Contrasting effects of verapamil and amlodipine on cardiovascular stress responses in hypertension

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Aims To compare the effects of two long-acting calcium antagonists of different types on cardiovascular stress responses in hypertension.

Methods One-hundred and forty-five patients with mild to moderate hypertension and a mean ($\pm$ s.e.mean) age of 51 ± 0.9 years received for 8 weeks the phenyl-alkylamine verapamil sustained release (240 mg) and the dihydropyridine amlodipine (5 mg) in a double-blind cross-over design, both after 4 weeks of placebo. Blood pressure, heart rate and plasma noradrenaline were monitored during 3 min of sustained isometric handgrip and 2 min of cold pressor.

Results Blood pressure was equally reduced by both drugs. After 3 min handgrip, systolic blood pressure, heart rate and rate-pressure product were lower with verapamil compared with amlodipine. Verapamil attenuated the increases in systolic blood pressure (25 ± 2 vs 30 ± 2 mmHg, difference 4.6, 95% CI (1.0, 8.1), $P < 0.01$) and rate-pressure product (3.1 ± 0.2 vs $3.6 \pm 0.3 \times 10^3$ mmHg $\times$ beats min^{-1} , difference 0.5, 95% CI (0.1, 0.9), $P < 0.01$) during handgrip compared with amlodipine. Similar results were observed during cold pressor. Plasma noradrenaline levels were lower with verapamil compared with amlodipine at rest and after both tests, but the increases in plasma noradrenaline were not significantly different.

Conclusions Verapamil is more effective in reducing blood pressure and rate-pressure product responses to stress compared with amlodipine. Although plasma noradrenaline is lower with verapamil at rest and after stress, the increase during stress is not different.

Keywords: amlodipine, noradrenaline, rate-pressure product, stress responses, verapamil

Introduction

Increased cardiac output and heart rate at rest and adrenergic hyperreactivity to stress in patients with borderline hypertension [1–3], as well as normotensive offspring of hypertensive patients [4], have characterized the pathophysiological haemodynamic changes in the development of hypertension. In established hypertension, increased peripheral resistance rather than increased cardiac output is characteristic [5]. The increased pressure

workload induces adaptive changes in the endothelium, the vascular smooth muscle and the extracellular matrix of vessels and the heart [6, 7]. Development of left ventricular hypertrophy adds to the increased cardiovascular risk in hypertensive patients [8]. Furthermore, increased blood pressure and heart rate responsiveness during stress could trigger myocardial ischaemia and infarction due to inability to supply oxygen during this high demand at increased workload [9, 10]. The incidence of ischaemic events follows a pattern similar to rises in heart rate and blood pressure [11, 12]. Thus, drugs that would reduce cardiac load both at rest and during exertion could be beneficial in hypertension.

Calcium antagonists are widely used to treat hypertension. Although the blood pressure reducing efficacy of different types of calcium antagonists is comparable, their

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Received 24 November 2000, accepted 2 August 2001.

mechanisms of action are not the same. While dihydropyridines induce peripheral vasodilatation and have little or no effect on myocardial contractility and sinus node automaticity, nondihydropyridines have less influence on peripheral vascular smooth musculature and direct effects on cardiac inotropy and chronotropy [13, 14]. The aim of the present study was to compare the effects of a long acting dihydropyridine (amlodipine) and a phenylalkylamine (verapamil) on cardiovascular stress responses by noninvasive methods during isometric handgrip and cold pressor stress tests in patients with mild to moderate hypertension.

This paper was presented as an abstract at the Eighteenth Scientific Meeting of the International Society of Hypertension in Chicago, August 2000.

Methods

Study design and subjects

The study was a double-blind randomized cross-over comparison of verapamil Sustained Release (SR, 240 mg) and amlodipine (5 mg), corresponding to the registered and recommended starting dosage of these drugs in The Netherlands. All patients were at least 18 years of age and had mild to moderate hypertension, defined as a diastolic blood pressure between 95 and 110 mmHg on at least three occasions. In these patients, either hypertension was newly diagnosed, or current antihypertensive treatment did not meet therapeutic goals. Patients were excluded if secondary hypertension was suspected or if they had had a recent cardiovascular event. Seven centres in six European Community countries participated. Informed consent was obtained from all patients. The local ethics committees at each participating hospital approved the protocol.

