A comparative study of atenolol, nifedipine and their combination in the treatment of hypertension

D. H. G. SMITH, J. M. NEUTEL, D. JANKELOW, J. J. L. PRETORIUS, D. P. MYBURGH

Summary

The antihypertensive effects, as assessed by clinical and ambulatory blood pressure measurement, of nifedipine slow-release (SR), atenolol and the two in combination were evaluated in 28 known hypertensives in a placebo-controlled, double-blind, randomised cross-over trial. Clinical blood pressure was significantly lower on combination therapy ($P < 0,025$) than on either agent alone, although all therapeutic agents reduced blood pressure significantly when compared with placebo ($P < 0,01$).

All ambulatory blood pressure measurements obtained on any therapeutic agent were significantly lower than those obtained on placebo ($P < 0,01$). The mean daytime (08h00 - 17h00) ambulatory blood pressure measurement as well as the percentage of this monitoring period during which patients were hypertensive were significantly lower ($P < 0,01$) on combination therapy than on nifedipine SR. A similar pattern was observed for 24-hour ambulatory blood pressure measurements. Headache was the most significant adverse effect. This was most common with nifedipine SR, less common with combination therapy and least common with atenolol.

Combination therapy with nifedipine SR and atenolol is therefore a viable therapeutic alternative in the treatment of patients with benign essential hypertension.

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The dihydropyridine calcium-channel blocker nifedipine is gaining increasing acceptance as providing an alternative therapeutic approach in the treatment of hypertension when used alone[1-5] or in combination with other antihypertensive agents.[3,6-13] This trend has been enhanced because of recent suspicions that the adverse effects of diuretics and β-adrenergic blocking agents may outweigh the cardioprotective effects of blood pressure reduction.[14,15] Furthermore, by administering small doses of two antihypertensive agents the synergistic action of the two drugs may provide clinically worth while additional antihypertensive effects in patients who respond inadequately to either drug alone,[3,6,8,10,12,13] and studies have indicated that side-effects secondary to the vasodilatory properties of calcium-channel blocking agents can be reduced by combining the calcium antagonist with a β-blocker.[16]

This study was conducted to compare the antihypertensive efficacy, as assessed by office (casual) and ambulatory blood pressure measurements, and the symptomatic tolerability of the cardioselective β-adrenergic blocker atenolol and the calcium antagonist nifedipine slow-release (SR) when used alone and in combination.

Department of Cardiology, Institute for Aviation Medicine, Verwoerdburg, Tvl
D. H. G. SMITH, M.B. B.CH.
J. M. NEUTEL, M.B. B.CH.
D. JANKELOW, M.B. B.CH.
J. J. L. PRETORIUS, M.B. CH.B.
D. P. MYBURGH, M.SC., M.B. CH.B., DIP. A.C.P., F.A.C.C.

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Material and methods

Thirty white patients (28 males and 2 females) with a mean age of 44 years (range 19 - 60 years) were studied in a placebo-controlled, double-blind randomised trial. All were known hypertensives. After informed consent had been obtained from each patient and a 12-lead ECG and routine biochemical and haematological tests had been assessed as normal, all those with World Health Organisation class I and II essential hypertension were placed on placebo for a 2-week run-in period. After this all patients had their blood pressure measured in the sitting position with a mercury sphygmomanometer after 5 minutes of rest. Two measurements 2 minutes apart were made and all those with a diastolic blood pressure mean (Korotkoff phase V) above 100 mmHg but below 120 mmHg were randomised to one of three treatment regimens.

The regimens consisted of: (*i*) nifedipine SR 20 mg twice daily; (*ii*) atenolol 50 mg once daily; and (*iii*) a combination of the two (nifedipine SR 20 mg plus atenolol 50 mg) once daily. After another 2-week period patients returned for blood pressure measurement as described above. All those with a mean diastolic blood pressure above 95 mmHg had their respective doses increased to nifedipine SR 40 mg twice daily, atenolol 100 mg once daily, or the combination of nifedipine SR 20 mg and atenolol 50 mg twice daily. Each treatment regimen lasted for 1 month and each was intercalated with a 1-week wash-out period on placebo before the next random phase was started. The sequence of events was repeated for all three treatment regimens. The placebo and all the drugs were presented in identical capsules, and patient compliance was assessed by capsule counting.

