day. At week 4, all treatment dosages were doubled. At week 8, dosages could be halved if tolerance of the treatment was poor. After 6 months of treatment, a significant reduction from baseline in proteinuria (adjusted for baseline values and SBP and DBP) occurred in recipients of trandolapril (40.2%) and trandolapril/verapamil SR (48.0%). Moreover, the reduction in proteinuria in recipients of trandolapril/verapamil SR was significantly greater ($p = 0.001$) in recipients of combination therapy than verapamil SR monotherapy. Creatinine clearance did not change throughout the study in any treatment group, although serum creatinine increased significantly ($p = 0.013$) in all treatment groups (there was no significant between-group difference). There was no significant difference in the BP reductions between the groups (see section 4.5.2).

3. Pharmacokinetic Profile

Available data on the pharmacokinetic effects of trandolapril and verapamil when coadministered are currently limited (section 3.3). Consequently, this review also provides a brief overview of the pharmacokinetic properties of each individ-

ual agent (section 3.1 and section 3.2) administered as monotherapy. Data reported in section 3.3 are primarily derived from the US prescribing information for the fixed combination of trandolapril and verapamil SR (dosage not clearly stated)[17] and from a clinical study.[43]

3.1 Trandolapril

The pharmacokinetic properties of trandolapril have been published previously in *Drugs* [5,6] and are summarised in this section. Details regarding the pharmacokinetics of trandolapril have also been obtained from the US prescribing information for trandolapril/verapamil SR[16] and that for trandolapril.[17]

Trandolapril was rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentrations (C_{max}) of 1.68 to 1.88 μg/L within 0.5 to 1.5 hours when a single oral dose of 2mg was administered to healthy volunteers.[44,45] C_{max} values for trandolaprilat (the biologically active diacid metabolite) were 2.09 to 2.80 μg/L, and were reached after approximately 3 to 12 hours.[44,45]

The absolute bioavailability of trandolapril is about 10% and that of trandolaprilat is about 70%.[16] Serum protein binding of trandolapril is about 80% and is independent of drug concentration.[6] However, binding of trandolaprilat is concentration-dependent: 94% at 0.04 μg/L decreasing to 80% at 22.5 μg/L.[6]

Trandolapril is converted to trandolaprilat in the liver.[5,6] In addition to trandolaprilat, at least seven other metabolites (principally glucuronide or de-esterification products) have been identified.[16]

After an oral radioactive dose of trandolapril, about 82% of the radioactivity was excreted over 48 hours and excretion was virtually complete (99.2%) after 7 days.[6] Approximately 33% of the radioactivity was recovered in the urine and 66% was recovered in the faeces.[6]

Trandolapril is rapidly eliminated, with a mean elimination half-life of about 1 hour.[6] Elimination of trandolaprilat is triphasic (initial rapid decline, effective elimination phase and terminal elimination phase).[17] The effective elimination half-life of trandolaprilat is about 10 hours.[17] The prolonged terminal elimination phase (see table II) probably represents binding/dissociation kinetics of the trandolaprilat/ACE complex.[6]

The pharmacokinetics of trandolapril were unchanged in patients with renal impairment; however, renal clearance of trandolaprilat decreased with increasing renal insufficiency.[6] The C_{max} and the area under the plasma concentration-time curve from 0 to 24 hours (AUC_{24h}) values of trandolaprilat in patients with severe renal impairment (creatinine clearance ≤1.8 L/h/1.73m^2) were approximately 2-fold higher than those in healthy individuals.[6]

3.2 Verapamil

The pharmacokinetic properties of verapamil have been reviewed previously in *Drugs*[7,8] and are summarised in this section. Additional infor-

Table II. Pharmacokinetic parameters of verapamil and trandolaprilat[a] in patients with hypertension with, or without, fatty liver disease administered oral trandolapril/verapamil sustained-release 1/180mg once daily for 7 days[43]

Pharmacokinetic parameter	Patients with hypertension (n = 10)		Patients with hypertension and fatty liver disease (n = 9)	
	trandolaprilat	verapamil	trandolaprilat	verapamil
t_{max} (h)	5.3	5.6	5	7
C_{max} (μg/L)	3.1	76.5	4.4*	110.5
AUC_{24h} (μg • h/L)	50	941.2	65.1*	1260.6
$t_{½}$ (h)	75	9.2	92.8	9.8

a The active metabolite of trandolapril.

AUC_{24h} = area under the plasma concentration-time curve from 0 to 24 hours; **C_{max}** = maximum plasma concentration; **t_{max}** = time to reach C_{max}; **$t_{½}$** = terminal elimination half-life; * $p < 0.05$ *vs* patients with hypertension without fatty liver disease.

mation from the US prescribing information for verapamil SR is also included.[46]

Following oral administration, about 90% of verapamil, administered as the immediate-release formulation, is absorbed.[8] A similar extent, but a delayed rate, of absorption is observed with the SR formulation.[8] Verapamil undergoes hepatic first-past metabolism and has a low systemic bioavailability of 10 to 20% after oral administration.[7,8] Verapamil is extensively bound to plasma proteins (about 90%).[46]

Twelve metabolites have been identified in the plasma; all except norverapamil, the active desmethyl metabolite, are present in trace amounts.[46] About 3 to 4% of a single dose of verapamil is excreted unchanged in the urine. Approximately 70% of verapamil is excreted as metabolites in the urine and 15% in the faeces within 5 days.[7,8]

The terminal elimination half-life of verapamil SR is 5 to 10 hours.[8] Verapamil pharmacokinetic parameters are unchanged in patients with impaired renal function.[8]

3.3 Trandolapril/Verapamil SR

The pharmacokinetic parameters of verapamil and trandolapril in patients with hypertension (with [n = 9] or without [n = 10] fatty liver disease) administered oral trandolapril/verapamil SR 1/180mg once daily for 7 days are summarised in table II.[43]

Following administration of a single dose of trandolapril/verapamil SR (dose not stated) in healthy volunteers, C_{max} was achieved within 0.5 to 2 hours for trandolapril and within 4 to 15 hours for verapamil.[17] C_{max} values for norverapamil were reached within 5 to 15 hours, and within 2 to 12 hours for trandolaprilat.[17]

The pharmacokinetics of trandolapril and trandolaprilat were the same, irrespective of whether trandolapril was administered as monotherapy or in combination with verapamil.[17] In contrast, the AUC for verapamil and norverapamil increased by 65 and 32% when verapamil SR 240mg was administered concomitantly with trandolapril 4mg; the verapamil and norverapamil C_{max} values increased by 54 and 30%, respectively.[17]

Plasma concentrations of verapamil and trandolaprilat at steady-state (reached after approximately 1 week of once-daily trandolapril/verapamil SR) were up to 2-fold higher than those obtained with a single dose of trandolapril/verapamil SR.[17]

The bioavailability of verapamil, but not trandolapril, was altered by the presence of a high fat meal in volunteers administered trandolapril/verapamil SR 4/240mg. The verapamil C_{max} and AUC decreased by 37 and 28%, respectively. Food decreased the time to C_{max} for both verapamil and norverapamil by approximately 7 hours.[17]

In elderly individuals aged ≥65 years administered a fixed dose of trandolapril/verapamil SR [dosage not stated], the bioavailability values of verapamil, norverapamil and trandolapril were 87, 77 and 35% higher than those in younger individuals.[17]

The presence of fatty liver disease did not alter verapamil pharmacokinetic parameters in patients with hypertension (see table II for details of dosages and study design). However, trandolaprilat C_{max} and AUC_{24h} values for patients with fatty disease were significantly higher (42 and 30%; $p < 0.05$) than in patients with normal liver function.[43]

4. Therapeutic Use

The antihypertensive efficacies of verapamil[7,8] and trandolapril[5,6] administered as monotherapy have been previously reviewed in *Drugs*. This review focuses on the antihypertensive efficacy of verapamil SR and trandolapril administered as combination therapy in dose-ranging studies (section 4.1), and in comparison with placebo (section 4.1 and section 4.2), verapamil SR or trandolapril monotherapy (section 4.1 and section 4.3) or other fixed combination antihypertensive therapies (section 4.4). Although a fixed combination of trandolapril/verapamil SR was used in some studies, it was not always possible to determine whether verapamil SR and trandolapril were

coadministered or administered as a fixed tablet or capsule. The blood pressure lowering effects of trandolapril/verapamil SR have also been studied in special populations of patients with hypertension (section 4.5), including those with type 2 diabetes (section 4.5.1) or primary renal disease (section 4.5.2), black patients (section 4.5.3) and elderly patients (section 4.5.4).

The review focuses on randomised, double-blind trials of up to 6 months' duration. In these trials, combinations of trandolapril/verapamil SR were administered orally at dosages of 1/180 (not commercially available), 2/180, 2/240, 4/240 or 8/240mg (not commercially available) once daily.

Patients included in these trials generally had mild to moderate hypertension (sitting DBP ranging from 90 to 115mm Hg) after a 2- to 4-week, placebo run-in period. In addition, two studies assessed the efficacy of trandolapril/verapamil SR in patients inadequately controlled with verapamil SR[47] or trandolapril[48] monotherapy.

Generally, the primary endpoint was the mean reduction from baseline in trough (24 hour after administration) sitting DBP values, but reductions in trough supine DBP, trough sitting or supine SBP, and standing DBP and SBP were also reported. In some studies, patients were classified as responders (patients whose DBP was reduced to ≤90mm Hg or by ≥10mm Hg[24,25,49-52] or <95mm Hg[53]). Monitoring of 24-hour ambulatory BP also occurred in some studies.[23,24,26,36,37,54]

4.1 Dose-Ranging Studies

In two 6-week, randomised, double-blind, placebo-controlled dose-ranging studies, the optimal antihypertensive combinations of trandolapril/verapamil SR were 1/180 (not commercially available), 2/180, 2/240 and 8/240mg (not commercially available) administered once daily in 746[49,50] and 456[55] patients with mild to moderate hypertension (see table III for results of commercially available fixed-dose combinations and the respective monotherapies; see section 4.2 for other studies comparing trandolapril/verapamil SR with placebo).