At the first patient visit, any antihypertensive treatment was stopped and 4 weeks of placebo treatment was started. Sitting blood pressure was measured three times after 10 min of rest with 2 min intervals. Randomization to sequence 1 (8 weeks of verapamil—4 weeks of placebo—8 weeks of amlodipine) or 2 (8 weeks of amlodipine—4 weeks of placebo—8 weeks of verapamil) followed at the second visit if diastolic blood pressure was ≥ 95 and ≤ 110 mmHg and systolic blood pressure ≤ 180 mmHg. The first placebo period was open, both active drug periods were double-blind and the second placebo period was single-blind. All tablets were taken in the evening.

Study procedures

All tests were performed in the morning in a warm, quiet room. Patients refrained from eating, smoking and drinking alcohol, coffee and tea that day. A Finapres

(Ohmeda 2300, Englewood, Colo., USA) blood pressure monitor was attached to the third finger of the patient's right hand. Ten minutes after insertion of a catheter in an antecubital vein of the left arm, heart rate and sitting sphygmomanometric blood pressure were measured and the Finapres blood pressure monitoring was started. After another 10 min of supine rest, the isometric handgrip test was performed; the patient had to squeeze a dynamometer at 30% of the predetermined maximum strength, during 3 min, with his left hand. After a recovery period of 10 min, the cold pressor test was performed; the left hand was immersed in ice-water ($0-4^{\circ}\text{C}$) for 2 min. Then, a second recovery period of 10 min followed. Since the autonomic nervous system is very much influenced by mental stress, the sole purpose of the first visit was to get the patient acquainted with the study procedures.

Venous blood (6 ml) was sampled in a prechilled EGTA-glutathion tube 1 min before and 1 min after both handgrip and cold pressor. Plasma noradrenaline concentrations were determined by electrochemical detection after high-pressure liquid chromatography in a central laboratory (Analytico, Breda, the Netherlands) for all centres.

Beat to beat systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR) were obtained from the RS232 interface of the Finapres and stored on a personal computer. Rate-pressure product was calculated by multiplying HR by SBP. Mean SBP, DBP, HR and rate-pressure product were determined for consecutive periods of 20 s. The changes in SBP, DBP, HR and rate-pressure product were calculated for every minute.

Statistical analysis

The primary endpoint of this analysis was defined as the difference in increase of the rate-pressure product with verapamil and amlodipine during the stress tests. Sample-size calculation was based on the rate-pressure product responses to different types of stress of a recent trial comparing verapamil and amlodipine in hypertensive subjects [15]. Anticipating a standard deviation of 1100, 134 evaluable patients were needed to detect a difference of $500\text{ mmHg} \times \text{beats min}^{-1}$ in a 2-sided *t*-test for $\alpha = 0.05$ with 95% power.

A mixed ANCOVA model was defined to test the null hypothesis of no difference between both treatments. Period, treatment and centre were defined as fixed factors, the placebo period preceding the active drug as covariate and patient within centre as random effect. Bonferroni's correction for multiple comparisons was used. A *P* value < 0.05 in the 2-sided test was considered statistically significant. A Wilcoxon test was used for all parameters that had a skewed distribution and could not be normalized by log transformation. Student's *t*-test was performed

for all parameters, to check for any differences between the first and second placebo period. A secondary model tested the possibility of a carry-over effect. All data are shown as mean $\pm$ s.e.mean. Differences between both drugs are shown as mean with 95% CI or natural log (LN) mean with 95% CI for parameters that were log transformed before analysis.

Results

One hundred 45 patients were randomized at the second visit. Patient characteristics at randomization are summarized in Table 1. Twenty-two patients later dropped out of the study due to adverse events, lack of compliance and withdrawal of their consent. The data were analysed according to the intention-to-treat (ITT) principle: all patients that had used at least one tablet of active treatment entered the ITT-population. The design of the study does not allow an unbiased assessment of the relation between adverse events and study drugs. The adverse events with a probable relation with the drugs (verapamil/amlodipine) were most frequently common side-effects: headache (2/1), dizziness (3/1), palpitations (0/1), constipation (1/1) and peripheral oedema (2/1). In addition, three generalized allergic responses to verapamil that faded after withdrawal were observed. The mean compliance, assessed by tablet count, was $>95\%$ for all treatments. Because no significant difference between both placebo periods existed for any parameter, the mean of both is presented.