At the end of the placebo run-in period and at the end of each of the three treatment phases each patient was subjected to 24-hour ambulatory blood pressure monitoring using the ICR Spacelabs 5200 system. Blood pressure was recorded automatically and non-invasively at half-hourly intervals between 06h00 and 00h00 (midnight) and at hourly intervals between 00h00 and 06h00. Readings were then averaged per hour for the 24-hour period for the purpose of analysis. Missing values were ignored and unrealistic values were edited out. Each machine was checked for accuracy at the beginning of each monitoring period and all patients were instructed to continue with their normal daily activities.

Adverse effects were assessed by direct questioning at each visit and answers were recorded on a standard form of analysis. Three methods of adverse effects analysis were used. At each visit each patient was asked to give a health rating using a score of 1 for very well, 2 for well, 3 for neutral, 4 for unwell and 5 for very ill. Each was also asked if they thought the medication had agreed with them and whether they had developed any symptom that in their opinion was a direct result of taking the medication.

Statistical analysis of all blood pressure data and health scores was done using an analysis of variance with allowance for multiple comparison between groups by comparing the difference between means with the standard error of the difference

as computed from the 'within' variance value. Adverse effects were analysed by a chi-square test using Yates's correction where appropriate. Results are quoted as mean ± standard error. All results are rounded off to the nearest unit. A P value of $< 0,05$ was regarded as significant.

Results

Twenty-eight of the 37 patients recruited for the study completed all three treatment regimens. One patient was withdrawn because of intolerable headaches while taking nifedipine SR and 1 was transferred away from the trial centre. The remaining 7 withdrawals were for protocol violations (poor compliance or not keeping appointment dates).

Clinical measurements of blood pressure

Medication versus placebo (Table I). Each agent produced significant reductions in blood pressure, as assessed clinically at week 2, when compared with measurements on placebo. Twelve patients on nifedipine SR and 12 on atenolol were considered hypertensive after 2 weeks of therapy, while 8 were considered hypertensive on the combination therapy. In each of these cases the respective dosage was doubled, leading to further reductions in blood pressure. On completion of therapy (week 4) all agents had produced significantly lower blood pressure than that measured on placebo, while 2 and 4 patients and 1 patient were still hypertensive on nifedipine SR, atenolol and combination therapy, respectively.

Nifedipine SR v. atenolol. No significant differences were observed after 2 or 4 weeks of therapy when nifedipine SR was compared with atenolol.

Combination therapy v. nifedipine SR alone or atenolol alone. No significant differences were noted between combination therapy and either agent alone after 2 weeks of therapy. Once respective dosages had been doubled in those patients who were still hypertensive after the 2 weeks of therapy, the mean blood pressure for the group and for patients who were hypertensive at week 2 was significantly lower on combination therapy than on either agent alone ($P <$ 0,025).

Ambulatory measurements of blood pressure. The highest ambulatory blood pressure levels were generated during the day (08h00 - 17h00) in each patient's normal working environment, while the mean obtained by averaging pressures over the 24-hour period was significantly lower ($P < 0,01$). This could be attributed to the diurnal rhythm of blood pressure, which falls at night during sleep.[17,18] To assess the antihypertensive efficacy of the respective agents with ambulatory blood pressure monitoring we used the daytime mean and the 24-hour mean as well as an analysis of the number of hours (expressed as a percentage of the daytime and 24-hour monitoring periods) during which each patient could be considered hypertensive (diastolic blood pressure > 95 mmHg).

