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The antihypertensive efficacy and tolerability of a low dose combination of ramipril and felodipine ER in mild to moderate essential hypertension

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1 The antihypertensive efficacy and tolerability of a low dose combination of the angiotensin converting enzyme inhibitor ramipril (2.5 mg) and the extended release formulation of the dihydropyridine calcium channel antagonist felodipine (5 mg) were assessed in a double-blind, double dummy placebo controlled, randomised, crossover study in 20 patients (mean age 55.4 years; range 46–69) with uncomplicated mild to moderate hypertension (supine diastolic >90 mmHg <115 mmHg after 4 weeks of single-blind wash-out on placebo). The four randomised, double-blind, crossover study phases evaluated the response to 4 weeks of once daily treatment with placebo, monotherapy with each drug and the combination. Noninvasive ambulatory blood pressure monitoring (Spacelabs 90207) was performed for 24 h at the end of each phase.

2 The mean 24 h ambulatory blood pressure (mmHg) was 147.9/92.0 following placebo, 141.3/87.8 following monotherapy with ramipril 2.5 mg, 136.8/85.8 following monotherapy with felodipine ER 5 mg and 131.1/82.6 following the combination of ramipril 2.5 mg and felodipine ER 5 mg. All active treatment phases significantly reduced mean 24 h ambulatory diastolic pressure by comparison with placebo. The antihypertensive efficacy of the combination was additive.

3 The coadministration of ramipril did not attenuate the incidence of headache attributable to felodipine ER.

Keywords ramipril felodipine ER ambulatory blood pressure hypertension interaction study

Introduction

The use of relatively low doses of antihypertensive drugs in combination is an approach to treatment which may circumvent the risk of dose related adverse events associated with high dose monotherapy [1]. Combination therapy with an angiotensin converting enzyme (ACE) inhibitor and a calcium channel antagonist is both effective and safe in the treatment of severe hypertension. Morgan and colleagues [2] reported a synergistic (more than additive) antihypertensive effect with the combination of nifedipine and enalapril. Guazzi *et al.* [3] found that the tendency to ankle oedema attributable to nifedipine was attenuated by the coadministration of captopril.

The present study evaluated the combination of a calcium channel antagonist and an ACE inhibitor in mild to moderate hypertension.

Methods

Design

This was a double-blind, double dummy placebo controlled, randomised, crossover study of the ambulatory antihypertensive efficacy and tolerability of a fixed dose combination of 2.5 mg of the long acting ACE inhibitor ramipril [4] and 5 mg of the extended release formulation (ER) of the calcium channel antagonist felodipine [5] in 20 patients with mild to moderate hypertension (defined below). These doses are both at the lower end of the dose ranges recommended for hypertension by the British National Formulary [6]. The study evaluated 4 weeks of once daily treatment with placebo, monotherapy with each drug and the combination. Antihypertensive efficacy was evaluated by noninvasive 24 h ambulatory blood pressure monitoring (Spacelabs

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90207). The study design was approved by the local ethics review committee and patients gave their written informed consent to take part. The study was conducted in the Blood Pressure Clinic of the Unviersity Department of Medicine and Therapeutics at Sobhill Hospital, Glasgow.

In addition, a subgroup of 12 patients opted to complete an extension phase at the end of the double-blind, crossover study during which they received the 'half dose' combination of ramipril 1.25 mg and felodipine ER 2.5 mg under single (patient) blind conditions.

Patients

All of the participating patients had mild to moderate hypertension, as defined by a clinic supine diastolic blood pressure greater than 90 mmHg, but less than 115 mmHg, after 4 weeks of single-blind wash-out on placebo. Clinic supine blood pressure was taken as the mean of three readings obtained with a semi-automatic sphygmomanometer (Sentron, Bard, Sunderland, UK) after 10 min rest in the supine position. Patients were aged between 45 to 70 years, females of child-bearing potential were excluded. Other criteria for exclusion were: secondary hypertension, malignant hypertension, stroke within the previous 3 months, unstable angina or myocardial infarction in the previous 3 months, heart failure, renal impairment, hepatic impairment, other serious concomitant disease and drug or alcohol abuse. Patients with abnormalities on prestudy laboratory screening were also excluded, as were patients with a history of allergy or a previous adverse event from exposure to either a calcium channel antagonist or an ACE inhibitor. Patients were to be withdrawn from the study if supine diastolic blood pressure rose to greater than 120 mmHg on two assessments a week apart during any phase, if compliance was poor (as determined by tablet count) or if any significant adverse events occurred.