Sphygmomanometric blood pressure and heart rate

During placebo, mean systolic and diastolic blood pressure were 153 ± 1 and 100 ± 1 mmHg, respectively. Both were

equal after verapamil and amlodipine treatment: SBP 139 ± 2 vs 138 ± 2 mmHg, difference 0.86, 95% CI ($-1.65, 3.38$), $P=0.50$ and DBP 91 ± 1 vs 91 ± 1 mmHg, difference 0.43, 95% CI ($-1.36, 2.22$), $P=0.59$. During placebo, mean heart rate was 68 ± 1 beats min^{-1} . Heart rate was lower with verapamil than with amlodipine: 65 ± 1 vs 69 ± 1 beats min^{-1} , difference -4.0 , 95% CI ($-6.6, -2.7$), $P<0.0001$.

Haemodynamic responses to handgrip and cold pressor

SBP, DBP, HR and rate-pressure product responses to handgrip and cold pressure are depicted in Figures 1 and 2. Before both tests, SBP and DBP were not different with verapamil and amlodipine; HR and rate-pressure product were significantly lower with verapamil compared to amlodipine ($P<0.0001$ and $P=0.002$, respectively).

Handgrip. During 3 min handgrip, SBP, DBP, HR and rate-pressure product increased significantly with both drugs ($P<0.0001$ for all). SBP was significantly lower with verapamil compared with amlodipine during the last 40 s of the test (after 3 min handgrip: 169 ± 3 vs 177 ± 4 mmHg, natural log difference 0.048, 95% CI (0.013, 0.083), $P<0.01$). The difference in DBP did not reach statistical significance (after 3 min handgrip: 100 ± 2 vs 103 ± 3 mmHg, natural log difference 0.037, 95% CI ($-0.006, 0.079$), $P=0.09$). HR and rate-pressure product remained significantly lower during and after the test with verapamil compared with amlodipine (after 3 min handgrip: HR 71 ± 1 vs 75 ± 1 beats min^{-1} , natural log difference 0.057, 95% CI (0.029, 0.085), $P<0.0001$; rate-pressure product 11.8 ± 0.3 vs $13.2 \pm 0.4 \times 10^3$ mmHg $\times$ beats min^{-1} , natural log difference 0.107, 95% CI (0.060, 0.153), $P<0.0001$). The increase in SBP was significantly smaller during the third minute of handgrip and the increase in rate-pressure product was significantly smaller during all 3 min of handgrip with verapamil compared with amlodipine (third minute of handgrip: increase in SBP 25 ± 2 vs 30 ± 2 mmHg, difference 4.6, 95% CI (1.0, 8.1), $P<0.01$; increase in rate-pressure product 3.1 ± 0.2 vs $3.6 \pm 0.3 \times 10^3$ mmHg $\times$ beats min^{-1} , difference 0.5, 95% CI (0.1, 0.9), $P<0.01$).

Cold pressor. During 2 min cold pressor, SBP, DBP, HR and rate-pressure product increased significantly with both drugs ($P<0.0001$ for all). With verapamil, SBP was significantly lower from 40 s after the start of cold pressor until 3 min and 20 s after the test, compared to amlodipine (after 2 min cold pressor: 174 ± 4 vs 184 ± 4 mmHg, natural log difference 0.059, 95% CI (0.020, 0.099), $P<0.01$). DBP was significantly higher with amlodipine compared with verapamil during the recovery period, during the third minute after the test. HR and rate-pressure product remained significantly lower during and after the test with verapamil compared with

Table 1 Patient characteristics at randomization. Dyslipidaemia is defined as total cholesterol >6.5 mmol l^{-1} or low-density lipoprotein >5 mmol l^{-1} or high-density lipoprotein <0.9 mmol l^{-1} or triglycerides >2.5 mmol l^{-1} .