Daytime ambulatory blood pressure (Table II). All agents produced significantly lower systolic blood pressures than that measured on placebo. Diastolic blood pressures achieved with atenolol and combination therapy were significantly lower than the corresponding blood pressure on placebo

TABLE I. CLINICAL MEASUREMENTS OF BLOOD PRESSURE (mmHg) (MEAN ± SE)

	Placebo	Nifedipine SR	Atenolol	Combination
BP after 2 wks therapy	**148 ± 3/102 ± 1**	**137 ± 2/91 ± 2**	**135 ± 3/90 ± 2**	**134 ± 3/88 ± 2**
Subjects hypertensive at 2 wks	**28**	**12**	**12**	**8**
Mean BP of hypertensives		**143 ± 3/99 ± 1**	**148 ± 4/100 ± 2**	**145 ± 3/100 ± 2**
BP after doubling dose (4 wks)		**137 ± 3/90 ± 2**	**142 ± 5/93 ± 4**	**117 ± 4/80 ± 4***
Subject hypertensive at 4 wks		**2**	**4**	**1**
BP after 4 wks therapy (whole group)		**128 ± 2/88 ± 2**	**126 ± 3/88 ± 2**	**119 ± 3/82 ± 2***

All BP results are significantly lower than placebo.
*BPs significantly lower than nifedipine SR or atenolol ($P < 0,025$).
BP = blood pressure.

TABLE II. DAYTIME (08h00 – 17h00) AMBULATORY BLOOD PRESSURE RESULTS (mmHg) (MEAN ± SE)

	Placebo	Nifedipine SR	Atenolol	Combination
Daytime BP measurements	**150 ± 2/97 ± 2**	**141 ± 2/93 ± 2**	**133 ± 3/89 ± 2****	**131 ± 3/86 ± 2****
% of period hypertensive	**60 ± 7**	**42 ± 7**	**30 ± 5****	**17 ± 4****
Subjects hypertensive on mean measurement	**16**	**10***	**6****	**3****

* Measurements not significantly lower than placebo ($P > 0,05$).
** Measurements significantly lower than nifedipine SR ($P < 0,025$).
BP = blood pressure.

and nifedipine SR but were not significantly different from each other. The mean proportion of this monitoring period during which each patient could be considered hypertensive was significantly reduced on all agents, with combination therapy improving significantly on nifedipine SR alone but not on atenolol. When considering the daytime ambulatory mean blood pressure the number of patients considered hypertensive was significantly lower among those taking atenolol and combination therapy than those on placebo or nifedipine SR.

Twenty-four-hour ambulatory blood pressure (Table III). Similar results were achieved with 24-hour ambulatory blood pressure assessment. When considering mean 24-hour blood pressure and proportion of the monitoring period during which each patient could be considered hypertensive, all agents were significantly better than placebo while combination therapy was also significantly better than nifedipine SR alone. Interestingly, no agent improved on placebo when considering the number of patients with a hypertensive 24-hour mean ambulatory BP.

Adverse effects

Since each patient was questioned twice (at weeks 2 and 4) during each therapeutic arm of the trial a total of 56 adverse effects assessments were analysed for each therapeutic agent. These were compared with each other and with the adverse effects assessments made at the end of the placebo run-in phase.

Mean health score on placebo (2,2 ± 0,2) was not significantly different from that on any of the other agents (1,9 ± 0,1 on nifedipine SR and atenolol; 1,7 ± 0,1 on combination therapy). The majority of patients on each agent felt that the medication agreed with them (77% for placebo, 82% for nifedipine SR, 88% for atenolol and 98% for the combination therapy), but no significant differences existed.

The most common symptomatic adverse effect recorded was headache (27% for placebo, 50% for nifedipine SR, 16% for atenolol and 22% for the combination therapy). Our results show that headache was more common on nifedipine SR alone ($P < 0,01$), while no other significant comparisons were noted. Other adverse effects are listed in Table IV, but no significant differences were detected.