In one study,[49,50] patients were randomised to placebo, trandolapril 0.5, 2 or 8 mg/day and verapamil SR 120, 180, or 240 mg/day administered as monotherapy or coadministered. Reductions in supine DBP (primary endpoint) and sitting DBP and SBP were significantly ($p < 0.05$ for all comparisons) greater with all trandolapril/verapamil SR combinations than placebo (see section 4.2 and table III). All combinations had a significantly greater percentage of responders than the placebo group ($p < 0.01$).[49,50] The combination of trandolapril/verapamil SR 2/240 mg/day achieved the highest percentage of responders (63%); this value was significantly greater than those with the corresponding monotherapies. Mean trough-to-peak ratios of supine DBP were >0.5 for all trandolapril/verapamil SR combinations, except trandolapril/verapamil SR 2/120, 8/120 and 0.5/180 mg/day.[49] Mean trough-to-peak ratios for sitting DBP for all trandolapril/verapamil SR combinations were ≥0.5[50]; that of trandolapril/verapamil SR 2/180 mg/day was 0.74.

Similarly, in another dose-ranging study,[55] all combinations of trandolapril (0.5, 1.0 or 2.0 mg/day) and verapamil SR (120 or 180 mg/day) reduced sitting DBP and SBP to a significantly greater extent than placebo ($p < 0.005$).

In these two studies,[49,50,55] trandolapril/verapamil SR 0.5/180 (not commercially available), 1/180, 2/180, 2/240 and 8/240 (not commercially available) mg/day generally had a significantly greater antihypertensive effect than that of the corresponding monotherapies administered at the same dosage (also see section 4.3 for other studies comparing trandolapril/verapamil SR with the corresponding monotherapies).

In one study,[49,50] reductions in mean sitting trough DBP were significantly greater in recipients of trandolapril/verapamil SR 2/180 and 2/240 mg/day (see table III) than the respective monotherapies administered at the same dosages (2/240 mg/day; $p < 0.05$ and 2/180 mg/day; $p < 0.01$). In the other dose-ranging study,[55] the mean reduction in sitting DBP was significantly greater ($p < 0.05$) in recipients of trandolapril/verapamil SR

Table III. Efficacy of trandolapril/verapamil SR (TRA/VER) compared with that of trandolapril (TRA), verapamil SR (VER) or placebo (PL) in patients with mild to moderate[26,48-53,55] or mild to severe[47] hypertension in randomised, double-blind studies. All agents were administered orally once daily.

Reference	Treatment duration (wk)	Placebo run-in period (wk)	Treatment regimen (mg/day)	No. of evaluable pts	Mean baseline[a] sitting SBP/DBP (mm Hg)	Mean reduction in sitting SBP/DBP (mm Hg) from baseline[a]	Responders (%)[b]
Dose-ranging multifactorial studies[c]							
Scholze et al.[55]	6	4	TRA/VER 2/180	50	NR/100-115[d]	18.8**§§/15.2**§§‡‡e	NR
			VER 180	29	NR/100-115[d]	9.3**/8.9**e	NR
			TRA 2	30	NR/100-115[d]	16.4**/13.9**e	NR
			PL	30	NR/110-115[d]	8.1**/8.7**e	NR
DeQuattro et al.[49,50]	6	4	TRA/VER 2/180	66	152.1/NR	10.2§§/NR	55§§‡f
			TRA/VER 2/240	43	152.0/NR	12.0§§†/NR	63§§†
			VER 180	57	153.4/NR	6.7/NR	37§§f
			VER 240	48	150.3/NR	5.5§/NR	30§§f
			TRA 2	67	149.7/NR	5.1§/NR	40§§f
			PL	53	153.7/NR	3.5/NR	4
Trandolapril/verapamil SR 1/180 mg/day							
Veratran Study Group[26]	8	4	TRA/VER 1/180	77	160.3/104.1	18.9*§/13.4*§	NR
			VER 180	56	156.0/104.2	10.5*/10.0*	NR
			TRA 1	50	159.3/103.6	21.2*§/13.0*§	NR
			PL	51	158.2/103.5	9.7*/6.1*	NR
Trandolapril/verapamil SR 2/180 mg/day							
Karlberg et al.[53]g	8	4	TRA/VER 2/180	192	166.1/102.0[h]	19.6†††/15.1†††	93
			VER 240	96	166.1/102.0[h]	13.3/12.4	89
			TRA 2	96	166.1/102.0[h]	14.2/10.5	79
Viskoper et al.[51]	8	4	TRA/VER 2/180	103	164.7/103.3	17.6††/13.2†e	69.9
			VER 180	102	162.2/103.1	10.3/9.6e	49.0
			TRA 2	105	161.6/103.3	12.5/10.9e	59.0
Trandolapril/verapamil SR 4/240 mg/day							
Messerli et al.[52]	6	4	TRA/VER 4/240	163	152.3/101.4	12.9§§††/8.1§§††i	64§§†††f
			VER 240	155	151.1/100.8	8.0§§/4.3§§i	38§§f
			TRA 4	155	151.8//101.3	9.0§§/4.5§§i	41§§f
			PL	152	153.6/100.5	NA	18f
Nonresponders to monotherapy							
Beevers et al.[48]	12	2	TRA/VER 2/180	381[l]	NR/101.5[m]	8.0**/6.2**e	NR
[TRA non-responders[j]][k]			TRA 2		NR/101.3[m]	0.6**/2.3**e	NR
Sever et al.[47]	12	2	TRA/VER 2/240	230	156.7/102.3[o]	9.8**/6.4**e	NR
[VER non-responders[n]][k]			VER 240	233	158.2/101.8[o]	4.5**/3.8**e	NR

a End of the placebo run-in period.
b Pts whose DBP was reduced to ≤90mm Hg or by ≥10mm Hg[49-52] or <95mm Hg.[53]
c Only the values for the commercially available fixed-combination dosages and the respective monotherapies are shown.
d Inclusion criteria.
e Adjusted mean value.
f Estimated from a graph.
g Crossover study.
h Mean value for all patients.
i Difference from PL for both DBP and SBP.
j DBP ≥95mm Hg and difference from wk 6 to wk 8 was ≤5 mm Hg after 8 wks of treatment with TRA 2 mg/day.
k Published as an abstract.
l Total randomised to both TRA/VER and TRA.
m Assessed at the end of 8 wks of single-blind treatment with TRA 2 mg/day.
n DBP > 95mm Hg after 8 wks of treatment with VER 240 mg/day.
o Assessed at the end of 12 wks of single-blind treatment with VER 240 mg/day.

DBP = diastolic blood pressure; **NA** = not applicable; **NR** = not reported; **pts** = patients; **SBP** = systolic blood pressure; **SR** = sustained-release.
* $p < 0.01$, ** $p < 0.001$ *vs* baseline; † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ *vs* monotherapy with VER or TRA; ‡ $p < 0.05$, ‡‡ $p < 0.001$ *vs* VER; § $p < 0.05$, §§ $p < 0.01$ *vs* PL.

2/180 mg/day than that in recipients of verapamil SR 180 mg/day (p = 0.0003), but not in recipients of trandolapril 2 mg/day (see table III). Reductions in mean trough sitting DBP were significantly greater with combinations of verapamil SR 180 mg/day and trandolapril 0.5 and 1 mg/day than with either of the monotherapies administered at the same dosage.[55]

4.2 Comparisons with Placebo

Data from randomised, double-blind trials in patients with mild to moderate hypertension indicated that the combination of once-daily verapamil SR (120 to 240mg) and once-daily trandolapril (0.5 to 8mg) was more effective in lowering sitting SBP and DBP than placebo (see table III, table IV and section 4.1).[24,26,49,50,52,55]

In one study,[26] clinic sitting SBP and DBP, but not mean 24-hour SBP/DBP, were significantly reduced from baseline after treatment with placebo for 8 weeks. The reductions in both clinic sitting and 24-hour SBP and DBP after treatment with combination therapy were significantly greater than those with placebo.

The number of responders to treatment with trandolapril/verapamil SR 2/180, 2/240 and 4/240 mg/day (55 to 72%) was significantly higher than that with placebo (4 to 32%), according to data from three comparative trials (table III and table IV).[24,49,50,52]

4.3 Comparisons with Verapamil SR or Trandolapril Monotherapy

In most studies, trandolapril/verapamil SR 1/180 (not commercially available), 2/180, 2/240, 4/240 and 8/240 (not commercially available) mg/day was significantly more effective than either of the corresponding monotherapies administered at the same dosage in lowering sitting BP in patients with mild to moderate hypertension (table III and section 4.1).

Trandolapril/verapamil SR 2/180 mg/day reduced sitting DBP and SBP to a significantly greater extent than verapamil SR 180 mg/day or trandolapril 2 mg/day in two 8-week trials[51,53] (table III) and a dose-ranging study[49,50] (see section 4.1). The response rate was higher in recipients of combination therapy than in recipients of monotherapy administered at the same dosage in both the 8-week trials; however, significance values were not reported (table III).[51,53]

Similarly, trandolapril/verapamil SR 2/240,[49,50] 4/240[52] (see table III) and 8/240 mg/day[49,50] (see section 4.1) was significantly more effective in reducing mean sitting SBP and DBP than either of the monotherapies administered at the same dosage. In addition, the percentage of patients responding to trandolapril/verapamil SR 4/240 mg/day was significantly higher than that with either of the monocomponents in one trial ($p < 0.01$).[52] In this same trial,[52] trough-to-peak sitting DBP ratios were >0.5 in both the recipients of trandolapril 4 mg/day (0.75) and trandolapril/verapamil SR 4/240 mg/day (0.67) at the end of treatment. The trough-to-peak sitting DBP ratio for verapamil SR 240 mg/day was 0.47.