	Mean (range) or Number (%)
Male/female n (%)	95/50 (65%/35%)
Age (years)	51 (20–72)
Systolic blood pressure (mmHg)	153 (124–180)
Diastolic blood pressure (mmHg)	100 (95–110)
Heart rate (beats min^{-1})	67.8 (51–102)
Body mass index (kg/m^2)	28.6 (19.9–46.8)
Smokers current n (%)	33 (23%)
Dyslipidaemia n (%)	57 (40%)
Family history of premature atherosclerotic disease n (%)	13 (9%)
Serum creatinine ($\mu\text{mol l}^{-1}$)	85 (59–141)

Figure 1 Mean $\pm$ s.e. mean for blood pressure, heart rate and rate pressure product during and after 3 min of handgrip (HG), for segments of 20 s. For the delta systolic blood pressure and delta rate pressure product the change from before the test are shown for each minute. * $P < 0.01$, ** $P < 0.0001$, for verapamil *vs* amlodipine. *, $\square$ placebo; $\bullet$, $\blacksquare$ verapamil; $\circ$, $\blacksquare$ amlodipine.

Figure 2 Mean $\pm$ s.e. mean for blood pressure, heart rate and rate pressure product during and after 2 min of cold pressor (CP), for segments of 20 s. For the delta systolic blood pressure and delta rate pressure product the change from before the test are shown for each minute. * $P < 0.01$, ** $P < 0.0001$, for verapamil *vs* amlodipine. *, $\square$ placebo; $\bullet$, $\blacksquare$ verapamil; $\circ$, $\blacksquare$ amlodipine.

amlodipine (after 2 min cold pressor: HR 67 ± 1 *vs* 72 ± 1 beats min⁻¹, natural log difference 0.069, 95% CI (0.043, 0.095), $P < 0.0001$; rate-pressure product 11.6 ± 0.3 *vs* $13.2 \pm 0.4 \times 10^3$ mmHg $\times$ beats min⁻¹, natural log difference 0.13, 95% CI (0.08, 0.19), $P < 0.0001$). The increase in rate-pressure product was significantly smaller with verapamil compared with amlodipine during the second minute of cold pressor (after 2 min cold pressor: 3.2 ± 0.2

vs $3.9 \pm 0.3 \times 10^3$ mmHg $\times$ beats min⁻¹, difference 0.7, 95% CI (0.2, 1.1), $P < 0.01$).

Plasma noradrenaline before and after handgrip and cold pressor (Table 2)

Before and after the handgrip as well as before and after the cold pressor test, plasma noradrenaline concentrations

Table 2 Mean $\pm$ s.e. mean for plasma noradrenaline before and after isometric handgrip and cold pressor. Median (Q1, Q3) for changes in plasma noradrenaline. Mean (95% CI) for the difference between verapamil and amlodipine, except for the difference in changes (*median, Q1, Q3).

Noradrenaline ($\mu\text{mol l}^{-1}$)	Placebo	Verapamil	Amlodipine	Difference	P value
<i>Handgrip</i>					
1 min before test	1.30 $\pm$ 0.03	1.39 $\pm$ 0.07	1.60 $\pm$ 0.08	-0.14 (-0.21, -0.06)	<0.001
1 min after test	1.38 $\pm$ 0.03	1.49 $\pm$ 0.07	1.68 $\pm$ 0.08	-0.19 (-0.28, -0.09)	<0.001
Change	+0.04 (-0.13, 0.26)	+0.09 (-0.11, 0.34)	+0.04 (-0.20, 0.27)	-0.07 (-0.37, 0.41)*	0.94
<i>Cold pressor</i>					
1 min before test	1.35 $\pm$ 0.03	1.32 $\pm$ 0.07	1.59 $\pm$ 0.09	-0.17 (-0.23, -0.10)	<0.0001
1 min after test	1.81 $\pm$ 0.05	2.06 $\pm$ 0.11	2.31 $\pm$ 0.13	-0.30 (-0.51, -0.07)	0.01
Change	+0.40 (0.19-0.72)	+0.57 (0.30-0.93)	+0.59 (0.28-0.94)	0.13 (-0.42, 0.45)*	0.34

were higher with amlodipine compared with verapamil ($P<0.001$, $P<0.001$, $P<0.001$ and $P=0.01$). The increases in plasma noradrenaline concentration after both tests were not different between the drugs.