Clinical protocol

Patients were reviewed every 2 weeks throughout the study and all trial medication was taken at 09.00 h. Following the discontinuation of any previous medication and completion of the 4 week single-blind wash-out period on placebo, patients were randomised to the double blind, crossover trial, provided that they met the inclusion criteria. A balanced Latin square design was employed to minimise period effects. Matching placebo tablets for each active drug were used. During the 16 weeks of the double-blind, crossover trial patients were randomised to receive 4 weeks of once daily treatment with each of the following four combinations: Placebo + Placebo; Ramipril 2.5 mg + Placebo; Placebo + Felodipine ER 5 mg; Ramipril 2.5 mg + Felodipine ER 5 mg.

During the optional 'half dose' single-blind extension phase patients received 4 weeks of one daily treatment with the combination of: Ramipril 1.25 mg + Felodipine ER 2.5 mg.

Patients were asked in an open manner at each visit concerning any adverse events which they graded as mild, moderate or severe.

The following measurements were made at the end of each 4 week treatment phase:

1) Noninvasive ambulatory blood pressure monitoring was performed for 24 h post dosing using the Spacelabs 90207 system, which utilises the oscillometric method.

2) Clinic blood pressure was measured by semi-automatic sphygmomanometer (Sentron, Bard UK) at 3 h post dosing: in triplicate supine (after 10 min rest) and in duplicate erect (after 5 min standing).

3) Venous blood samples were taken at 3 h post dosing. Plasma ACE activity was measured by an h.p.l.c. assisted assay [7], for which the inter- and intra-assay coefficients of variation were 3.3% and 2.0% respectively and the limit of detection was 0.5 eu l^{-1}. The normal range was 15.3–26.9 eu l^{-1}.

Power

The design of the double-blind, crossover trial had adequate power to evaluate mean ambulatory blood pressure over a full 24 h period. With respect to mean 24 h ambulatory diastolic blood pressure, 20 patients gave a 90% power of detecting a difference of 5.5 mmHg between any two treatment phases. The standard deviation of the difference in mean 24 h ambulatory diastolic blood pressure over a 4 week period was taken as 6.3 mmHg [8]. The power calculation used an alpha of 0.0083 to allow for the evaluation of the 6 paired treatment comparisons from placebo, monotherapy with each agent and the combination (0.05/6 tests).

Statistical methods

For the ambulatory blood pressure data the area under each individual ambulatory profile was determined by the trapezoidal rule and divided by the duration of the recording period to derive the mean. Artefactual outlying readings were addressed in the individual profiles by the technique of robust nonlinear data smoothing [9]. Values were determined for the total 24 h period, for day (0–12 h post dosing) and for night (14–20 h post dosing). The haemodynamic data of the double-blind, crossover trial were analysed by ANOVA. Although the study employed a Latin square design, a preliminary analysis was performed to check for period effects. An overall probability value of less than 5% was taken as significant and multiple linear contrasts were performed using the conservative Scheffé method [10] to identify significant differences between the treatment means. The possibility of a synergistic (different from additive) effect with combination treatment was evaluated by adjusting the linear ANOVA model to code for the presence or absence of each drug and examining the significance of the interaction term betwen the drugs.

Results

The demographic details of the study group are given in Table 1. There were 20 patients, 9 men and 11 women, mean age 55.4 years (range 46–69), who were on a

Table 1 Demographic details of the study population

Sex	Previous treatment	Age (years)	Supine Systolic (mm Hg)	Supine Diastolic (mm Hg)	Erect Systolic (mm Hg)	Erect Diastolic (mm Hg)
F	β-blocker and calcium antagonist	60	155	96	167	98
F	β-blocker and calcium antagonist	61	175	103	174	108
F	β-blocker and thiazide	58	175	98	176	109
F	β-blocker and thiazide	56	179	94	175	98
F	β-blocker and thiazide	63	177	96	174	103
F	β-blocker	49	197	101	181	100
F	β-blocker	58	150	99	147	97
F	β-blocker	58	169	96	156	98
F	β-blocker	59	162	94	165	101
F	β-blocker	69	165	109	144	112
F	none	55	158	104	155	106
M	calcium antagonist and hydralazine	53	177	100	165	101
M	calcium antagonist	64	186	106	192	106
M	ACE inhibitor	46	185	98	190	101
M	frusemide and ACE inhibitor	46	197	102	185	106
M	none	49	163	99	171	97
M	none	51	188	97	184	100
M	none	51	174	98	183	99
M	calcium antagonist	47	183	103	191	96
M	thiazide and ACE inhibitor	55	162	97	168	101
	Mean	55.4	173.9	99.5	172.2	101.9
	s.d.		13.3	14.0	14.0	4.5

Demographic details of the study population (n = 20). Blood pressure (mmHg) was recorded after 4 weeks of single-blind placebo washout using a Sentron semi-automatic sphygmomanometer.

variety of initial medications. After 4 weeks of single-blind wash-out on placebo their mean clinic blood pressure (mmHg) was 173.9/99.5 supine and 172.2/101.9 erect.