Reductions in 24-hour ambulatory SBP and DBP were generally greater with combination trandolapril/verapamil SR therapy than with either of the corresponding monotherapies administered at the same dosages, according to results from two trials.[23,26]

An analysis of 24-hour ambulatory BP monitoring of a subset of 90 patients[23] from a randomised double-blind trial[51] (see table III for study design details) indicated that the reductions in DBP and SBP were significantly greater with trandolapril/verapamil SR 2/180 mg/day (18.1/11.1mm Hg) than after monotherapy with verapamil SR 180 mg/day (6.9/6.7mm Hg) or trandolapril 2 mg/day (10.7/6.4mm Hg). The antihypertensive agents were administered between 08.00 and 10.00 hours. Reductions with combination therapy during the day- and night-time periods were also significantly greater than those with the corresponding monotherapies. Combination therapy had the most pronounced effect on blunting the early morning rise in BP; however, the between-group difference was not statistically significant.[23]

Table IV. Efficacy of trandolapril/verapamil SR (TRA/VER) compared with that of other drug combinations in patients with mild to moderate hypertension with or without type 2 diabetes mellitus in randomised, double-blind studies. All agents were administered orally once daily.

Study	Duration (wk)	Placebo run-in period (wk)	Treatment regimen (mg/day)	No. of evaluable patients	Baseline[a] mean sitting SBP/DBP (mm Hg)	Mean reduction in sitting SBP/DBP (mm Hg) from baseline[a]	Responders[b] (%)
Patients without type 2 diabetes							
Breithaupt-Grögler et al.[25]	24	2	TRA/VER 1/180	26	155.9/101.0	22.3*/14.4*†	81
			MET/HCTZ 100/12.5	25	149.9/100.8	15.9*/9.2*	64
de Leeuw et al.[24]	8	4	TRA/VER 2/180	50	170/106	27‡‡/13‡‡	72‡
			ATE/CHL 100/25	50	171/107	28‡‡/13‡‡	76‡
			LIS/HCTZ 20/12.5	52	169/107	23‡‡/12‡‡	69‡
			PL	53	169/107	3/3	32
Ramos et al.[27]c	24	2	TRA/VER 2/180	19	149/102	15/15	NR
			ATE/CHL 100/25	22	156/103	33†/22†	NR
Patients with type 2 diabetes							
Fernández et al.[37]	24	4	TRA/VER 2/180	48	158/97	16.0***/11.2***	NR
			ENL/HCTZ 20/12.5	45	157/99	17.7***/13.2***	NR
Schneider et al.[36]	12	4	TRA/VER 1.6/180[d]	12	171/108	20**/9	NR
			ATE/CHL 71/18[d]	12	159/106	18*/12*	NR

a End of the placebo run-in period.

b Patients with sitting DBP <90mm Hg or reduction of ≥10mm Hg.

c Published as an abstract.

d Mean dosage.

ATE/CHL = atenolol/chlorthalidone; **DBP** = diastolic blood pressure; **ENL/HCTZ** = enalapril/hydrochlorothiazide; **LIS/HCTZ** = lisinopril/hydrochlorothiazide; **MET/HCTZ** = metoprolol/hydrochlorothiazide; **NR** = not reported; **PL** = placebo; **SBP** = systolic blood pressure; **SR** = sustained-release; **wk** = week(s). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* baseline; ‡ $p < 0.001$, ‡‡ $p = 0.0001$ *vs* PL; † $p < 0.05$ *vs* other antihypertensive combinations.

Similarly, in another 8-week trial [26] (see table III for details of trial design), the mean reduction in 24-hour ambulatory SBP was significantly greater with trandolapril/verapamil SR 1/180 mg/day therapy than with verapamil 180 mg/day ($p < 0.05$), and the mean reduction in 24-hour ambulatory DBP was significantly greater with combined therapy than treatment with either monotherapy ($p < 0.05$).

Data from two randomised, double-blind trials (both published as abstracts) in patients with hypertension uncontrolled by verapamil SR[47] or trandolapril monotherapy[48] (see table III for details of trial design and dosages) indicated that treatment with trandolapril/verapamil SR was significantly ($p < 0.001$) more effective than continued therapy with the respective monocomponent (verapamil SR[47] or trandolapril[48]).

4.4 Comparisons with Other Combinations of Antihypertensives

In randomised, double-blind trials in patients with mild to moderate hypertension (without or with type 2 diabetes [also see section 4.5.1]), reductions in BP were generally similar in recipients of trandolapril/verapamil SR to those in recipients of various other antihypertensive combinations (metoprolol/hydrochlorothiazide, atenolol/chlorthalidone, lisinopril/hydrochlorothiazide, enalapril/ hydrochlorothiazide; see table IV).

The reductions in sitting DBP and SBP were not significantly different in recipients of trando-

lapril/verapamil SR 2/180 mg/day, atenolol/chlorthalidone 100/25 mg/day and lisinopril/hydrochlorothiazide 20/12.5 mg/day in an 8-week trial; all combination therapies were significantly more effective than placebo (table IV).[24] The percentages of trandolapril/verapamil SR recipients with normalisation of blood pressure (DBP <90mm Hg) or showing a response to treatment (table IV) were broadly similar with all combined antihypertensive treatments; these response rates were significantly greater with all combination therapies than with placebo treatment.[24] However, in another trial of longer duration (24 weeks) treatment with atenolol/chlorthalidone 100/25 mg/day resulted in significantly greater reductions for both sitting DBP and SBP than those achieved with trandolapril/verapamil SR 2/180 mg/day (table IV) [published as an abstract].[27]

In a 24-week trial,[25] the reduction in sitting DBP, but not SBP, was significantly greater in recipients of trandolapril/verapamil SR 1/180 mg/day than in recipients of metoprolol/hydrochlorothiazide 100/12.5 mg/day (table IV).

4.5 Special Patient Populations

4.5.1 Patients with Type 2 Diabetes

In randomised, double-blind trials, trandolapril/verapamil SR was effective in controlling BP in patients with mild to moderate[36,37] hypertension and type 2 diabetes (see table IV and section 4.4 for details of study design, drug dosage and baseline BP). This fixed combination was also effective in reducing proteinuria (see section 2.3.3) and did not have an adverse effect on metabolic parameters in these patients (see section 2.3.2).

Moreover, in these trials, trandolapril/verapamil SR was as effective in controlling BP as other antihypertensive combinations (enalapril/hydrochlorothiazide, atenolol/chlorthalidone) in patients with type 2 diabetes and hypertension (see table IV and section 4.4).[36,37] In a 6-month, multicentre trial,[37] reductions in sitting SBP and DBP were broadly similar for recipients of trandolapril/verapamil SR 2/180 mg/day and recipients of enalapril/hydrochlorothiazide 20/12.5 mg/day (see table IV). Likewise, there were no significant between-group differences in the reduction in 24-hour ambulatory SBP and DBP.[37] Reductions in mean sitting (see table IV), supine and ambulatory daytime BP were also similar in recipients of trandolapril/verapamil SR (mean dosage 1.6/180 mg/day) and atenolol/chlorthalidone (mean dosage 71/18 mg/day) in a 12-week trial, with no significant between-group differences.[36]

Similarly, trandolapril/verapamil SR 2/180 mg/day reduced BP in a randomised, double-blind trial in previously untreated patients with type 2 diabetes with high-normal and borderline isolated systolic hypertension (SBP >130 and <159mm Hg, and DBP >80 and <89mm Hg) [data presented as an abstract].[56] After 16 weeks of treatment, the reduction in mean SBP from baseline was similar in 165 recipients of trandolapril 2 mg/day (10.1mm Hg) and 172 recipients of trandolapril/verapamil SR (10.9mm Hg), but greater than that in 84 placebo recipients (3.9mm Hg; $p < 0.001$). However, the reduction in mean SBP from baseline after 16 weeks of treatment was greater in recipients of trandolapril/verapamil SR (7mm Hg) than in recipients of trandolapril alone (5.3mm Hg; $p < 0.05$) or placebo (3mm Hg; $p < 0.001$). At 16 weeks, 36.5, 37.8 and 14.9% of recipients of trandolapril monotherapy, trandolapril/verapamil SR or placebo, respectively, had a SBP <130mm Hg and DBP <85mm Hg.[56]

In a large (n = 727 evaluable patients), randomised, nonblind, multicentre trial in patients with type 2 diabetes and hypertension inadequately controlled with antihypertensive monotherapy (drugs and dosages not stated),[57] 8 weeks of treatment with trandolapril/verapamil SR 2/180 mg/day was significantly more effective in reducing sitting DBP (5.6mm Hg; $p < 0.0005$) than antihypertensive monotherapy (2.9mm Hg; drugs and dosages not specified). However, the reduction in sitting SBP was not significantly different between the two treatment groups (11.1 *vs* 10.0mm Hg). In addition, a significantly greater number of patients treated with combination therapy (82%; p

= 0.012) than monotherapy (74%) reached normalisation of DBP (<90mm Hg).

4.5.2 Patients with Primary Renal Disease

Trandolapril/verapamil SR was effective in reducing BP in a randomised, double-blind, multicentre trial in patients with hypertension (BP ≥130/85mm Hg) who had primary renal disease (proteinuria ≥1 g/day and creatinine clearance ≥50 ml/min/1.73m^2).[42] This trial was conducted by the PROCOPA study group. Patients were randomised to receive trandolapril/verapamil SR 2/180 mg/day, atenolol 50 mg/day, trandolapril 2 mg/day or verapamil SR 240 mg/day. All drug dosages were doubled after 4 weeks of active treatment. In patients with a poor tolerance, the dosages were reduced by half after 8 weeks of treatment. In addition, furosemide (40 mg/day) was added in the case of poor response (DBP ≥85mm Hg).

