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ORIGINAL ARTICLE

Double-blind crossover study of the interaction between perindopril and amlodipine on blood pressure and hormones related to fluid and electrolyte balance in patients with essential hypertension

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This study was to investigate the interaction between low doses of perindopril (2 mg daily) and amlodipine (2.5 mg daily) on ambulatory blood pressure (BP), clinic BP, serum angiotensin-converting enzyme (ACE), plasma levels of renin (PRA), angiotensin II (Ang II), aldosterone, and atrial natriuretic peptide (α-h ANP) in subjects with essential hypertension. The study design was a parallel, two-period, placebo-controlled, double-blind crossover design, with 11 subjects receiving perindopril and 10 receiving amlodipine during the run-in phase.

The addition of amlodipine to perindopril had no effect on ambulatory BP, whereas the addition of perindopril to amlodipine reduced both systolic ($P = 0.027$) and diastolic ($P = 0.049$) ambulatory BP. By contrast, the opposite result was obtained for clinic BP at trough, whereby the addition of amlodipine to perindopril reduced erect systolic BP ($P = 0.036$) and both supine and erect diastolic BP ($P = 0.038$) whereas the addition of perindopril to amlodipine was without effect.

The addition of perindopril to amlodipine decreased serum ACE by 72% and increased PRA two-fold, without change in plasma levels of Ang II, aldosterone or α-h ANP. The addition of amlodipine to perindopril increased plasma aldosterone 1.7-fold but did not affect serum ACE, PRA, Ang II, or α-h ANP.

These interactions between perindopril and amlodipine may have been conditioned by the specific effects of the therapy first given, as well as by the different circumstances of BP measurement (ambulatory *vs* clinic).

Keywords: amlodipine; perindopril; ACE; PRA; aldosterone; ANP

Introduction

True synergism in clinical anti-hypertensive therapy, over and above a simple additive effect, is not easy to detect reliably. Numerous clinical studies have demonstrated beneficial additive effects between angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists in hypertensive patients.[1–8] However, synergism between these two classes of anti-hypertensive agent is theoretically possible. Potentiation of the calcium antagonist verapamil by the ACE inhibitor enalaprilat has been demonstrated in rats.[9] The anti-hypertensive activity of ACE inhibitors, well known to be enhanced by diuretics, could be potentiated by the natriuretic action of calcium antagonists.[10] A pharmacokinetic interaction is also conceivable whereby, for example, interference with binding to plasma protein or changes in hepatic blood flow due to a calcium channel blocker might alter the bioavailability of ACE inhibitors.

In the present study, an attempt has been made to determine whether a long-active ACE inhibitor and a long-acting calcium antagonist, both given in doses below the dosage generally recommended for a therapeutic effect, can result in a significant anti-hypertensive effect when in combination. Collateral evidence of efficacy at the doses given as well as possible indicators of the mechanism of any drug interaction, was sought by measurement of blood levels of ACE, atrial natriuretic peptide (α-h ANP), plasma renin activity (PRA), aldosterone and angiotensin II (Ang II).

Materials and methods

The study was of a parallel, two-period, placebo-controlled, randomised, double-blind crossover design.