The double-blind crossover study

Ambulatory blood pressure and heart rate Ambulatory profiles were recorded at the end of each 4 week treatment phase during the double-blind, crossover trial in 18 patients using the Spacelabs 90207 noninvasive ambulatory monitoring system. One patient refused to wear the monitor and another was withdrawn from the study (see below).

The ABP data are illustrated in Figure 1 and summarised in Table 2. There was no period effect. All active treatment phases produced significant reductions in mean 24 h ambultory diastolic pressure by comparison with placebo. The mean 24 h ABP (mmHg) was 147.9/92.0 following placebo, 141.3/87.8 folowing monotherapy with ramipril 2.5 mg, 136.8/85.8 following monotherapy with felodipine ER 5 mg and 131.1/82.6 following the combination of ramipril 2.5 mg and felodipine ER 5 mg. Results are also given for both day (0–12 h post dosing) and night (14–20 h post dosing) subperiods.

The observed reduction in 24 h mean ABP (mmHg) following combination therapy (16.8 systolic and 9.4 diastolic) was similar to the sum of the observed effects following monotherapy (17.7 systolic and 10.4 diastolic). The interaction between the treatments was not statistically significant (systolic P = 0.699; diastolic P = 0.542): the antihypertensive efficacy of the combination was additive and not synergistic.

The ambulatory heart rate data are summarised in Table 3. There were no significant differences in heart rate between the treatment phases. All active treatment phases were associated with a trend towards a reduction of the heart rate-systolic pressure product, which is an index of myocardial oxygen consumption [11], by comparison with placebo.

Clinic blood pressure Clinic blood pressure was measured by semi-automatic sphygmomanometer (Sentron, Bard UK) at 3 h post dosing (range 1.5–5) following 4 weeks of once daily treatment. The clinic blood pressure data of the 19 patients who completed the double-blind, crossover trial is summarised in Table 4. The observed rank order of treatment effect was consistent with the ambulatory data, but the results of statistical analysis are not presented as the sample size was not sufficient to evaluate clinic blood pressure.

Adverse events All of the adverse study events which occurred are listed in Table 5. There were no adverse events during treatment with ramipril monotherapy, but there were five reports of headache whilst taking felodipine ER, including one patient who withdrew due to severe headache on the combination. The relative incidence of headache attributable to felodipine ER between treatment with felodipine ER monotherapy and the combination was examined by the tabulation of discordant pairs and calculation of exact binomial probabilities. The coadministration of ramipril did not alter the incidence of headache attributable to felodipine ER (P = 0.625).

Angiotensin converting enzyme Venous blood sampling for plasma ACE activity was performed at 3 h post dosing (range 1.5–5) following 4 weeks of once daily treatment. The mean (s.d.) plasma ACE (eu l^{-1})

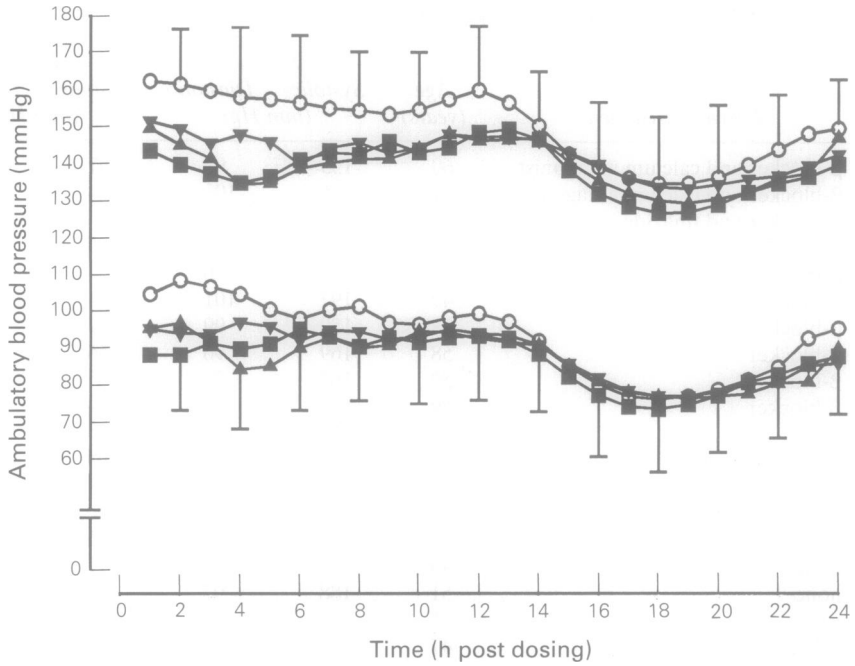

Figure 1 Ambulatory blood pressure in the double-blind trial. Ambulatory blood pressure (Spacelabs 90207) was recorded for 24 h post dosing following 4 weeks of once daily treatment with placebo (○), felodipine ER 5 mg (▲), ramipril 2.5 mg (▼) and the combination of felodipine ER 5 mg and ramipril 2.5 mg (■) (n = 18; hourly means and s.d.).

Table 2 Ambulatory blood pressure in the double-blind crossover trial

	24 h	*Day*	*Night*
Systolic (mm Hg)			
Placebo	147.9	154.4	137.5
	145.3 – 150.4	150.7 – 158.2	133.8 – 141.3
Ramipril 2.5 mg	141.3	144.9	133.2
	138.7 – 143.8	141.2 – 148.6	129.4 – 137.0
Felodipine 5 mg	136.8	140.2	129.4
	134.3 – 139.4	136.4 – 143.9	125.6 – 133.1
Felodipine 5 mg	131.1	135.7	121.4
and ramipril 2.5 mg	128.6 – 133.7	131.9 – 139.4	117.6 – 125.2
Diastolic (mm Hg)			
Placebo	92.0	99.0	81.1
	90.3 – 93.7	96.3 – 101.7	78.1 – 84.2
Ramipril 2.5 mg	87.8	93.0	78.8
	86.1 – 89.5	90.3 – 95.8	75.8 – 81.8
Felodipine 5 mg	85.8	91.2	75.3
	84.1 – 87.5	88.5 – 93.9	72.2 – 78.3
Felodipine 5 mg	82.6	87.8	72.6
and ramipril 2.5 mg	80.9 – 84.3	85.1 – 90.5	69.6 – 75.7

Ambulatory blood pressure (mm Hg) during the double-blind, crossover trial. Noninvasive ambulatory blood pressure (Spacelabs 90297) was recorded for 24 h following 4 weeks of once daily treatment (n = 18; mean and 95% confidence interval).

was 27.3 (7.3) following placebo, 28.5 (6.2) following felodipine ER alone, 8.0 (4.0) following ramipril alone and 7.6 (4.7) following combination treatment. These results are consistent with the known influence of ramipril on plasma ACE and suggest that compliance was good.

Single-blind half dose combination extension phase

Ambulatory profiles were recorded in a subgroup of 12 subjects who opted to complete the single-blind extension phase with the 'half dose' combination of ramipril 1.25 mg and felodipine ER 2.5 mg. The ABP data of this

Table 3 Ambulatory heart rate and heart rate-systolic pressure product in the double-blind crossover trial

	24 h	*Day*	*Night*
Heart rate (beats min^{-1})			
Placebo	73.3	80.3	63.2
	71.4 – 75.2	77.9 – 82.6	60.5 – 65.9
Ramipril 2.5 mg	74.8	81.4	65.4
	72.9 – 76.7	79.1 – 83.8	62.8 – 68.1
Felodipine 5 mg	74.4	81.7	63.1
	72.5 – 76.3	79.4 – 84.1	60.4 – 65.7
Felodipine 5 mg	74.1	79.8	63.9
and ramipril 2.5 mg	72.2 – 76.0	77.5 – 82.1	61.2 – 66.6
Rate pressure product (beats min^{-1}·mm Hg/100)			
Placebo	110.2	125.3	88.0
	106.6 – 113.8	120.2 – 130.5	83.9 – 92.1
Ramipril 2.5 mg	106.9	118.7	88.2
	103.3 – 110.5	113.6 – 123.9	84.1 – 92.3
Felodipine 5 mg	102.7	115.0	82.2
	99.1 – 106.3	109.8 – 120.1	78.1 – 86.3
Felodipine 5 mg	98.2	108.7	78.4
and ramipril 2.5 mg	94.6 – 101.8	103.6 – 113.9	74.3 – 82.5

Ambulatory heart rate (beats min^{-1}) and heart rate-systolic pressure product (beats min^{-1} mm Hg/100) during the double-blind, crossover trial (n = 18; mean and 95% confidence interval).

Table 4 Clinic blood pressure in the double-blind crossover trial

	Systolic (mmHg)	*Diastolic*
Supine		
Placebo	169.6	97.2
	163.4 – 175.8	92.2 – 102.2
Ramipril 2.5 mg	163.3	97.7
	153.6 – 173.0	92.8 – 102.6
Felodipine 5 mg	154.8	92.3
	148.9 – 160.7	87.4 – 97.2
Felodipine 5 mg	152.9	90.4
and ramipril 2.5 mg	148.0 – 157.8	86.0 – 94.8
Erect		
Placebo	162.8	101.2
	155.8 – 169.8	96.4 – 106.0
Ramipril 2.5 mg	160.3	97.0
	152.0 – 168.6	91.5 – 102.5
Felodipine 5 mg	154.5	92.6
	146.4 – 162.6	87.6 – 97.6
Felodipine 5 mg	147.8	90.4
and ramipril 2.5 mg	143.1 – 152.5	85.9 – 94.9

Clinic blood pressure (mm Hg) during the double-blind, crossover trial (n = 19; mean and 95% confidence interval). Readings were taken using a Sentron semi-automatic sphygmomanometer at 3 h (range 1.5–5) post dosing following 4 weeks of once daily treatment.

Table 5 Adverse events and withdrawals during all trial phases

Placebo	Mild headache; subsided Palpitations; subsided
Felodipine 5 mg	Mild headache; subsided Moderate headache; subsided Moderate headache; subsided
Ramipril 2.5 mg	None
Felodipine 5 mg and ramipril 2.5 mg	Moderate headache; subsided Severe headache and severe flushing; withdrew
Felodipine 2.5 mg and ramipril 1.25 mg	None

All of the adverse events and withdrawals which occurred are listed for trial phases. Twenty patients entered the double-blind, crossover trial: there were 7 adverse events and 1 subject withdrew. 12 subjects entered the optional single-blind extension phase with the half dose combination: there were no adverse events in this subgroup.

subgroup for both the single-blind extension phase and the double-blind, crossover trial is summarised in Table 6. The rank order of treatment effect on mean 24 h ABP suggests that the 'half dose' combination of ramipril 1.25 mg and felodipine ER 2.5 mg (143.3/88.9) was slightly more effective than ramipril 2.5 mg monotherapy (145.0/90.1), but not as effective as felodipine ER 5 mg monotherapy (139.5/87.6). Statistical analysis is not presented due to the confounding effect of treatment order.

There were no adverse events with the 'half dose' combination, but all subjects in this subgroup had tolerated prior exposure to the 'full dose' combination during the double-blind trial.

Table 6 Ambulatory blood pressure in the subgroup who completed the single-blind extension phase with the half dose combination

	24 h	*Day*	*Night*
Systolic (mm Hg)			
Placebo	152.4	157.6	143.3
	149.1 – 155.7	153.2 – 162.1	139.0 – 147.6
Ramipril 2.5 mg	145.0	147.6	138.0
	141.7 – 148.3	143.2 – 152.1	133.8 – 142.3
Felodipine 2.5 mg	143.3	145.8	135.6
and ramipril 1.25 mg	140.0 – 146.6	141.4 – 150.3	131.3 – 139.8
Felodipine 5 mg	139.5	140.8	135.2
	136.3 – 142.8	136.3 – 145.2	130.9 – 139.4
Felodipine 5 mg	134.2	138.5	124.1
and ramipril 2.5 mg	130.9 – 137.5	134.1 – 143.0	119.8 – 128.4
Diastolic (mm Hg)			
Placebo	95.4	101.6	85.1
	93.1 – 97.7	98.4 – 104.8	81.5 – 88.8
Ramipril 2.5 mg	90.1	94.9	81.6
	87.8 – 92.3	91.7 – 98.1	78.0 – 85.3
Felodipine 2.5 mg	88.9	94.3	78.1
and ramipril 1.25 mg	86.6 – 91.2	91.1 – 97.5	74.5 – 81.8
Felodipine 5 mg	87.6	92.0	78.8
	85.4 – 89.9	88.8 – 95.2	75.1 – 82.4
Felodipine 5 mg	85.1	90.3	74.6
and ramipril 2.5 mg	82.8 – 87.3	87.1 – 93.5	71.0 – 78.2

Ambulatory blood pressure (mm Hg) in the subgroup of 12 subjects who completed the optional single-blind extension phase with the half dose combination (mean and 95% confidence interval). Results are given for this subgroup for all trial phases, but statistical comparisons were not made due to the confounding effect of treatment order.

Discussion

This study was a double-blind, double dummy placebo controlled, randomised, crossover study of the ambulatory antihypertensive efficacy and tolerability of a low dose combination of the long acting ACE inhibitor ramipril and the extended release formulation of the calcium channel antagonist felodipine in mild to moderate hypertension. Additional interest lay in whether the combination of a calcium channel antagonist with an ACE inhibitor might lead to a synergistic antihypertensive response and attenuate the adverse event profile of the calcium channel antagonist. The principal findings were:

1) Ramipril 2.5 mg and felodipine ER 5 mg were both effective as once daily monotherapy in reducing mean 24 h diastolic ABP.

2) The antihypertensive efficacy of the combination was additive.

3) The adverse events attributable to felodipine ER were not attenuated by the coadministration of ramipril.

Recent years have seen the introduction of reliable, portable, noninvasive ABP monitoring equipment. The potential role of ABP monitoring in clinical trials is being increasingly recognised [12]. The SpaceLabs 90207 system has been compared with intra-arterial readings [13] and publication of validation according to the protocol of the British Hypertension Society is imminent [14].

Felodipine is an effective antihypertensive treatment which has been evaluated as monotherapy [15], as a second line agent [16, 17] and as a third line agent in refractory hypertension [18]. Ramipril is comparable with enalapril [19] in terms of antihypertensive efficacy. Heber and colleagues [4] used intra-arterial ABP monitoring to confirm a 24 h duration of antihypertensive effect following optimised steady state dosing with ramipril (minimum dose 10 mg). Using clinic blood pressure Villamil *et al.* [20] suggested that the minimum effective dose of ramipril was 5 mg daily. In contrast, the present study found a significant reduction in mean 24 h diastolic ABP following monotherapy with 2.5 mg ramipril.

There have been several previous assessments of the combination of an ACE inhibitor with a calcium channel antagonist. Morgan [2] has reported a synergistic antihypertensive effect in the context of severe hypertension, but most other authors have found only an additive effect. The combination of nicardipine and enalapril was effective and well tolerated [21], as were verapamil and captopril [22], verapamil and enalapril [23], nifedipine and captopril [3] and nifedipine and enalapril [24]. In these studies the hypotensive effect of the combination was not reported as significantly different from additive and the adverse events were generally attributed to the calcium channel antagonist.

There are at least two theoretical mechanisms by which synergism between ACE inhibitors and calcium channel antagonists might arise. Dihydropyridine calcium channel antagonists induce acute vasodilatation with consequent release of renin and reflex sympathetic activation. ACE inhibitors blunt the activation of the

renin-angiotensin system and have parasympathomimetic properties [25]. However, the present study provided no evidence that the antihypertensive effect of the combination of ramipril and felodipine ER was different from additive.

Our previous acute dosing study of the combination of ramipril and felodipine ER in normotensives [26] found that the addition of ramipril attenauted the tachycardia and abolished the elevation of the heart rate-systolic pressure product attributable to felodipine ER. However, the heart rate response to felodipine resolves after about 1 week of continued treatment [27] so it was not anticipated that heart rate changes would be found in the present study.

The adverse event profile of felodipine is mainly related to peripheral vasodilatation producing vasogenic oedema and headache. The withdrawal rate can be up to 42% when higher doses of felodipine are used as monotherapy [28]. Bossini and colleagues [15] reported the incidence of adverse events in 28 mild hypertensives who attempted to take 10 mg felodipine ER for 4 weeks: five patients had to be withdrawn. The incidence of adverse events with ramipril monotherapy has been estimated as 6.7% for a range of doses [29]. In the present study ramipril was well tolerated, but felodipine ER caused headache. The incidence of headache attributable to felodipine was not reduced by the coadministration of ramipril.

In conclusion, this study of the ambulatory efficacy and tolerability of ramipril 2.5 mg and felodipine ER 5 mg in mild to moderate essential hypertension confirmed that both drugs are effective as once daily monotherapy in reducing mean 24 h diastolic ABP. The antihypertensive effect of the combination was additive and the incidence of headache attributable to felodipine ER was not attenuated by the coadministration of ramipril.

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