After 6 months of treatment, mean reductions from baseline in SBP/DBP were similar in all treatment groups; 13.6/11.9mm Hg for trandolapril/verapamil SR (n = 29), 11.5/9.6mm Hg for atenolol (n = 31), 13.6/10.2mm Hg for trandolapril (n = 30) and 8.3/7.0mm Hg for verapamil (n = 29).[42] The effects of these agents on proteinuria and creatinine clearance in these patients are reviewed in section 2.3.3.

4.5.3 Black Patients

Hypertension is common in African-Caribbean and African-American Blacks.[58,59] Moreover, in the US, the prevalence of essential hypertension is greater in Black patients than in White patients.[60]

A noncomparative[54] and a comparative, nonblind, multicentre, nonrandomised[61] trial demonstrated that trandolapril/verapamil SR was effective in Black patients with mild to moderate (mean 12-hour daytime DBP ≥90 and ≤114mm Hg)[54] or severe (supine DBP 115 to 135mm Hg)[61] hypertension.

In one trial,[54] Black patients (n = 21) received trandolapril/verapamil SR (2/180 to 4/360 mg/day or 4/360 mg/day plus hydrochlorothiazide 12.5 mg/day) titrated according to response. Significant reductions in mean 24-hour ambulatory BP (from 150/96 to 131/82mm Hg; p < 0.001) occurred after 16 weeks. Significant reductions in 12-hour daytime or night-time SBP and DBP also occurred (p < 0.001). Two patients required additional hydrochlorothiazide.[54]

Similarly, 58 White patients and 32 Black patients received trandolapril (2 to 8 mg/day) or trandolapril/verapamil SR (4/180 or 8/180 mg/day), titrated according to response in the comparative trial.[61] Hydrochlorothiazide 12.5 to 25 mg/day was added as required to achieve the goal BP (supine DBP ≤90mm Hg). Reductions from baseline in mean supine SBP/DBP were significant in both Black (14.5/13.1mm Hg) and White (14.6/14.3mm Hg) recipients of trandolapril/verapamil SR (p = 0.001). The addition of hydrochlorothiazide to combination therapy also resulted in significant reductions from baseline in mean supine BP in both Black and White patients (p = 0.001). In Black patients, the reductions in mean supine SBP/DBP were significantly greater in recipients of combination therapy than those in recipients of trandolapril monotherapy (1.2/6.2mm Hg; p = 0.001).

4.5.4 Elderly Patients

A noncomparative, multicentre trial demonstrated that trandolapril/verapamil SR reduced BP in 254 elderly (aged 63 to 92 years) patients with mild to moderate hypertension.[62] Trandolapril/verapamil SR (0.5/120 to 2/180 mg/day) was administered for 6 months, starting with a response-dependent titration period of 12 weeks. At the end of treatment, the mean reduction in sitting SBP/DBP was 21.9/17.1mm Hg, with most of the BP reduction occurring in the first 3 months of treatment (mean reduction 21.4/15.8mm Hg). Moreover, 82% of patients showed normalisation of DBP (<90mm Hg) and 85% of patients were responders (normalisation and/or reduction in DBP by ≥ 10mm Hg).

5. Tolerability

5.1 Therapeutic Oral Dosages

The tolerability profile of trandolapril/verapamil SR reported during clinical trials in patients

with hypertension was similar to that of verapamil SR or trandolapril administered as monotherapy (see section 4 for design details).[17,26,49-53,55,63] Trandolapril/verapamil SR was generally well tolerated.

Combined analysis of four double-blind, randomised trials (data presented in a review[63]) indicated that the percentages of patients with hypertension with documented adverse events during treatment with trandolapril/verapamil SR 2/180 mg/day (n = 208), verapamil SR 120 to 240 mg/day (n = 263), trandolapril 0.5 to 8 mg/day (n = 411) or placebo (n = 199) were 27.9, 34.2, 27.3 and 25.6%, respectively. Corresponding percentages of patients who withdrew due to adverse events were 3.4, 4.9, 1.9 and 3.0%, respectively. The tolerability profile of combined therapy with trandolapril/verapamil SR 2/180 mg/day was similar to that of monotherapy with trandolapril and verapamil (see figure 1).[63] Headache, constipation, cough and asthenia were the most commonly reported adverse events, and were reported in 4.8, 2.9, 1.9 and 1.4% of patients treated with combined therapy in this pooled analysis.[63]

Adverse events occurring in ≥1% of 541 recipients of combinations of trandolapril (0.5 to 8 mg/day) and verapamil SR (120 to 240 mg/day) who participated in placebo-controlled trials conducted in the US are presented in figure 2.[17]

The incidence of prolongation of the PQ interval was similar in recipients of trandolapril/verapamil SR, the monotherapy components of this combination or placebo.[63] The PQ interval increased from <200ms at the start of therapy to >200ms after therapy in 3 of 253 (1.2%) verapamil SR recipients, 7 of 397 (1.8%) trandolapril recipients, 4 of 205 (2.0%) trandolapril/verapamil SR 2/180 mg/day recipients, 1.2% of recipients of all the dosage combinations of trandolapril/verapamil SR (0.5/120, 1/180 or 2/180 mg/day) and 2 of 185 (1.1%) placebo recipients.[63]

No changes in laboratory parameters were reported, apart from an increase in serum potassium levels of 0.1 and 0.08 mmol/L during treatment with trandolapril/verapamil SR 1/180 and 2/180 mg/day.[63] Liver abnormalities have been reported in 3.2% of patients receiving trandolapril/verapamil SR (see section 6).[17]

In addition, there were no significant differences in the incidence of adverse events after treatment with trandolapril/verapamil SR 2/180 mg/day (34%), atenolol/chlorthalidone 100/25 mg/day (32%), lisinopril/hydrochlorothiazide 20/12.5 mg/day (29%), or placebo (21%) during a well designed, 8-week trial in 205 patients with hypertension (see section 4.4 for details of trial design).[24]

5.2 Overdose

No specific data are available regarding the effects of overdose with trandolapril/verapamil SR.[17]

However, reports of overdose with conventional and SR verapamil have been thoroughly reviewed.[7,64-67]

Clinical features of verapamil intoxication are pronounced hypotension, and cardiac rhythm disturbances, ranging from sinus bradycardia to complete heart block and asystole.[7] Other symptoms such as hyperglycaemia, hypokalaemia, renal failure, and convulsions may be present.[7,17]

Treatment of verapamil intoxication is aimed at preventing the further absorption of verapamil from the gastrointestinal tract, increasing atrioventricular nodal conduction, increasing vascular tone and maintaining tissue oxygenation and metabolic support.[7,17] β-Adrenergic stimulation or parenteral administration of calcium solutions have been effectively used in the treatment of deliberate overdosing with verapamil.[17] Other measures, including atropine, isoprenaline (isoprotenerol), epinephrine and norepinephrine, dopamine, dobutamine, glucagon and a pacemaker have been used with varying success.[17,65]

The most likely clinical manifestations of trandolapril intoxication are symptoms attributable to severe hypotension.[17] Suggested treatment of trandolapril overdose is the administration of an infusion of normal saline solution.[17]

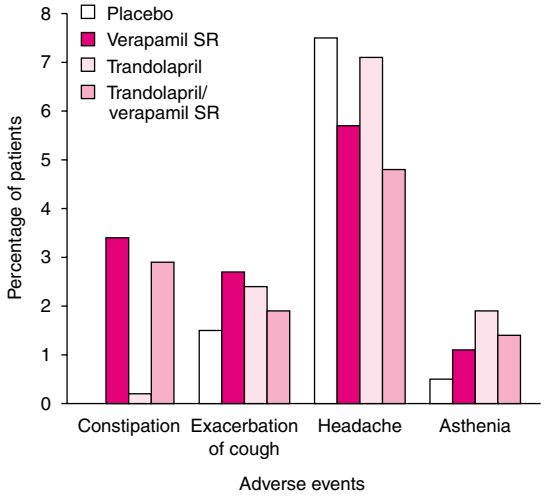

Fig. 1. Adverse event profile of trandolapril/verapamil sustained-release (SR) 2/180 mg/day (n = 208), trandolapril 0.5 to 8 mg/day (n = 411), verapamil SR 120 to 240 mg/day (n = 263) and placebo (n = 199) in a pooled analysis of randomised, double-blind trials in patients with hypertension.[63]

6. Dosage and Administration

6.1 Dosage Recommendations

In the US, the fixed combination of trandolapril/verapamil SR is approved for the treatment of hypertension, but not for initial therapy.[17] The recommended usual dosage of verapamil SR is 120 to 480 mg/day administered as a single dose or as two divided doses.[17] The recommended usual dosage of trandolapril is 1 to 4 mg/day administered as a single dose or as two divided doses.[17] Clinical trials of trandolapril/verapamil SR have only investigated once-daily administration. In the US, the fixed combination of trandolapril/verapamil SR is available as 2/180, 1/240, 2/240 and 4/240 tablets. Trandolapril/verapamil SR should be taken with food.[17]

In European countries, the fixed combination of trandolapril/verapamil SR is available as 2/180mg capsules. The usual dosage is one capsule, taken once-daily in the morning, with or after breakfast.[68]

The safety and efficacy of trandolapril/verapamil SR has not been established in patients aged under 18 years. Trandolapril/verapamil SR therapy is contraindicated in patients with:

- hypersensitivity to any ACE inhibitor or verapamil
- severe left ventricular dysfunction (ejection fraction <30%, pulmonary wedge pressure >20mm Hg or severe symptoms of cardiac failure)
- hypotension (SBP <90mm Hg) or cardiogenic shock
- sick sinus syndrome (except in patients with an artificial ventricular pacemaker)
- or second or third degree atrioventricular block (except in patients with an artificial ventricular pacemaker)
- atrial flutter or atrial fibrillation with an accessory bypass tract.[17]

In addition, patients with a history of ACE inhibitor-related angioedema should not receive trandolapril/verapamil SR therapy.[17]

Liver abnormalities have been reported in 3.2% of patients receiving trandolapril/verapamil SR; periodic monitoring of liver function in trandolapril/verapamil SR recipients is therefore advisable.[17] Trandolapril/verapamil SR should be administered with caution to patients with renal or hepatic impairment.