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The study group consisted of 26 patients with moderate essential hypertension treated with an established anti-hypertensive drug regimen that included either an ACE inhibitor or a calcium antagonist, or both. A 4-week run-in period preceded the 8-week randomised study period. At entry to the run-in period, patients receiving any ACE inhibitor had this replaced by perindopril 2 mg/day (Group A); patients receiving any calcium antagonist had this replaced by amlodipine 2.5 mg/day (Group B); other therapy was suspended. Patients receiving both an ACE inhibitor and a calcium antagonist had one or the other suspended and were allocated to either Group A or Group B so as to maintain the size of these groups approximately equal. During the 4-week run-in period, Group A took active perindopril, 2 mg/day and placebo amlodipine, and Group B took active amlodipine 2.5 mg/day and placebo perindopril. Patients did not proceed into the 8-week randomised period unless their supine diastolic blood pressure (BP) was greater than 90 mm Hg and less than 115 mm Hg. Half of Group A was randomised to receive active perindopril 2 mg/day and placebo amlodipine for 4 weeks, followed by active perindopril 2 mg/day and active amlodipine 2.5 mg/day for 4 weeks. The other half of Group A was randomised to receive the same 4-week phases of therapy, but in the reverse sequence. For Group B, half received active amlodipine and placebo followed by active amlodipine and active perindopril, and the other half received the reverse sequence. All medications were taken in a single dose daily either at 08.00 hours or at the end of the clinic visit. Eleven patients of Group A and 10 patients of Group B completed the randomised period.

Five patients were withdrawn from the study, three because of non-qualifying BP values at the end of the run-in period, one because of a side effect (headache) and one because the patient withdrew consent. The study was approved by the institutional ethics committee.

Patients attended clinic between 08.00 and 11.00 hours every 2 weeks during the randomised period. Prior to entry, a complete clinical examination was performed, including a blood count, and measurement of serum electrolytes, creatinine, urate, glucose, cholesterol, triglycerides, protein, bilirubin and transminases. Patients with serum creatinine greater than 0.15 mmol/L or other abnormal biochemical or haematological values were excluded, as were those with secondary hypertension. The biochemical and haematological tests were repeated at week 4 of each of the two randomised phases. Blood (30 ml) was also taken at these times for measurement of serum ACE, plasma ANP, Ang II, aldosterone and PRA. At every clinic visit, BP was measured by an Accoson mercury sphygmomanometer three times each in the supine and the upright posture. Values reported are the mean of the three readings taken by the same observer throughout, which were obtained at the trough of plasma drug concentration. In the week prior to the week 4 visit of both phases, ambulatory and night-time BP was measured by an Accutraker II ABP Monitor (Suntech Medical Instruments Inc; Raleigh NC, USA) at 30 min intervals, over a 23-h period from 09.00 on one day to 08.00 on the next. The 1-h period between 08.00 and 09.00 on the second day was omitted because there was a low rate of data capture in this hour, owing to artefacts and removal of the recorder during travel to the clinic. Analysis of the recordings was in three arbitrary periods of the day: 09.00–15.59 (period a); 16.00–22.59 (period b) and 23.00–07.59 (period c), and systolic and diastolic BP recordings were averaged for each of these three periods. Acceptability of medications was evaluated by recording of spontaneous complaints by the patient and by a general open question at each visit.

All plasma samples from a given patient were included in the same assay batch.

Measurements of PRA, plasma aldosterone and plasma ANP were by radioimmunoassay (RIA), and measurements of serum ACE by radioenzymatic assay. Intra-assay coefficients of variation were in the range 4–7%; other details are reported elsewhere.[11,12] Angiotensin II was determined using RK-A22 I^{125} RIA kit (Buhlmann Laboratories, Allshwill, Switzerland), following extraction on phenyl reverse phase columns (Cat. No. 7095-01, JT Baker, Phillipsberg, NJ, USA); intra-assay coefficient of variation was 8.6% and cross-reactivity of the kit antibody with angiotensin decapeptide was 0.14%. Statistical analysis was by multivariate analysis of variance with repeated measures and was performed using the SAS system (SAS Institute Inc, Cary, NC, USA). Sequence was a covariate in all analyses. The null hypothesis was that the two drugs had the same effect as one drug. Baseline data were analysed by Student's *t*-test. Otherwise paired *t*-tests were used as appropriate.

Results

The characteristics of subjects are shown in Table 1. There were no significant differences between Groups A and B in mean values for age, body weight or BP. Gender distribution was similar. Six patients in Group A were randomised to receive amlodipine placebo from week 0 to week 4 of the first phase and active amlodipine (together with continued active perindopril), from week 0 to week 4 of the second phase. The other five patients in Group A received active amlodipine in the first phase and amlodipine placebo in the second phase. In Group B, five patients were randomised to placebo for the first

Table 1 Characteristics of patient groups at randomisation (week 0)

	Group A	*Group B*
Number of patients	11	10
Gender (male : female)	6 : 5	5 : 5
Mean age (years)	55.3 (2..7)*	55.1 (4.0)
Mean weight (kg)	75.8 (3.1)	77.4 (2.8)
Mean supine blood pressure (mm Hg)		
systolic	148 (2)	151 (4)
diastolic	98 (2)	96 (1)
Anti-hypertensive treatment	perindopril	amlodipine

* s.e.m.

phase followed by active perindopril for the second, and five patients were randomised to active perindopril followed by placebo.

Ambulatory and night-time blood pressure

Figure 1 shows the results of automated BP recordings in the 10 patients of Group A and the nine patients of Group B in whom the monitoring process was satisfactory during both the placebo and active phases. In two patients, data capture was insufficient for analysis. In both groups, there was a significant nocturnal dip, with systolic BP (SBP) and diastolic BP (DBP) lower between 23.00 and 07.59 hours than in the daytime periods. By analysis of variance, in Groups A and B combined the additional drug had no significant effect when all data was used: both groups; periods a, b and c; SBP and DBP. When Group A was analysed separately there was no significant added drug effect. The same result was obtained when SBP and DBP in Group A were analysed separately. When Group B was analysed separately, a drug effect ($P = 0.028$) was found. A significant drug effect was also obtained when SBP or DBP in Group B were analysed separately ($P = 0.027$ and $P = 0.049$, respectively). No sequence effects were found in these analyses.

Clinic blood pressure

In Figure 2 are shown the results for clinic measurements of SBP and DBP in Groups A and B. When these groups were analysed together, using all data for weeks 2 and 4 of each crossover phase (both groups, SBP and DBP – both supine and erect), a significant drug effect ($P = 0.020$) was found. There was no sequence effect. When Group A was analysed separately, there was a significant drug effect ($P = 0.046$); when SBP (supine and erect) was analysed separately, the drug effect was not significant. Separate analysis of supine SBP and erect SBP in Group A showed that the drug effect was significant

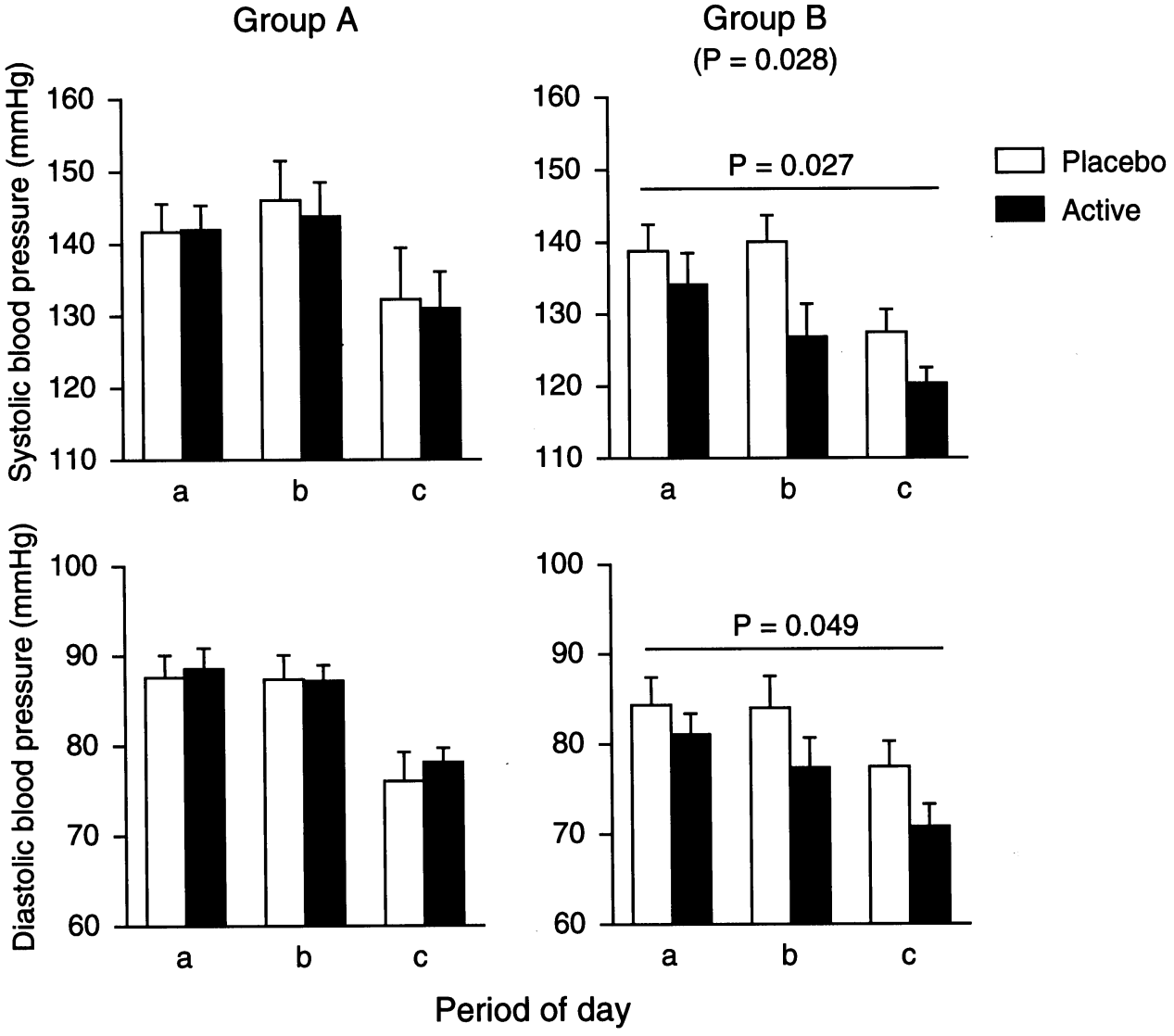

Figure 1 Mean values (s.e.m.) for ambulatory BP (mm Hg) during a 23-h span divided into morning (a), afternoon (b) and night (c) periods (for timing, see text) in Group A patients treated with perindopril + placebo (□) or perindopril + amlodipine (■), and in Group B patients treated with amlodipine + placebo (□) or amlodipine + perindopril (■). Ambulatory BP was measured in the third week of the two 4-week randomised crossover periods.

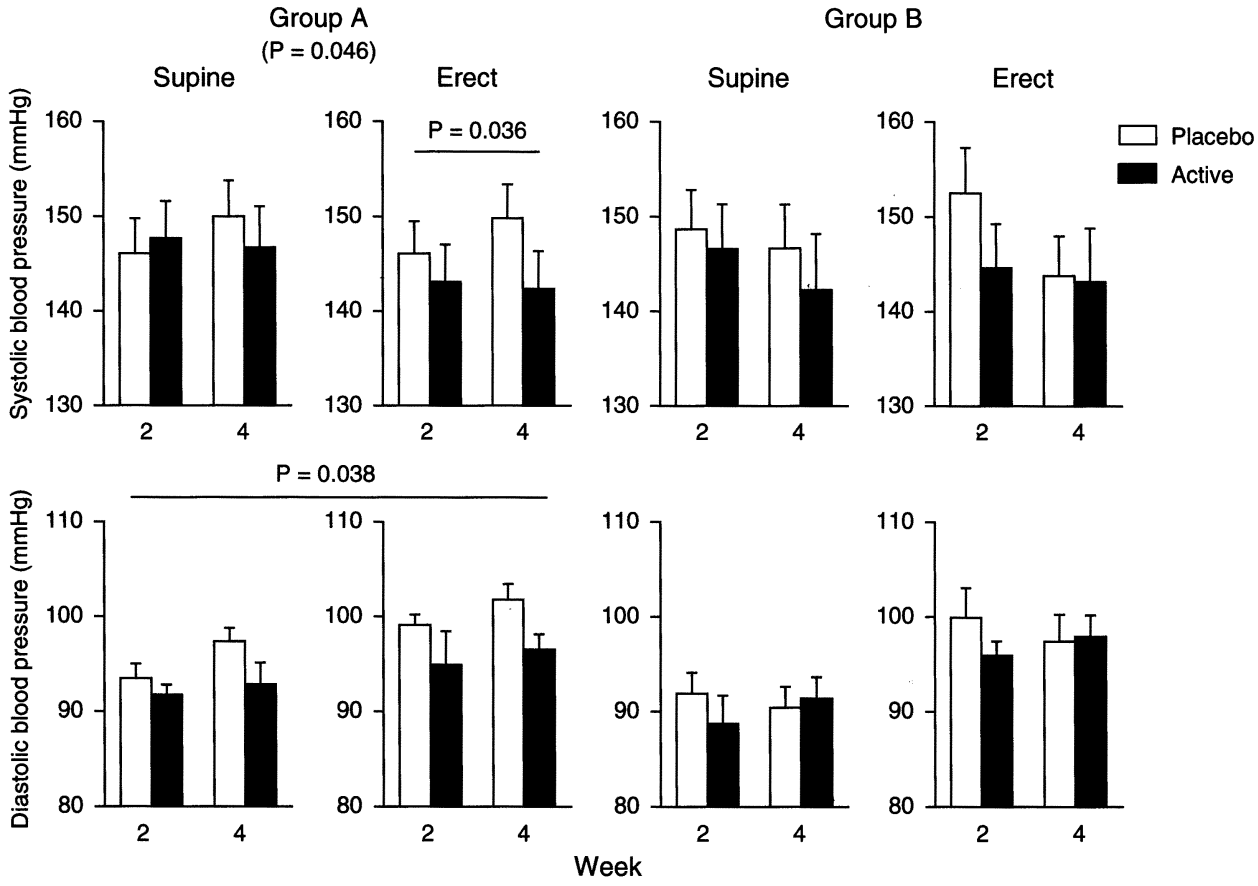

Figure 2 Mean values (± s.e.m.) for clinic BP measurements (mm Hg) at trough (24 h after dosing) in hypertensive patients treated with perindopril to which amlodipine was added (Group A), or amlodipine to which perindopril was added (Group B). (□) treatment with one active drug; (■) treatment with two active drugs. Week 2 and week 4 refer to the second and fourth weeks of the two 4-week randomised crossover periods.

for erect SBP ($P = 0.036$), but not for supine SBP. When DBP in Group A was analysed separately, the drug effect was significant ($P = 0.038$). However, both supine DBP and erect DBP showed drug effects of only marginal significance ($P < 0.07$) separately. When Group B was analysed separately, the drug effect was not significant; also, no significant drug effect was found when SBP and DBP, supine or erect, were analysed separately. There were no sequence effects in either Group.

Hormonal effects (Table 2)

In Group A, the addition of active amlodipine to active perindopril had no significant effect on serum ACE activity. In Group B addition of perindopril to amlodipine resulted in a significant reduction in serum ACE. For PRA the addition of amlodipine to perindopril had no effect, whereas addition of perindopril to amlodipine increased PRA. Addition of amlodipine to perindopril increased plasma aldosterone concentration, whereas addition of perindopril to amlodipine was without such effect. However, the plasma aldosterone levels for the perindopril–amlodipine combination in Group A were not statistically significantly different from the aldosterone levels for combination therapy in Group B. There were no changes in plasma Ang II or in plasma α-h ANP concentration in either Group A or Group B. No significant sequence effects were obtained in analysis of the hormonal data.

No significant changes in heart rate were observed in either group and no side effects attributable to the added active medication were seen in either group.

Table 2 Mean values (s.e.m.) for plasma hormone concentrations and during randomised crossover phases with an additional medication

	Group A		*Group B*	
Phase	1	2	1	2
Medication:				
perindopril	active	active	placebo	active
amlodipine	placebo	active	active	active
Angiotensin-converting enzyme (nmol/mL/min)	25.6 (4.2)	31.6 (4.8)	66.3 (4.5)	18.4* (2.4)
Angiotensin II (pg/mL)	10.1 (2.9)	12.5 (2.9)	9.9 (1.8)	8.5 (2.7)
PRA (ng/mL/h)	2.34 (0.82)	3.22 (1.04)	1.66 (1.45)	3.58* (0.77)
Plasma aldosterone concentration (pg/ml)	244 (29)	425* (86)	305 (41)	314 (45)
Plasma α h-ANP concentration (pg/mL)	51.0 (7.4)	42.5 (5.5)	74.5 (12.8)	68.4 (15.3)

* Phase 2 significantly different from phase 1 ($P < 0.02$).

Discussion

Previous studies have indicated that perindopril 2 mg once daily and amlodipine 2.5 mg once daily are sub-therapeutic or minimally effective dosages of these drugs as single-agent therapy for hypertension. In a dose-response study of perindopril,[13] a dose of 2 mg/day given for 12 weeks to 62 patients with essential hypertension produced changes at trough (24-h post-dose) in SBP and DBP, respectively, of –2.7 and –4.5 mm Hg. These changes were not significantly different from the corresponding effects of placebo (–0.7 and –1.8 mm Hg), whereas the changes with 4, 8 or 16 mg/day were greater than with placebo. In this study, 6-h post-dose measurements were also made, and again showed changes in SBP and DBP (–7.2 and –7.5 mm Hg) with the 2/mg/day dose which were not significantly different from placebo (–4.8 and –2.9 mm Hg, respectively). Other dose-response studies with perindopril[14] have also shown minimal anti-hypertensive effects with the 2 mg of dose, of borderline significance.

In a dose-response study of amlodipine,[15] 2.5 mg/day given for 4 weeks to 46 patients with essential hypertension produced changes at trough in supine SBP and DBP of –10.1 and –6.4 mm Hg, respectively. These changes were greater than those with placebo (–4.1 and –3.6 mm Hg) and the differences were of borderline significance ($P < 0.05$). Amlodipine 5 mg/day produced changes of –17.1 and –9.1 mm Hg, respectively, which were highly significant ($P < 0.001$) against placebo. A recent review has reported that the minimum effective dose of amlodipine is 2.5 to 5 mg/day.[16]

In the present study, we did not obtain data for the anti-hypertensive effects of either perindopril or amlodipine alone, for the patients included were receiving sustained therapy with one or the other of these drugs at the time of their study entry. Instead, we determined the effects of adding one drug to the other when both were given in borderline sub-therapeutic dosages. As the doses of drugs used were low and the numbers of available subjects rather small, a parallel, two-period, crossover design was employed so as to optimise the power of the study. However, it is acknowledged that more reliable results would have been expected from a larger study group.

We found that ambulatory BP was decreased when perindopril was added to amlodipine, but not when amlodipine was added to perindopril. These results could simply reflect more effective reduction of BP by 2 mg perindopril than by 2.5 mg amlodipine. However, the possibility must be considered that the interaction between perindopril and amlodipine was determined by baseline therapy.

The addition of perindopril to amlodipine decreased ACE activity and produced a reflex increase in PRA[17] together with a fall in ambulatory BP. Plasma AII did not fall. However, it is well known that immunoreactive Ang II levels fail to decrease after ACE inhibition; the reasons include reflex rise in angiotensin decapeptide (together with the minor cross-reactivity of the assay antibody for the decapeptide), cumulation of angiotensin metabolites and generation of true Ang II by ACE-independent pathways.[18,19]

By contrast, the addition of amlodipine to perindopril increased plasma aldosterone, which could have tended to counter any anti-hypertensive effect the combination may otherwise have had. The mechanism of the aldosterone increase in Group A is unknown. There is considerable evidence that amlodipine alone does not influence plasma aldosterone[16,20] suggesting that the effect of amlodipine observed in Group A was dependent upon pre-existing ACE inhibition. A potential pharmacokinetic explanation is that amlodipine, which has a high affinity for protein,[21] might have displaced perindoprilat by non-specific binding to ACE. In that case, circulating and tissue ACE would increase, with a concomitant increase in adrenocortical ACE, AII and aldosterone production, explaining the observed rise in plasma aldosterone. Against this possibility is that serum ACE was not found to be significantly increased in Group A at trough (24–27 h after the last dose of amlodipine), although it is conceivable that it was increased at peak during the ambulatory BP recording.

Whatever the mechanism, our data are consistent with the hypothesis that the interaction was dependent on the pre-existing therapy. It would be of interest to formally test this hypothesis in a four-period crossover design in order that the different interactions (perindopril added to amlodipine and amlodipine added to perindopril) could be studied on ambulatory BP in the same subjects.

Contrasting results were obtained with regard to the effects of adjunctive therapy on BP measured at the clinic visits. The addition of perindopril to amlodipine had no effect on clinic BP values, either in the supine or erect posture. These observations could simply relate to an insufficient duration of action of the 2 mg dose of perindopril given 24–27 h earlier, for 4 mg is the lowest dose that has been shown to have a clear BP lowering effect 24 h after administration.[13,22] However, inspection of the time block of ambulatory BP from 23.00–07.59 h (Figure 1: Group B, block c) suggests that there was no diminution in the hypotensive effect in the period immediately prior to the clinic visits. Therefore, the possibility remains that the sympathetic neural activation implicit in waking, rising and travelling to the clinic may have overcome any residual effect of perindopril; such an effect may have been well maintained during sleep because of interaction between the ACE inhibitor and the known heightened activity of the renin-angiotensin system during rapid eye movement (REM) sleep.[23]

Conversely, the addition of amlodipine to perindopril produced a fall in erect BP at clinic, but had no effect on ambulatory BP. Apart from the fact that clinic BP values were higher than ambulatory, there is no ready explanation for this apparent anomaly. Thus, we speculate that there may have been a clinic component to BP, perhaps expressing higher sympathetic nervous activity and vascular resistance in the morning hours,[24] which was more effectively reduced by amlodipine than by perindopril.

Chronic ACE inhibition has been reported to lower plasma ANP in normal volunteers[25] and in patients with essential hypertension.[26] Calcium antagonists can lower initially elevated levels of plasma ANP in spontaneous hypertensive rats (SHR)[27] and in patients with severe or diabetic hypertension.[28,29] For neither Group A nor Group B of the present study was there a significant decrease in plasma ANP upon addition of the second active agent (amlodipine or perindopril, respectively). However, such a response could have been pre-empted by a long-term effect of baseline therapy.

In conclusion, perindopril, 2 mg/day, can be shown to be an effective adjunct to treatment with amlodipine, 2.5 mg/day, or *vice versa*, when different methods and timing of BP measurement are taken into account. With perindopril, the adjunctive benefit was evident with ambulatory BP monitoring between doses but not with clinic BP readings taken at trough. With amlodipine the converse was observed. No evidence was obtained from the present study to indicate that benefit was other than an additive effect. However, our findings highlight the point that ambulatory BP and clinic BP provide quite different types of information about response to anti-hypertensive drugs or their interaction.

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