Discussion

With increasing concern over the role of diuretics in the development of coronary artery disease,[14] β-adrenergic blockers are being advocated increasingly as first-line monotherapy in the treatment of hypertension.[19] For patients who require additional antihypertensive therapy, the traditional stepped-care approach recommends that a vasodilatory agent be added.[19] Since 1982[8] it has been demonstrated that nifedipine SR is an effective vasodilatory agent that can be combined safely with atenolol. Further studies[12,13] have indicated that atenolol and nifedipine SR used in combination give enhanced control of blood pressure, especially in patients who respond inadequately to either agent alone. The results of this study are comparable. While nifedipine SR and atenolol are individually effective in controlling blood pressure, clinical measurements of blood pressure showed combination therapy to produce significantly lower casual blood pressure than either agent alone.

Ambulatory blood pressure monitoring was used in this study because none of the major clinical studies concerning atenolol and nifedipine used in combination for the treatment of hypertension have made use of this device.[6,8,13] The obvious benefit of using ambulatory blood pressure monitoring in this study is that it generates more observations over an extended period of time, involving the patient's place of work, home and sleep. Studies[20–22] claim that mean 24-hour and daytime

TABLE III. TWENTY-FOUR-HOUR (08h00-07h00) AMBULATORY BLOOD PRESSURE RESULTS (mmHg) (MEAN ± SE)

	Placebo	Nifedipine SR	Atenolol	Combination
24-hour BP measurements	**139 ± 2/90 ± 2**	**131 ± 2/85 ± 2**	**126 ± 3/83 ± 2**	**124 ± 2/80 ± 1****
% of period hypertensive	**37 ± 4**	**26 ± 4**	**20 ± 3**	**13 ± 3****
Subjects hypertensive on mean measurement	**4**	**2***	**1***	**0***

* Measurements not significantly lower than placebo ($P < 0,05$).
** Measurements significantly lower than nifedipine SR ($P < 0,01$).
BP = blood pressure.

TABLE IV. ADVERSE EFFECTS (% OF PATIENTS)

	Placebo	Nifedipine SR	Atenolol	Combination
Headache	**27**	**50**	**16**	**22**
Tiredness	**–**	**–**	**9**	**2**
Oedema	**–**	**4**	**–**	**–**
Flushing	**–**	**4**	**–**	**2**
Impotence	**–**	**–**	**4**	**5**
Dizziness	**2**	**–**	**–**	**2**
Palpitations	**4**		**–**	**2**
Dreams	**–**	**–**	**2**	**–**

ambulatory blood pressure correlates more closely with the degree of hypertensive target organ damage than does casual blood pressure. Because blood pressure falls at night during sleep,[17,18] the 24-hour mean and thus the percentage of time that patients can be considered hypertensive will be falsely low if conventional diastolic blood pressures are used as the hypertensive cut-off point. This will continue to be a problem until 'normal' 24-hour ambulatory blood pressure values are obtained from normotensive patients. The use of daytime (or awake) values solves this problem partly because it is easily agreed upon that the majority of these blood pressure readings should ideally be lower than the conventional diastolic blood pressure cut-off value for hypertension.

The ambulatory daytime measurements revealed that atenolol and nifedipine SR control blood pressure independently and that the combination of the two agents produces lower blood pressure than nifedipine SR alone. The same can be said for the percentage of the monitoring period during which patients could be considered hypertensive and for the number of patients who had a hypertensive mean daytime ambulatory blood pressure. Despite the difficulty in interpreting 24-hour ambulatory blood pressure results, a similar pattern is observed.

While the side-effect of headache was a problem when patients took nifedipine SR alone, it was significantly less of a problem on atenolol alone and on combination therapy, indicating that this specific adverse effect of nifedipine SR is indeed attenuated by the addition of atenolol.

In conclusion, this study demonstrates that while nifedipine SR and atenolol were individually effective in controlling hypertension in the majority of patients, the combination therapy produced significantly lower clinical and ambulatory blood pressure measurements and was more effective in hypertension control as assessed by the number of patients with a diastolic blood pressure below 95 mmHg.

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