ACE inhibitors can cause injury and death to the developing fetus if used in pregnancy during the second and third trimesters. Therefore, trandolapril/verapamil SR should be discontinued as soon as pregnancy is detected.[17]

6.2 Drug Interactions

The information in this section was largely obtained from the US prescribing information for trandolapril/verapamil SR[17] and verapamil SR.[46]

Verapamil may increase levels of digoxin (maintenance digoxin doses should be reduced) and lithium; patients should be carefully monitored during coadministration.[17] Coadministration with verapamil may also increase exposure to ethanol, carbamazepine, cyclosporin or theophylline.[17]

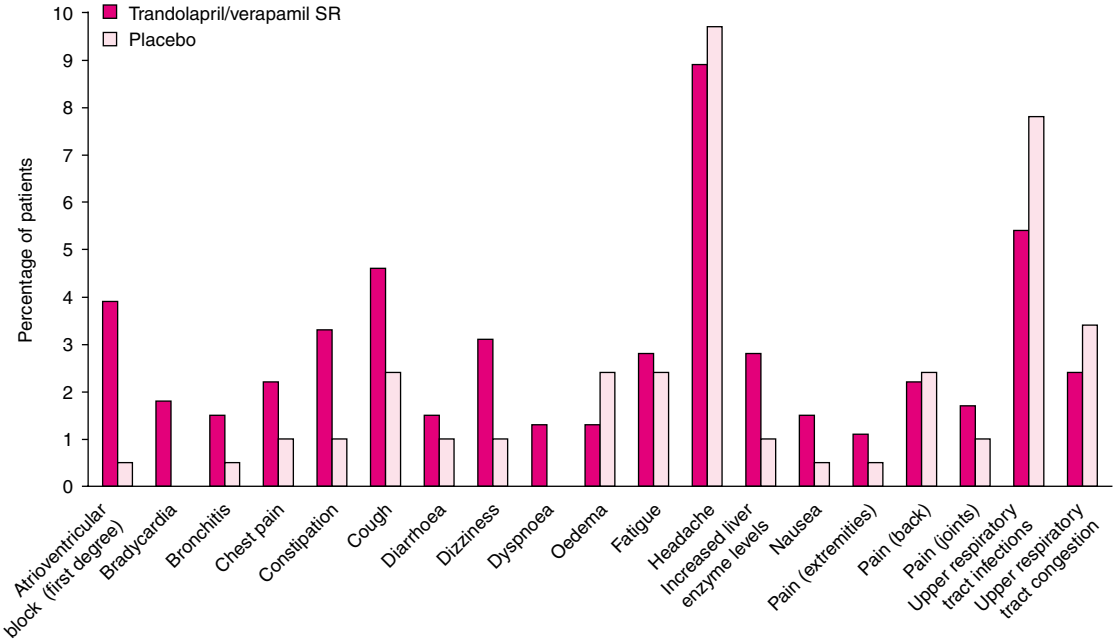

Fig. 2. Adverse events occurring in ≥1% of 541 recipients of combinations of trandolapril 0.5 to 8 mg/day and verapamil sustained-release (SR) 120 to 240 mg/day and 206 recipients of placebo who participated in trials conducted in the US.[17]

Verapamil may also increase levels of simvastatin, [69,70] but does not appear to significantly increase pravastatin levels.[69]

Phenobarbital may increase verapamil clearance.[46] The clearance of single doses of verapamil was reduced after coadministration with cimetidine in healthy volunteers.[46]

Inhibitors of cytochrome P3A4 (such as erythromycin, ritonavir) may reduced plasma levels of verapamil.[46] Elevations in plasma levels of verapamil have been reported with inducers of cytochrome P3A4 (such as rifampicin).[17,46] Intake of grapefruit juice has also been associated with increased levels of verapamil.[46]

An increase in bleeding time may occur when verapamil is coadministered with aspirin.[46]

Additive adverse effects on heart rate, atrioventicular conduction and/or cardiac contractibly may result from coadministration of verapamil and beta blockers; caution and close monitoring are recommended.[17]

Data on interactions between verapamil and antiarrhythmic agents are limited; adverse cardiovascular interactions are possible. Coadministration of flecainide and verapamil may have an additive effect on myocardial contractibility, AV conduction and repolarisation.[46] Disopyramide and quinidine should not be coadministered with verapamil.[17] Careful dose titration is recommended during coadministration of verapamil and inhalation anaesthetics to avoid excessive cardiovascular depression.[17]

Verapamil may potentiate the effects of neuromuscular blocking agents; dosage reduction may be necessary for one or both agents.[17]

An additive effect on the lowering of BP usually occurs when verapamil is administered concomitantly with oral antihypertensive agents such as vasodilators, ACE inhibitors, diuretics and β-blockers.[46]

Initiation of trandolapril in patients receiving diuretic therapy may result in hypotension; the possibility of such effects can be minimised by dis-

continuing the diuretic or cautiously increasing salt intake prior to starting trandolapril/verapamil SR treatment.[17] Alternatively, the initial trandolapril/verapamil SR dosage can be reduced.[17]

Trandolapril may increase potassium levels; careful monitoring of serum potassium levels is recommended for patients receiving trandolapril in addition to potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes in order to avoid hyperkalemia.[17]

7. Place of Trandolapril/Verapamil SR in the Management of Essential Hypertension

Hypertension plays a central role in the pathogenesis of coronary artery disease, congestive heart failure, stroke and renal failure.[1-3,71] These conditions impose an enormous financial burden on healthcare systems and have major social implications.[1,2] Consequently, the effective prevention and treatment of hypertension is a major public health challenge in most countries. In the US, for example, it is estimated that 50 million adults have hypertension.[1] Moreover, nearly three of four adults in the US are not controlling their BP to below 140/90mm Hg.[1]

The goal of antihypertensive treatment is to reduce morbidity and mortality by the least intrusive means possible.[1,72] Current guidelines differ slightly in their recommended BP goals, but they all take into consideration the patient's risk category.[1-3]

For patients with uncomplicated hypertension, the sixth report of the Joint National Committee on prevention, detection and treatment of high blood pressure (JNC-VI)[1] recommends reducing BP below 140/90mm Hg if tolerated, the World Health Organisation-International Society of Hypertension (WHO-ISH)[2] recommends BP levels below 130/85mm Hg, and the British Hypertension Society (BHS) recommends BP below 140/85mm Hg.[3]

More aggressive reductions in BP may be recommended in hypertensive patients with additional risk factors, including cardiovascular disease, evidence of target organ disease or comorbid conditions (such as diabetes mellitus or renal failure).[1-3,73,74] Guidelines have emphasised the importance of aggressive BP reduction in patients with diabetes mellitus. The WHO-ISH[2] and JNC-VI[1] guidelines suggest a BP goal of <130/85mm Hg to be optimal for hypertensive patients with diabetes mellitus. However, recent recommendations by the American Diabetes Association (ADA)[73] and the joint recommendations of the British Cardiac Society, British Hyperlipidaemia Association, BHS and the British Diabetic Association[75] suggest an even more aggressive target of <130/80mm Hg is optimal in these patients.

Lifestyle modifications such as weight reduction, reduced salt intake, limited alcohol consumption, regular physical exercise and a healthy diet are an integral part of the management of patients with less than optimal BP.[3,72] Although sustained changes in lifestyle may be difficult to achieve, they can obviate or reduce the need for pharmacological intervention.[1] Nevertheless, pharmacological intervention is required for a large proportion of patients in order to optimise BP control.[1]

There is a vast array of pharmacological interventions available for the optimisation of BP, including diuretics, ACE inhibitors, α- and β-blockers, angiotensin II receptor antagonists, and calcium channel antagonists.[76] The JNC-VI guidelines for the initial treatment of mild uncomplicated hypertension emphasise, as the principle strategy, single-drug therapy with step-wise dose increases or the substitution of an alternative drug if the response is minimal.[1] The JNC-VI and BHS guidelines recommend diuretics and β-blockers as initial therapy for hypertension, unless there are strong indications for another drug class (or β-blockers or diuretics are contraindicated).[1] This recommendation is based on evidence from numerous clinical trials that have shown a reduction in mortality and morbidity in patients treated with these agents. In contrast, the WHO-ISH guidelines state that all drug classes (diuretics, α- and β-blockers, calcium channel antagonists, ACE inhibitors, angiotensin

II antagonists) are suitable for the initiation and maintenance of treatment.

However, as acknowledged in the JNC-VI, the WHO-ISH and the BHS guidelines,[1-3] most patients with hypertension will require a combination of antihypertensives to achieve optimal control. Consequently, the JNC-VI, WHO-ISH and BHS guidelines recommend the addition of a second agent in patients who have tolerated the first agent but are not able to reach the target BP.[1-3]

On average, the number of antihypertensive agents required to achieve optimal control of BP varies between two to four, with comorbid conditions such as diabetes mellitus or renal failure necessitating greater drug requirements. Although underpowered, the Hypertension Optimal Treatment (HOT) study indicated that 3.3 antihypertensives were needed on average to attain BP goals.[77] In the United Kingdom Prospective Diabetes Study (UKPDS), tight BP control (<150/85mm Hg) in patients with type 2 diabetes required a greater increase in the number of antihypertensives administered than did less tight BP control (<1/18005mm Hg).[78] Similarly, in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, 2.8 antihypertensives were need to achieve a BP goal of <75mm Hg DBP.[79]

JNC-VI and WHO-ISH guidelines emphasise the use of long-acting antihypertensives that are able to provide 24-hour efficacy on a once-daily basis.[1] The JNC-VI also recommends that at least 50% of the peak effect should remain at the end of 24 hours.[1] Such agents improve adherence to therapy, minimise BP variation and result in smoother more consistent BP control.[2] As a consequence, they may provide greater protection against the risk of major cardiovascular events and the development of target organ damage.[1,2]

Drugs from different classes generally affect different pathophysiological mechanisms, resulting in an additive effect on BP when used in combination. Thus, lower dosages of the individual components of the combination therapy can be administered for the same antihypertensive efficacy as that achieved with high dosages of monotherapy.[3,80] Given the fact that many of the adverse effects associated with antihypertensive therapy are dose related, an improved tolerability profile with low-dose combination therapy over high-dose monotherapy could also be expected.