Discussion

This study demonstrates that the effects of the long-acting dihydropyridine amlodipine and the phenylalkylamine verapamil on cardiovascular stress responses to exertion are markedly different, whereas the reduction in resting blood pressure by the two drugs is similar. Calcium antagonists reduce blood pressure mainly by decreasing peripheral resistance. We found a similar reduction in blood pressure by verapamil and amlodipine at rest. This is in agreement with a study of Nazarro *et al.* [15] in 23 hypertensive patients that reported an equal reduction of blood pressure with verapamil and amlodipine after 4 weeks treatment. Furthermore, they found both drugs equally reduced peripheral resistance. The blood pressure reducing efficacy at rest therefore seems to be the same for both drugs. However, the effects on resting rate-pressure product and heart rate are different. We found that verapamil reduced resting rate-pressure product while amlodipine did not. This resulted from reduction in resting heart rate by verapamil, which directly effects sinus node automaticity [16].

During stress, the effects of verapamil and amlodipine on haemodynamics showed even more contrasts. Blood pressure lowering efficacy during handgrip in hypertensive patients has been reported with both verapamil [17] and amlodipine [18]. However, the present study also shows diminished systolic blood pressure and rate-pressure product responsiveness during handgrip with verapamil compared with amlodipine. Diminished blood pressure responsiveness during handgrip has been reported with verapamil only [17]. Isometric handgrip is a potent α -adrenergic stimulus. Verapamil has been shown to bind to the α -adrenergic receptor [19]. Furthermore,

verapamil might directly inhibit presynaptic release of noradrenaline [20, 21]. However, although plasma noradrenaline concentrations before and after isometric handgrip were lower with verapamil compared with amlodipine, the increase in plasma noradrenaline concentration during handgrip was not different in our study.

The cold pressor test is less frequently used to study the effects of calcium antagonists on cardiovascular stress responses in hypertension. Both handgrip and cold pressor test increase sympathetic outflow and peripheral resistance that results in an increase in blood pressure. The blood pressure and heart rate responses to handgrip showed a linear increase through time in our study (Figure 1). In contrast, the cold pressor test induced changes which exhibited a hyperbolic time course. However, the effects of verapamil and amlodipine showed interesting contrasts. Verapamil blunted the systolic blood pressure, heart rate and rate-pressure product response during cold pressor compared to amlodipine. The change in rate-pressure product was lower with verapamil although the difference in systolic blood pressure response did not reach statistical significance. In an earlier study of 13 hypertensive patients, verapamil reduced systolic blood pressure but not the increase in systolic blood pressure during cold pressor compared with placebo [22].

Although the present study showed a clear reduction in blood pressure and rate-pressure product responses to stress and a reduction of plasma noradrenaline at rest and after stress with verapamil compared with amlodipine, the potential advantage of these observations in the treatment of hypertension remains to be confirmed. Still, the present study may have clinical implications. Firstly, the higher efficacy of verapamil in reducing blood pressure during exertion suggests that its antihypertensive effect is more preserved during normal daily activities that often contain isometric handgrip. Secondly, the reduction in rate-pressure product at rest and during exertion and the smaller increase in rate-pressure product during exertion with verapamil should decrease myocardial oxygen

consumption [23] at rest and during stress. This cardio-protective effect of verapamil could be especially useful in patients with associated coronary artery disease, as supported by a study of 551 patients with chronic stable angina, in whom verapamil reduced the total duration of ischaemic episodes, in contrast to amlodipine which increased the total duration of ischaemic episodes [24]. The DAVIT-II study showed a reduction in major cardiovascular events in post myocardial patients without heart failure by verapamil compared with placebo [25]. However, the use of a rate-limiting drug as primary prevention of ischaemic events remains speculative. To determine whether the favourable effects of verapamil on blood pressure reactivity and heart rate would translate into improved prognosis, a large outcome study in hypertensive patients is needed.

We conclude that verapamil is more effective in reducing blood pressure and rate-pressure product responses to stress compared with amlodipine, while resting blood pressure is equally reduced by both. Although plasma noradrenaline is lower with verapamil at rest and after stress, the increase during stress is not different compared with amlodipine.

This study was financially supported by KNOLL AG, Germany.

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