Another rationale for using combination therapy is that each component of the combination may neutralise the counter regulatory mechanism activated by the other.[4,80] For example, the activation of the sympathetic nervous system and the renin-angiotensin aldosterone axis by a dihydropyridine calcium channel antagonist can be counter-balanced by coadministration of an ACE inhibitor.[4]

Combinations of antihypertensive drugs may be given as fixed-dose combinations or as individual drugs. Some of the advantages of combination formulations of antihypertensive drugs are that before registration, their efficacy and tolerability have been evaluated in randomised, multifactorial, comparative trials and the optimal dosages of the individual components have been determined.[4] Moreover, combination formulations allow for simpler regimens because of the decrease in the number of tablets or capusles (in some countries outside the US). Thus, the likelihood of compliance is increased.[80] In addition, the acquisition cost of fixed combinations is generally lower than extemporaneous combinations. Fixed combinations involve only one dispensing fee, and the drug price is typically less than if the two components were administered separately.[81]

A potential disadvantage of fixed-dose combinations is the lack of dose administration flexibility. However, while it is common practice in clinical trials to titrate drug therapy to achieve target BP goals, this is often not the case in the community.[4,80] Although physicians generally increased the frequency of patient visits in response to high BP in the office, at five Department of Veteran Affairs sites in New England, US, they rarely titrated or modified BP therapy.[82] Moreover, this advantage of coadministering individual drugs may be counterproductive, given the inverse rela-

tionship between compliance and the complexity of the dose administration regimen.[80]

A plethora of fixed-dose combinations for use in the treatment of hypertension have become commercially available in the past twenty years, with the majority containing a diuretic.[4,80,83] Fixed-dose combinations outlined in the JNC-VI, BHS and WHO-ISH guidelines include not only the combination of diuretics with β-blockers and diuretics with ACE inhibitors (or an angiotensin II receptor antagonist), but also the combination of calcium channel antagonists with β-blockers and calcium channel antagonists with ACE inhibitors. To date, only the combination of captopril/hydrochlorothiazide and bisoprolol/hydrochlorothiazide have been approved in the US for first-line therapy in this indication.[83]

Theoretically, the combination of an ACE inhibitor and a calcium channel antagonist is appealing. Both ACE inhibitors and calcium channel antagonists reduce peripheral vasconstriction and facilitate salt and water excretion.[19] However, the mechanism of the two agents is distinctly different. The negative sodium balance induced by the calcium channel antagonist may facilitate the antihypertensive effects of the ACE inhibitor. Conversely, the ACE inhibitor may blunt the stimulatory effects of the calcium channel antagonist on the renin-angiotensin system.[84]

While not approved in the US for first-line therapy, fixed combinations of calcium channel antagonists and ACE inhibitors available for use in patients with hypertension in the US include amlodipine/benazepril, diltiazem/enalapril, felodipine/enalapril and trandolapril/verapamil SR.[1] The felodipine/ramipril combination is also available in Europe.[85]

The fixed combination of trandolapril/verapamil SR combines ACE inhibition with calcium channel antagonism to effectively lower BP in patients with mild to moderate essential hypertension. Both verapamil SR and trandolapril reduce total peripheral resistance without affecting cardiac output (see section 2 and table I). Importantly, verapamil is a nondihydropyridine calcium channel antagonist and its use is not associated with adverse effects (like tachycardia or flush) that are commonly reported with dihydropyridine calcium channel antagonists.[86] The use of two long-acting drugs (see section 3) provides BP control over a 24-hour period (see section 4.3). The potential advantages of such long-acting antihypertensive drugs include increased compliance, minimisation of blood pressure variation, and thus a greater protection against the risk of major cardiovascular events and the development of target organ damage.[2]

Trandolapril/verapamil SR had significantly greater antihypertensive efficacy than placebo (see section 4.2) and tended to have greater antihypertensive effect than that of the monotherapy components administered at the same dosage (see section 4.3). Combination therapy was also effective in patients with hypertension inadequately controlled with either trandolapril or verapamil (see section 4.3). Reductions in BP were generally similar in recipients of trandolapril/verapamil SR 2/180 mg/day to those in recipients of other antihypertensive combinations (metoprolol/hydrochlorothiazide, atenolol/chlorthalidone, lisinopril/hydrochlorothiazide, enalapril/hydrochlorothiazide) in patients with hypertension, including those with type 2 diabetes (see section 4.4 and section 4.5.1). Studies comparing the efficacy of trandolapril/verapamil SR with that of other fixed combinations of ACE inhibitors/calcium channel antagonists have not been conducted. Trandolapril/verapamil SR provided effective 24-hour ambulatory control that was significantly better than that provided by either of the monotherapies administered at the same dosage (see section 4.3). Interestingly, a randomised, double-blind study[23] showed that the attenuation of the early morning rise in BP was greater in recipients of combination therapy than monotherapy with either trandolapril or verapamil SR; however, the between-group difference was not significant. In this study, patients received once-daily doses of combination or monotherapies administered in the morning. The effect of evening

administration of these agents on 24-hour BP control was not investigated in this study.

A fixed combination of a calcium channel antagonist and an ACE inhibitor may be particularly useful because of the beneficial effects of each agent on cardiac and renal parameters.[20,87-89] Unless contraindicated, ACE inhibitors are recommended in hypertensive patients with heart failure, LV dysfunction or type 1 diabetic nephropathy in the JNC-VI, WHO-IS and BHS guidelines.

The ADA also recommends the use of ACE inhibitors or angiotensin receptor antagonists as first-line therapy in patients with diabetes and microalbuminuria or clinical albuminuria.[73] The ADA also notes that nondihydropyridine calcium channel antagonists reduce the level of albuminuria in diabetic patients.[90]

Trandolapril/verapamil SR was effective in reducing BP in patients with type 2 diabetes (see section 4.5.1). Moreover, data from a limited number of studies in patients with hypertension and type 2 diabetes indicated significant reductions in albuminuria in recipients of trandolapril/verapamil SR and enalapril/hydrochlorothiazide, but not atenolol/chlorthalidone (see section 2.3.3). The reduction in albuminuria with combination therapy was greater than that with either monotherapies (see section 2.3.3). Interestingly, this effect appeared to be independent of the BP lowering effect of trandolapril/verapamil SR in one of the studies.[40]

Further evidence of the renoprotective effects of trandolapril/verapamil SR 2/180 mg/day, verapamil SR 240 mg/day, trandolapril 2 mg/day and placebo therapy is being sought in the large (approximately 2400 patients), randomised Bergamo Nephrology Diabetes Complications trial (BENEDICT).[91] The effectiveness of these agents in the prevention of microalbuminuria in hypertensive (SBP ≥140mm Hg or DBP ≥90mm Hg) patients with type 2 diabetes will be assessed in the first 3-year phase of the trial. In the second phase of the trial (2 years), the efficacy of combination therapy and monotherapy with trandolapril in the prevention of the progression to macroalbuminuria (urinary albumin excretion rate >200 μg/min in two of three overnight urine collections) will be determined in those patients who developed microalbuminuria during the first phase of the trial.[91]

Trandolapril/verapamil SR demonstrated cardiovascular benefits in a limited number of randomised clinical studies in patients with hypertension (see section 2.3.1). Reductions in LV muscle mass, total peripheral resistance and pulse wave velocity were reported in these trials. Increases in LV ejection fraction and LV wall motion index were also reported in patients with angina pectoris and an ejection fraction of <40%. Nitroglycerin use and the number of angina pectoris attacks were also reduced. Preliminary data suggest that trandolapril/verapamil SR preserved LV function in patients with heart failure (see section 2.3.1). Moreover, fewer cardiac events occurred after therapy with trandolapril/verapamil SR than after trandolapril alone in post-myocardial infarction patients with congestive heart failure (see section 2.3.1).

Data regarding the cardiovascular outcomes after therapy with trandolapril/verapamil SR are expected with the completion of the large (n = 27 000) internet-based, randomised International Trandolapril/verapamil SR Study (INVEST).[92] The primary objective of this study is to compare the effects of calcium channel antagonist-based regimens (including trandolapril/verapamil SR) with those of β-blocker/diuretic-based regimens on mortality, nonfatal myocardial infarction and nonfatal stroke in patients with hypertension and coronary artery disease.[92]

Arterial hypertension may be associated with other comorbidities (such as diabetes mellitus, dyslipidaemia), which in themselves are risk factors for cardiovascular morbidity and mortality. Thus, antihypertensives should have at least a neutral or beneficial effect on these conditions.[80] In this regard, trandolapril/verapamil SR for 3 to 6 months was effective in maintaining glycaemic control in two randomised, double-blind studies in patients with hypertension and type 2 diabetes (see

section 2.3.2). In contrast, glycaemic control was not maintained in recipients of the ACE inhibitor/diuretic combination of enalapril/hydrochlorothiazide or the β-blocker/diuretic combination of atenolol/chlorthalidone in these studies.

Trandolapril/verapamil SR was also effective in reducing BP in other high risk groups, including Black patients (see section 4.5.3) and elderly patients (see section 4.5.4).

Hypertension is common in African-Caribbean and African-American Black patients.[1,3,58,59] These groups are associated with higher risks of complications, particularly stroke, renal failure and LV hypertrophy.[1,3] Interestingly, both the BHS and JNC-VI suggest that ACE inhibitors and β-blockers may be ineffective as monotherapy in Black patients, because the renin angiotensin system is frequently suppressed in this population group.[1,3] However, the BHS guidelines suggest that Black patients may respond to an ACE inhibitor or β-blocker, when used in combination with drugs that activate the renin-angiotensin system, such as diuretics, calcium channel antagonists or α-blockers.[3] A noncomparative trial and a nonrandomised, comparative trial demonstrated that trandolapril/verapamil SR (administered over a range of dosages) was effective in Black patients with mild to moderate or severe hypertension (see section 4.5.3). Notably, in one study in Black patients with mild to moderate hypertension, trandolapril/verapamil SR provided sustained antihypertensive effects over a 24-hour period.[54] Further comparative trials are required to determine the efficacy of trandolapril/verapamil SR in comparison with that of other appropriate antihypertensive combinations in Black patients.

In conclusion, trandolapril/verapamil SR is an effective treatment for patients with hypertension, including those with type 2 diabetes. Trandolapril/verapamil SR tended to be more effective than monotherapy with either verapamil SR or trandolapril, and generally showed antihypertensive efficacy similar to that of other combination antihypertensive therapies (metoprolol/hydrochlorothiazide, atenolol/chlorthalidone, lisinopril/hydrochlorothiazide, enalapril/hydrochlorothiazide). Current data support the use of trandolapril/verapamil SR as an alternative when monotherapy with either agent is not effective. Data from large clinical trials currently being conducted will assist in fully defining the role of trandolapril/verapamil SR as a cardio- and renoprotective agent.

References

1. Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure and the National High Blood Pressure Education Program Coordinating Committee. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997 Nov 24; 157: 2413-46
2. Alderman M, Arakawa K, Beilin L, et al. 1999 World Health Organization – International Society of Hypertension Guidelines for the Management of Hypertension. Blood Press 1999; 8 Suppl. 1: 9-43
3. Ramsay LE, Williams B, Johnston GD, et al. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. J Hum Hypertens 1999 Sep; 13: 569-92
4. Sica DA. Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. Drugs 2002; 62 (3): 443-62
5. Peters DC, Noble S, Plosker GL. Trandolapril: an update of its pharmacology and therapeutic use in cardiovascular disorders. Drugs 1998 Nov; 56: 871-93
6. Wiseman LR, McTavish D. Trandolapril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in essential hypertension. Drugs 1994 Jul; 48 (1): 71-90
7. Brogden RN, Benfield P. Verapamil: a review of its pharmacological properties and therapeutic use in coronary artery disease. Drugs 1996 May; 51: 792-819
8. McTavish D, Sorkin EM. Verapamil: an updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension. Drugs 1989 Jul; 38 (1): 19-76
9. Dooley M, Goa KL. Fixed combination trandolapril/verapamil SR. Drugs 1998 Nov; 56 (5): 837-44; discussion 845-6
10. Petrie JR, Morris AD, Ueda S, et al. Trandolapril does not improve insulin sensitivity in patients with hypertension and type 2 diabetes: a double-blind, placebo-controlled crossover trial. J Clin Endocrinol Metab 2000 May; 85 (5): 1882-9
11. Galletti F, Strazzullo P, Capaldo B, et al. Controlled study of the effect of angiotensin converting enzyme inhibition versus calcium-entry blockade on insulin sensitivity in overweight hypertensive patients: Trandolapril Italian Study (TRIS). J Hypertens 1999 Mar; 17: 439-45
12. New JP, Bilous RW, Walker M. Insulin sensitivity in hypertensive Type 2 diabetic patients after 1 and 19 days' treatment with trandolapril. Diabet Med 2000 Feb; 17 (2): 134-40
13. Lefrandt JD, Heitmann J, Sevre K, et al. The effects of dihydropyridine and phenylalkylamine calcium antagonist classes on autonomic function in hypertension: the VAMPHYRE study. Am J Hypertens 2001 Nov; 14 (11 Pt 1): 1083-9
14. Nazzaro P, Manzari M, Merlo M, et al. Antihypertensive treatment with verapamil and amlodipine: their effect on the functional autonomic and cardiovascular stress responses. Eur Heart J 1995 Sep; 16 (9): 1277-84
15. Schussheim AE, Diamond JA, Phillips RA. Left ventricular midwall function improves with antihypertensive therapy and

regression of left ventricular hypertrophy in patients with asymptomatic hypertension. Am J Cardiol 2001 Jan 1; 87: 61-5
16. Abbott Laboratories. Trandolapril [package insert]: US prescribing information. 2001
17. Abbott Laboratories. TARKA (Trandolapril/verapamil Hydrochloride ER tablets): US full prescribing information. 2001
18. Givertz MM. Manipulation of the renin-angiotensin system. Circulation 2001 Jul 31; 104 (5): e14-8
19. Ruschitzka FT, Lüscher TF. Concept for a combination of ACE inhibitors and calcium antagonists in cardiovascular disease. J Cardiovasc Pharmacol 1997; 30 Suppl. 1: S10-23
20. Ferrari R. Angiotensin converting enzyme inhibitor-calcium antagonist combination: an alliance for cardioprotection? J Hypertens 1997 Mar; 15 Suppl. 2: S109-117
21. Singh V, Christiana J, Frishman WH. How to use calcium antagonists in hypertension: putting the JNC-VI guidelines into practice. Joint National Committee for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Drugs 1999 Oct; 58 (4): 579-87
22. Grossman E, Messerli FH. Effect of calcium antagonists on plasma norepinephrine levels, heart rate, and blood pressure. Am J Cardiol 1997 Dec 1; 80 (11): 1453-8
23. Viskoper RJ, Compagnone D, Dies R, et al. Verapamil and trandolapril alone and in fixed combination on 24-hour ambulatory blood pressure profiles of patients with moderate essential hypertension. Curr Ther Res 1997; 58 (6): 343-51
24. de Leeuw PW, Notter T, Zilles P. Comparison of different fixed antihypertensive combination drugs: a double-blind, placebo-controlled parallel group study. J Hypertens 1997 Jan; 15 (1): 87-91
25. Breithaupt-Grögler K, Gerhardt G, Lehmann G, et al. Blood pressure and aortic elastic properties – verapamil SR/trandolapril compared to a metoprolol/hydrochlorothiazide combination therapy. Int J Clin Pharmacol Ther 1998 Aug; 36 (8): 425-31
26. Veratran Study Group. Effects of verapamil SR, trandolapril, and their fixed combination on 24-h blood pressure: the Veratran study. Am J Hypertens 1997; 10 (5): 492-9
27. Ramos F, Baglivo H, Sánchez R. Comparative double blind study at fixed dose of trandolapril + verapamil vs atenolol + chlortalidone in mild to moderate hypertensive patients [abstract]. J Hypertens 2001 Jun; 19 Suppl. 2: S236
28. Topouchian J, Asmar R, Sayegh F, et al. Changes in arterial structure and function under trandolapril-verapamil combination in hypertension. Stroke 1999 May; 30 (5): 1056-64
29. Messerli FH, Soria F. Ventricular dysrhythmias, left ventricular hypertrophy, and sudden death. Cardiovasc Drugs Ther 1994 Aug; 8 Suppl. 3: 557-63
30. Aepfelbacher FC, Messerli FH, Nunez E, et al. Cardiovascular effects of a trandolapril/verapamil combination in patients with mild to moderate essential hypertension. Am J Cardiol 1997 Mar 15; 79 (6): 826-8
31. Adalet K, Oflaz H, Sezer A, et al. Efficacy and tolerability of fixed, low-dose combination therapy with verapamil sustained-release and trandolapril in patients with mild to severe essential hypertension uncontrolled by monotherapy: an open-label, multicenter trial. Curr Ther Res Clin Exp 2001 Apr; 62: 261-71
32. Hansen JF, Tingsted L, Rasmussen V, et al. Verapamil and angiotensin-converting enzyme inhibitors in patients with coronary artery disease and reduced left ventricular ejection fraction. Am J Cardiol 1996; 77: 16D-21D
33. Mitrovic V, Parzeller M, Notter T, et al. Antihypertensive combination treatment with Verapamil SR 180 mg/Trandolapril 2 mg preserves left ventricular function in NYHA class I and II heart failure patients [abstract]. Cardiovasc Drugs Ther 1999 Mar; 13: 38
34. Hansen JF, Hagerup L, Sigurd B, et al. Cardiac event rates after acute myocardial infarction in patients treated with verapamil and trandolapril versus trandolapril alone. Am J Cardiol 1997; 79: 738-41
35. Hansen JF, Hagerup L, Sigurd B, et al. 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. Am Heart J 1997 Aug; 134 (2 Pt 2): S48-52
36. Schneider M, Lerch M, Papiri M, et al. Metabolic neutrality of combined verapamil-trandolapril treatment in contrast to beta-blocker–low-dose chlortalidone treatment in hypertensive type 2 diabetes. J Hypertens 1996 May; 14 (5): 669-77
37. Fernández R, Puig JG, Rodríguez-Pérez JC, et al. Effect of two antihypertensive combinations on metabolic control in type-2 diabetic hypertensive patients with albuminuria: a randomised, double-blind study. J Hum Hypertens 2001 Dec; 15 (12): 849-56
38. Cifková R, Nakov R, Novozámská E, et al. Evaluation of the effects of fixed combinations of sustained-release verapamil/trandolapril versus captopril/hydrochlorothiazide on metabolic and electrolyte parameters in patients with essential hypertension. J Hum Hypertens 2000 Jun; 14 (6): 347-54
39. Khaw K-T, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). BMJ 2001 Jan 6; 322 (7277): 15-8
40. Bakris GL, Weir MR, DeQuattro V, et al. Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. Kidney Int 1998 Oct; 54 (4): 1283-9
41. Rubio-Guerra AF, Treviño-Gomezharper C, Rodríguez-López L, et al. Renoprotective effects of the combination trandolapril/verapamil in patients with type 2 diabetes mellitus and hypertension. Clin Drug Invest 2002; 22 (8): 541-6
42. PROCOPA Study Group. Dissociation between blood pressure reduction and fall in proteinuria in primary renal disease: a randomized double-blind trial. J Hypertens 2002 Apr; 20 (4): 729-37
43. Siepmann M, Rao BR, Kirch W. Disposition, elimination and haemodynamic effects of verapamil and trandolapril in patients with fatty liver disease. Clin Drug Invest 1997 Nov; 14: 376-82
44. Danielson B, Querin S, LaRochelle P, et al. Pharmacokinetics and pharmacodynamics of trandolapril after repeated administration of 2 mg to patients with chronic renal failure and healthy control subjects. J Cardiovasc Pharmacol 1994; 23 Suppl. 4: S50-9
45. Lenfant B, Mouren M, Bryce T, et al. Trandolapril: pharmacokinetics of single oral doses in healthy male volunteers. J Cardiovasc Pharmacol 1994; 23 Suppl 4.: S38-43
46. Abbott Laboratories. Isoptin SR (verapamil HCL): US prescribing information. 2002
47. Sever PS, de Chatel R, Cifkova R, et al. Antihypertensive efficacy and safety of verapamil SR /trandolapril (2/240 mg) in patients insufficiently pretreated with verapamil SR 240 mg monotherapy [abstract]. Am J Hypertens 1999 Apr; 12 (Pt 2): 135A
48. Beevers DG, Gallet M, Middeke M, et al. Efficacy and safety of the fixed combination trandolapril/verapamil SR 2/180 mg in hypertensive patients insufficiently pretreated with trandolapril 2 mg monotherapy [abstract no. E019]. Am J Hypertension 1998; 11 (4) Pt 2:100a
49. DeQuattro V, Lee D. Fixed-dose combination therapy with trandolapril and verapamil SR is effective in primary hypertension. Trandolapril Study Group. Am J Hypertens 1997 Jul; 10 (7 Pt 2): 138S-45S

50. DeQuattro V, Lee D, Messerli F. Efficacy of combination therapy with trandolapril and verapamil SR in primary hypertension: a 4 x 4 trial design. Trandolapril Study Group. Clin Exp Hypertens 1997 Apr; 19 (3): 373-87
51. Viskoper RJ, Compagnone D, Dies R, et al. Verapamil and trandolapril alone and in fixed combination in moderate essential hypertension: a multicenter, double-masked study. Curr Ther Res 1997; 58 (6): 331-42
52. Messerli F, Frishman WH, Elliott WJ, et al. Effects of verapamil and trandolapril in the treatment of hypertension. Trandolapril Study Group. Am J Hypertens 1998 Mar; 11 (3 Pt 1): 322-7
53. Karlberg BE, Andrup M, Odén A. Efficacy and safety of a new long-acting drug combination, trandolapril/verapamil as compared to monotherapy in primary hypertension. Swedish TARKA trialists. Blood Press 2000; 9 (2-3): 140-5
54. Skoularigis J, Strugo V, Radevski I, et al. Once-daily fixed dose combinations of verapamil and trandolapril in Black patients with mild to moderate hypertension: a new choice for first line treatment. Int J Clin Pharmacol Ther 1997 Feb; 35 (2): 51-5
55. Scholze J, Zilles P, Compagnone D. Verapamil SR and trandolapril combination therapy in hypertension–a clinical trial of factorial design. German Hypertension Study Group. Br J Clin Pharmacol 1998 May; 45 (5): 491-5
56. Ruilope LM, Gascueña R, Investigators' Group. Treating high-normal and borderline isolated systolic hypertension in type-2 diabetic patients. Combined versus monotherapy [abstract]. Proceedings of the 38th Annual Meeting of the European Association for the Study of Diabetes; 2002 Sept; Budapest, Hungary, Diabetologia 2002; 45 Suppl. 2: A368-9
57. Ruilope LM, de la Sierra A, Moreno E, et al. Prospective comparison of therapeutical attitudes in hypertensive type 2 diabetic patients uncontrolled on monotherapy. A randomized trial: the EDICTA study. J Hypertens 1999 Dec; 17 (Prt 2): 1917-23
58. Kaufman JS, Tracy JA, Durazo-Arvizu RA, et al. Lifestyle, education, and prevalence of hypertension in populations of African origin. Results from the International Collaborative Study on Hypertension in Blacks. Ann Epidemiol 1997 Jan; 7 (1): 22-7
59. Cooper RS, Liao Y, Rotimi C. Is hypertension more severe among U.S. blacks, or is severe hypertension more common? Ann Epidemiol 1996 May; 6 (3): 173-80
60. Hall WD. A rational approach to the treatment of hypertension in special populations. Am Fam Physician 1999 Jul; 60 (1): 156-62
61. Punzi HA, Novrit BA. The treatment of severe hypertension with trandolapril, verapamil, and hydrochlorothiazide. Trandolapril/Verapamil Multicenter Study Group. J Hum Hypertens 1997 Aug; 11 (8): 477-81
62. Holzgreve H, Compagnone D, Zilles P. Trandolapril/verapamil SR combination therapy for the elderly hypertensive patient. German VeraTran Hypertension Study Group. J Hum Hypertens 1999 Jan; 13 (1): 61-7
63. Holzgreve H. Safety profile of the combination of verapamil and trandolapril. J Hypertens Suppl. 1997 Mar; 15 (2): S51-3
64. Watling SM, Crain JL, Edwards TD, et al. Verapamil overdose: case report and review of the literature. Ann Pharmacother 1992 Nov; 26 (11): 1373-8
65. Hofer CA, Smith JK, Tenholder MF. Verapamil intoxication: a literature review of overdoses and discussion of therapeutic options. Am J Med 1993 Oct; 95 (4): 431-8
66. Horowitz BZ, Rhee KJ. Massive verapamil ingestion: a report of two cases and a review of the literature. Am J Emerg Med 1989 Nov; 7 (6): 624-31
67. Ashraf M, Chaudhary K, Nelson J, et al. Massive overdose of sustained-release verapamil: a case report and review of literature. Am J Med Sci 1995 Dec; 310 (6): 258-63
68. Abbott Laboratories. TARKA Summary of Product Characteristics. 2002
69. Donahue S, Lachman L, Norton J, et al. Verapamil significantly increases serum concentrations of simvastatin but not pravastatin. Clin Pharmacol Ther 1999; 65 (2): 179
70. Kantola T, Kivisto KT, Neuvonen PJ. Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. Clin Pharmacol Ther 1998 Aug; 64 (2): 177-82
71. Schwartz GL, Sheps SG. A review of the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Curr Opin Cardiol 1999 Mar; 14: 161-8
72. Carretero OA, Oparil S. Essential hypertension : part II: treatment. Circulation 2000 Feb 1; 101 (4): 446-53
73. American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care 2002; 25: 199-201
74. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes; a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Disease 2000; 36: 646-61
75. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, British Diabetic Association . Joint British recommendations on prevention of coronary heart disease in clinical practice: summary. BMJ 2000 Mar 11; 320 (7236): 705-8
76. Ram CVS. Antihypertensive drugs; an overview. Am J Cardiovasc Drugs 2002; 2 (2): 77-89
77. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998 Jun 13; 351 (9118): 1755-62
78. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998 Sep 12; 317 (7160): 703-13
79. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998 Mar 5; 338 (10): 645-52
80. Ruzicka M, Leenen FHH. Monotherapy versus combination therapy as first line treatment of uncomplicated arterial hypertension. Drugs 2001; 61 (7): 943-54
81. Neutel JM. Low-dose antihypertensive combination therapy: its rationale and role in cardiovascular risk management. Am J Hypertens 1999 Aug; 12 (8 Pt 2): 73S-9S
82. Berlowitz DR, Ash AS, Hickey EC, et al. Inadequate management of blood pressure in a hypertensive population. N Engl J Med 1998 Dec 31; 339 (27): 1957-63
83. Moser M, Black HR. The role of combination therapy in the treatment of hypertension. Am J Hypertens 1998 Jun; 11 (6 Pt 2): 73S-8S; discussion 95S-100S
84. Skolnik NS, Beck JD, Clark M. Combination antihypertensive drugs: recommendations for use. Am Fam Physician 2000; 61 (10): 3049-56
85. AstraZeneca. Unimax (felodipine - ramipril): US prescribing information [on line]. Available from URL: http://astrazeneca.com [Accessed 2002 Oct 25]
86. Kailasam MT, Parmer RJ, Cervenka JH, et al. Divergent effects of dihydropyridine and phenylalkylamine calcium channel antagonist classes on autonomic function in human hypertension. Hypertension 1995 Jul; 26 (1): 143-9

87. Epstein M. The benefits of ACE inhibitors and calcium antagonists in slowing progressive renal failure: focus on fixed-dose combination antihypertensive therapy. Ren Fail 1996 Nov; 18 (6): 813-32
88. Bakris GL. The role of combination antihypertensive therapy and the progression of renal disease hypertension: looking toward the next millennium. Am J Hypertens 1998 Oct; 11 (10): 158S-62S
89. Taylor AA, Sunthornyothin S. The case for combining angiotensin-converting enzyme inhibitors and calcium-channel blockers. Curr Hypertens Rep 1999 Oct; 1 (5): 446-53
90. American Diabetes Association. Diabetic Nephropathy. Diabetes Care 2002; 25 Suppl .1: S85-9
91. Ruggenenti P, Remuzzi G. Primary prevention of renal function in diabetic patients: the Bergamo Nephrologic Diabetes Complication Trial. Bergamo Diabetic Nephropathy Study Group. J Hypertens 1998; 16 Suppl. 1: S95-7
92. Pepine CJ, Handberg-Thurmond E, Marks RG, et al. Rationale and design of the International Verapamil SR/Trandolapril Study (INVEST): an internet-based randomized trial in coronary artery disease patients with hypertension. J Am Coll Cardiol 1998 Nov; 32 (5): 1228-37

Correspondence: *Monique P. Curran*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz