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Comparison of the efficacy and acceptability of nicardipine and propranolol, alone and in combination, in mild to moderate hypertension

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1 We evaluated the relative efficacies and tolerability of various low-dose combinations of nicardipine and propranolol in patients with mild–moderate essential hypertension (DBP Phase V of >90–125 mmHg; WHO Grades I and II) in order to select the best one.
2 Sixty patients completed the double-blind, balanced, randomised three-way cross-over protocol, with each phase lasting 4 weeks, and in which twice daily nicardipine 40 mg or propranolol 80 mg was compared with four twice daily combinations of nicardipine (20 or 30 mg) plus propranolol (40 or 80 mg).
3 At 'peak' effect time (i.e., 2 h post-dosing) all four treatment combinations were significantly more effective than propranolol, with effects ranging from 9–23 mmHg (systolic) and 5–15 mmHg (diastolic). Only the two 30 mg nicardipine combinations with propranolol were more effective than nicardipine monotherapy, further reducing BP by 8–13 mmHg (systolic) and 5–7 mmHg (diastolic); there were no significant differences between them.
4 'Trough' diastolic pressures were not different between treatments and 'trough' BP control was sub-optimal on all treatments.
5 70% of patients on nicardipine monotherapy, 33% of those on propranolol monotherapy and 30% of patients during the placebo run-in complained of symptoms. In terms of complaint rates, there was little to choose between the four combinations (27–33%). Serum potassium and creatinine levels were elevated following propranolol monotherapy by 0.19 mmol l^{-1} and 6.5 μmol l^{-1} respectively ($P < 0.01$ for both) and following the nicardipine 30 mg/propranolol 80 mg combination. Nicardipine monotherapy elevated serum T_4 levels by an average of 0.57 ng dl^{-1} ($P < 0.05$).
6 The twice daily combination of nicardipine 30 mg plus propranolol 40 mg was therefore the optimum one in terms of its efficacy and tolerability. Further studies need to be performed to test the hypothesis that a higher dose of propranolol might ameliorate troublesome vasodilator side effects. However, none of the treatments studied was ideal for clinical use in the twice daily dosage used in this study.

Keywords nicardipine propranolol combination therapy hypertension

Introduction

In hypertension, the simultaneous administration of two classes of drug is one rational and increasingly popular strategy for optimising therapeutic effect yet minimising side effects. The combination of a calcium antagonist with a β-adrenoceptor blocker has the advantage that although both are effective antihypertensive drugs their modes of action are different and in some respects complementary. The β-adrenoceptor blocker, for example, will modulate any calcium antagonist-induced acute reflex increase in sympathetic activity and, conversely, the calcium antagonist might offset the peripheral vasospasm and drop in cardiac output caused by the β-adrenoceptor blocker, thus reducing the overall burden of side effects. Patient acceptability would thereby be enhanced. This is one key to securing better long-term compliance with therapy and thus to more effective long-term blood pressure control.

Combinations of nifedipine (Yagil *et al.*, 1983) or nitrendipine (de Divitiis *et al.*, 1985) with a β-adrenoceptor blocker have been shown to provide effective antihypertensive treatment. Indeed, greater reductions in blood pressures (BP) can be achieved by the concomitant use of nifedipine and atenolol than with either drug alone, despite reduced doses of each (Nifedipine – Atenolol Study Review Committee, 1988). Their simultaneous use may also result in fewer side effects (Maclean *et al.*, 1988a).

In this present study, the combination of nicardipine, a recently introduced dihydropyridine calcium antagonist, which acts principally via vascular smooth muscle as an arteriolar dilator (Takenaka *et al.*, 1976), with propranolol, a widely used lipophilic non-selective β-adrenoceptor blocker (Prichard & Gillam, 1969), was assessed in mild–moderate essential hypertension. Propranolol was chosen rather than a β_1-selective adrenoceptor blocker for commercial reasons of availability related to the possible development of a nicardipine-β-adrenoceptor blocker combination product.

Our aims were threefold:

1) to evaluate the relative efficacies and patient tolerability of various low-dose combinations of nicardipine and propranolol,
2) to assess the value of these combinations relative to an effective dose of either drug alone, and
3) to select the combination which maximised the therapeutic ratio and so seemed to be the one most suitable for further development as a fixed-dose combination.

Methods

Males and females aged 21–70 years, attending the Hypertension Clinic of Ninewells Hospital, were studied if they had a history of non-labile essential hypertension (WHO Grades I-II) and were suitable for treatment with either a calcium antagonist or a β-adrenoceptor blocking drug.

Exclusion criteria were: previous intolerance to or lack of antihypertensive efficacy of any β-adrenoceptor blocker or calcium antagonist; the standard accepted clinical contraindications to the use of either drug; 'sick sinus' syndrome, AV block or cardiac dysrhythmias; myocardial infarction within the previous 6 months; congestive heart failure and any other serious physical or mental illness.

After withdrawal of any previous antihypertensive therapy (Table 1) patients entered an initial 2–4 week placebo period to confirm the stability of their hypertension and to permit washout of previous drugs before active study medication was started.

Table 1 Previous antihypertensive therapy

Previous therapy	n
None	3
Diuretic	5
β-adrenoceptor blocker	3
Diuretic + β-adrenoceptor blocker	14
β-adrenoceptor blocker + calcium antagonist	19
Diuretic + β-adrenoceptor blocker + calcium antagonist	3
Diuretic + β-adrenoceptor blocker + ACE-inhibitor	4
Diuretic + β-adrenoceptor blocker + hydralazine	3
ACE-inhibitor	3
ACE-inhibitor + diuretic	1
ACE-inhibitor + β-adrenoceptor blocker	2

Study design

At the end of each 4 week treatment phase all patients were studied immediately before their morning doses of medication (i.e. 'trough' assessment at 12 h after their evening doses) and again 2 h later (i.e. approximately at 'peak' effect). Blood pressures were measured in the same arm on each occasion by one observer, using a Hawksley random-zero sphygmomanometer. Two readings were taken after 5 min sitting at rest and again after standing erect for 2 min. The pulse rate was measured over 30s after each BP reading. Body weight was also measured at each visit.

At each clinic visit all spontaneously volunteered side-effects were recorded, together with those assessed by indirect questioning, i.e. 'how have you felt' and direct questioning on certain calcium antagonist-related symptoms, namely flushing, palpitations, dizziness and faintness, but not oedema.

Blood and urine were collected pre-trial, at the end of the placebo phase and at the end of each treatment phase for haematology, clinical chemistry screening and urinalysis.

All patients gave their written informed consent to participate in the study which were approved by the Committee on Medical Ethics of the Tayside Health Board and performed in accordance with the Declaration of Helsinki and its subsequent amendments.

Nicardipine capsules, propranolol tablets and matching placebo capsules and tablets were all dispensed in individual bottles. The double dummy technique was used to maintain 'blinding'. Return medication was counted at each visit.

Once their mean sitting diastolic BP was stable (variation between 0–2 or 2–4 weeks of < 10 mmHg), 60 patients with a mean (two readings) sitting diastolic BP (DBP) of > 95–125 mmHg (Phase V) at the end of the placebo run-in period entered and were able to complete all three active treatment phases, which utilised a randomised, double-blind 3-way cross-over design, each phase having a duration of 4 weeks. The following twice daily combination treatments were compared:

N40	:Nicardipine 40 mg + placebo propranolol
P80	:Propranolol 80 mg + placebo nicardipine
N20 P40	:Nicardipine 20 mg + propranolol 40 mg
N30 P40	:Nicardipine 30 mg + propranolol 40 mg
N20 P80	:Nicardipine 20 mg + propranolol 80 mg
N30 P80	:Nicardipine 30 mg + propranolol 80 mg

No placebo 'treatment' phase was included in the randomised part of the study design in order to limit its complexity and because it was assumed at the start that all treatments would be effective. We sought information on the basis of between treatment comparisons.

The study design is shown in Figure 1.

A conventional study design with six parallel limbs would require approximately 300 patients in order to give a probability of 96% of detecting a difference of 10 mmHg in sitting diastolic BP between the treatment options at the 5% level of significance based on an assumed 'within patient' s.d. of 8 mmHg. The present study design was selected because it enabled the comparison of multiple treatment options with the same power yet without the necessity to resort to such large numbers of patients.

Each patient received either the nicardipine

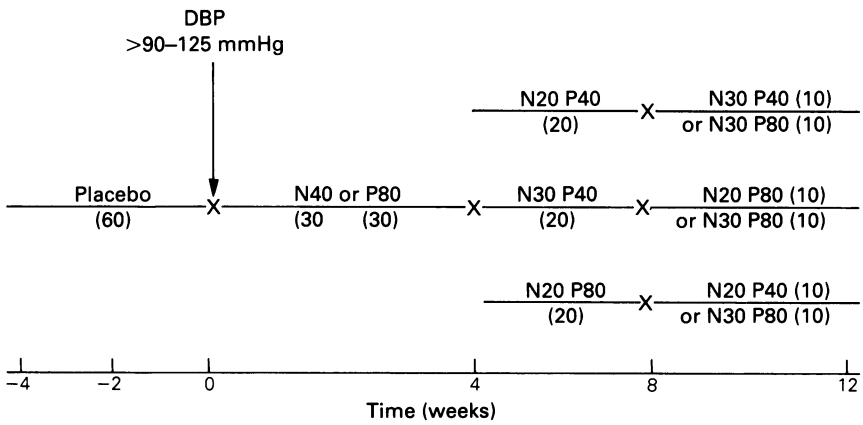

Figure 1 Study design. N.B. 1. The order of administration of all active treatments (including N40 or P80) was randomised for each treatment sequence. 2. The number of patients in each treatment group is indicated in brackets.

monotherapy or the propranolol monotherapy as one of their three active drug phases; in their other two phases they received two of the four combinations. This gave 72 possible treatment sequences, of which 60 were chosen so that each treatment would occur 10 times in each treatment phase (Figure 1). The 60 sequences were randomly assigned to the patients.

Statistical analysis

A 'within patient' analysis was performed separately for both the pre-dose and the post-dose haemodynamic data, by fitting a linear model (McCullagh & Nelder, 1983) which assumed that the effects of 'patient' and treatment (including the initial run-in on placebo) were additive. Treatment means were adjusted to take account of the fact that each patient did not receive all of the treatment options. Two-tailed *t*-tests were used for the following comparisons: (1) for pre-dose ('trough' effect) data, all six active treatments versus the effect of the initial placebo; (2) for pre-dose data both monotherapies versus each of the four combinations plus each combination *vs* each other combination which included a component of the same dose, and (3) as in (1) and (2) above, but for post-dose ('peak' effect) data. Phase effects, carry-over effects from the previous treatment, and the interaction between treatment and phase effects were investigated by adding these factors to the original model.

'Safety' blood parameters were analysed in a similar manner, with, in some cases, refinements as necessary. All treatments were compared against pre-trial values of these parameters using two-tailed *t*-tests. Analysis of co-variance, with the doses as co-variates, was used to investigate any dose response.

Results

Sixty-seven patients (33 male) initially entered the placebo run-in phase of the study. Seven were withdrawn at the end of this phase because of BP readings consistently outside the limits necessary to permit their inclusion in the randomised cross-over phases. Another two patients, both of whom were subsequently found to have been randomised first to N40 monotherapy twice daily, withdrew very early during that first phase, one who was side effect free for personal reasons unrelated to the study, the other because of severe vasodilator related side effects. Without breaking the 'blinding' of the trial, these two patients were therefore replaced with two others who then received all three of the same intended treatments. Only results from the 60 patients who completed all three phases of the study (the 58 randomised as initially planned and the two replacements for the two dropouts during the first randomised phase) were statistically analysed. The 30 males who completed the study had an average age of 53 years, height 172 cm and weight 84 kg. The 30 females had an average age of 51 years, height 160 cm and weight 66 kg.

The mean ± s.d. sitting BP at the end of the placebo run-in period was 177 ± 26/110 ± 9 mmHg. All six treatments, with the one exception of 'trough' erect DBP following N40 monotherapy ($P < 0.05$), both clinically and statistically ($P < 0.01$) significantly reduced BP relative to the initial end-placebo sitting (Figure 2) and standing values, as shown in Table 2. On no occasion were the carryover effects or the treatment-phase interactions statistically significant. The phase effects were, however, statistically significant for some BP parameters, but the effects were small relative to the overall effect, ranging between 0 and 6 mmHg.

'Trough' effects

A comparison of 'trough' BPs at the end of each treatment phase against the run-in placebo phase (Table 2) revealed that all treatments significantly reduced sitting BP by between 8–16 mmHg (systolic) and 5–11 mmHg (diastolic) (Figure 2). There were, however, only minor differences between the effects of each active treatment, ranging between 5 and 8 mmHg.

Pre-dose ('trough') erect systolic BP (SBP) was statistically significantly reduced by all the active treatments by between 10–17 mmHg and DBP by between 2 and 11 mmHg (not significant for N40 only). Again there were some differences between individual treatment effects, but these were small, ranging between 6–9 mmHg.

N40 had no effect on 'trough' sitting or erect heart rate relative to the placebo washout period. P80 and all propranolol combinations significantly reduced 'trough' heart rate by between 10 and 15 beats min^{-1} (sitting) and 12–16 beats min^{-1} (erect). There were only minor differences between the effects of these five treatments.

'Peak' effects

BP and heart rate 2 h after dosing with each treatment are also shown in Table 2.

The four treatment combinations were significantly more effective than P80 alone in reducing sitting (Figure 2) and erect BP 2 h post-dose

Table 2 Haemodynamic response pre- and 2 h post-dose : comparison of each treatment against placebo

		Placebo	*N40*	*P80*	*N20*	*P40*	*N30*	*N20*	*P80*	*N30*
Number of patients		60	30	30	30		30	30		30
Sitting										
SBP	Pre	177(170,184)	−10(−16,−4)	− 9(−14,−3)	− 8(−14,−2)		−12(−18,−6)	−16(−21,−10)		−12(−18,−6)
	Post		−34(−40,−28)	−24(−30,−18)	−33(−39,−27)		−42(−48,−36)	−35(−41,−29)		−44(−50,−38)
DBP	Pre	110(107,112)	− 5(−8,−2)	− 8(−11,−5)	− 6(−9,−3)		− 8(−11,−5)	−11(−14,−8)		−11(−14,−7)
	Post		−22(−25,−18)	−15(−18,−11)	−20(−24,−17)		−27(−30,−23)	−23(−26,−19)		−28(−32,−25)
HR	Pre	80(78,83)	0^{NS}(−3,+3)	−13(−16,−10)	−12(−16,−9)		−10(−13,−7)	−14(−17,−11)		−15(−18,−12)
	Post		+10(+7,+13)	−16(−20,−13)	−13(−16,−10)		−11(−14,−8)	−13(−16,−10)		−15(−18,−12)
Erect										
SBP	Pre	175(168,182)	−10(−16,−4)	−11(−17,−6)	−13(−18,−7)		−15(−21,−9)	−17(−23,−12)		−14(−19,−8)
	Post		−31(−37,−24)	−21(−28,−15)	−35(−42,−29)		−42(−48,−35)	−37(−43,−30)		−44(−50,−37)
DBP	Pre	115(113,118)	-2^{NS}(−6,+1)	− 7(−10,−4)	− 5*(−8,−2)		− 8(−12,−5)	−11(−14,−8)		−10(−13,−7)
	Post		−21(−25,−18)	−13(−17,−10)	−19(−23,−16)		−26(−30,−22)	−22(−26,−19)		−28(−32,−24)
HR	Pre	85(82,88)	$+1^{NS}$(−2,+4)	−16(−19,−13)	−13(−16,−10)		−12(−15,−8)	−16(−19,−13)		−16(−19,−13)
	Post		+14(+18,+11)	−18(−22,−15)	−16(−19,−12)		−12(−16,−9)	−16(−20,−13)		−18(−22,−15)

SBP Systolic blood pressure (mmHg); DBP diastolic blood pressure (mmHg); HR heart rate (beats min^{-1}); NS not significant; * $P < 0.05$.
Figures are mean values with (95% confidence intervals).

Unless otherwise indicated, all differences were significantly different from the placebo response at the 1% level.

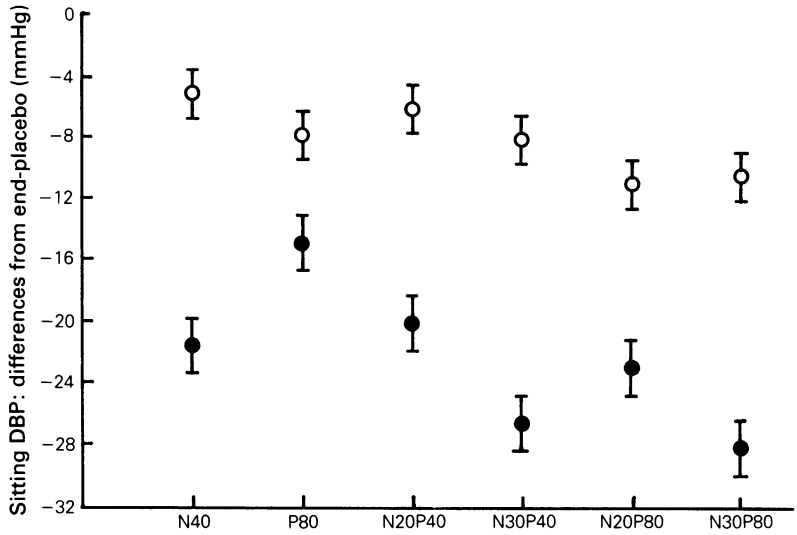

Figure 2 Sitting DBP ○ 'trough' (pre-dose), ● 'peak' (2 h post-dose) efficacy: differences ± s.e. mean from end-placebo (mmHg).

Table 3 Comparison of peak blood pressure responses : between combination treatments and the two monotherapies

(a) *Sitting systolic and diastolic pressure (mmHg)*

	N20	*N30*	*N20*	*N30*
	P40		*P80*	
N40	−1/+2	−8*/−5*	−1/−1	−10**/−6**
P80	−9**/−5*	−18**/−12**	−11**/−8**	−20**/−13**

s.e. = 3.6 (systolic), 2.1 (diastolic) mmHg

(b) *Erect systolic and diastolic pressure (mmHg)*

	N20	*N30*	*N20*	*N30*
	P40		*P80*	
N40	−4/+2	−11**/−5*	−6/−1	−13**/−7**
P80	−14**/−6**	−21**/−13**	−16**/−9**	−23**/−15**

s.e. = 3.8 (systolic), 2.3 (diastolic) mmHg

Figures are the differences between the mean values
s.e. Standard error of the difference; * $P < 0.05$; ** $P < 0.01$.

(Table 3). The difference between the responses following P80 and following the combinations ranged between 9–23 mmHg (SBP) and 5–15 mmHg (DBP). Only the two combinations N30 P40 and N30 P80 were more effective than N40, further reducing BP by between 8–13 mmHg (SBP) and 5–7 mmHg (DBP). Overall, these were the most effective combinations tested in the study, having significantly larger BP lowering effects than either P80 or N40 monotherapy, or the other combinations. This was a consistent result seen in both the sitting and erect postures and for SBP and DBP. There was no significant difference between the effects of N30 P40 and N30 P80 (Table 2). Nicardipine reduced SBP more effectively than propranolol as monotherapy and in this respect 30 mg was more effective than 20 mg twice daily in the combinations (Table 2).

By 2 h post-dose (Table 2), N40 had increased both sitting and erect heart rate by approximately 11 beats min^{-1} relative to pre-dose. P80 and the four combinations, however, had little effect, reducing heart rate by between 0–3 beats min^{-1} compared with the pre-dose value. A comparison

between treatments revealed that heart rate following N40 was significantly higher, by approximately 27 beats min^{-1} 2 h post-dose than on any other treatment.

Symptoms

A summary of the number of patients on each treatment who complained of symptoms, together with the frequency of symptoms is given in Table 4. One complaint of a chest infection, three of gastroenteritis, two of a urinary tract infection and one of indigestion and headaches, both of which pre-dated the study, were not included in these tabulations. The percentage of patients complaining of symptoms was highest (70%, i.e. 21 patients) in the N40 group, while on all other treatments, including placebo, this ranged between 37 and 27%. A comparison between the four treatment combinations showed little difference in terms of the number of complainers, with the lowest number, 8, following N30 P80.

The total number of side effects recorded differed between treatments, ranging from 12 following treatment with N30 P80 to 44 following N40. The two P80 combinations, i.e. N20 P80 and N30 P80 had a similar incidence to P80 alone, i.e. 16, 12 and 18 respectively and a lower incidence than the P40 combinations (24 each).

As detailed in Table 4, symptoms could be broadly broken down into three categories: (1) probably calcium antagonist related, (2) probably β-adrenoceptor blocker related, and (3) possibly attributable to either drug plus 'others' (i.e. with no obvious relationship to either drug).

The high number of calcium antagonist type side effects on placebo was principally accounted for by headaches, possibly related to the lack of blood pressure control. N40 had the highest and P80 the lowest incidence of this category of side effect. Within the combinations, there appeared to be little difference between the incidence of calcium antagonist side effects on N20 compared to N30, while the addition of P80 instead of P40 caused a small decrease in the number of calcium antagonist side effects. In five out of a possible 20 patients with no accompanying change in the nicardipine dose, calcium antagonist side effects were reported following P40, but not P80, and only one other patient did so following the higher

Table 4 Symptoms : incidence and frequency of symptoms on each treatment

	Placebo	*N40*	*P80*	*N20 P40*	*N30 P40*	*N20 P80*	*N30 P80*
Number of patients	60	30	30	30	30	30	30
Symptoms							
CA related*	17	23	3	10	10	8	5
β-adrenoceptor blocker related**	2	3	3	5	4	5	1
Either drug and others***	6	18	12	9	10	3	6
Total	25	44	18	24	24	16	12
Number of patients on each treatment who complained of symptoms	18	21	10	11	10	10	8
% complaining of symptoms	30%	70%	33%	37%	33%	33%	27%

CA calcium antagonist; *tachycardia, oedema, headache, flushing, nocturia, increase in urinary frequency; ** depressed, vivid dreams, tense, tired extremities, weight gain, blurred/hazy vision, insomnia; *** included malaise, fatigue, dyspepsia, constipation, diarrhoea, flatulence, dizziness, hair lifeless, sore throat, cold, backpain, irritable, felt unusual, runny nose, conjunctivitis, after-taste in mouth, rash, thirst, breathlessness on exertion, angina.

N.B. Several patients experienced more than one symptom during a treatment phase. This explains the higher number of listed symptoms than the number of complaints in each treatment group.

propranolol combination. This result indicates a slight tendency for the higher propranolol dose to reduce the incidence of side effects related to nicardipine but two patients experienced β-adrenoceptor blocker type symptoms following the higher, but not the lower, propranolol dose.

The incidence of β-adrenoceptor side effects was low (Table 4) with no distinctive differences between the treatment groups. On a 'within patient' comparison there was no indication that increasing the dose of nicardipine reduced β-adrenoceptor blocker related side effects.

Most complaints were reported as mild or moderate, as opposed to severe, and therefore no between-treatment comparison of severity has been undertaken. Five patients on the N40 regime complained of severe calcium antagonist type side effects (malaise, tired legs, constipation, facial and limb flushing, palpitations and dizziness – possibly attributable to micturition syncope, rather than drug-induced) and one of these was forced to withdraw from the study because of them. One patient complained of severe depression on the N20 P40 regime and three others had severe complaints on the N20 P80 regime (chest pain, sweating and vomiting – possibly caused by coincidental viral gastroenteritis, vivid dreams and headaches).

Clinical chemistry and haematology

Potassium and creatinine levels were both significantly elevated following P80 by 0.19 mmol l^{-1} and 6.5 μmol l^{-1} respectively (Table 5). Neither parameter was statistically significantly changed by N30 P40 or by nicardipine, but both were increased significantly by N30 P80.

Propranolol alone and in all combinations tended to increase T_4, FT_4 and rT_3 and to decrease T_3. TSH was not altered. Following P80 the changes were all significant at the 1% level, but the magnitudes of the changes were small, i.e., 0.74 and 0.027 ng dl^{-1} and 0.09 and 0.11 ng ml^{-1} respectively. Nicardipine significantly elevated T_4 alone, but to a lesser extent, averaging 0.57 ng dl^{-1}.

Neither propranolol nor nicardipine had a clinically significant effect on Hb, WBC, ESR, Na, urea, AST, γGT or random blood glucose values.

Discussion

Previous nicardipine studies

Nicardipine monotherapy (20–30 mg three times daily) has been shown to be effective and well tolerated in the treatment of mild–moderate essential hypertension (Taylor *et al.*, 1985). One study has also shown that a twice daily regime (40 mg twice daily) may be equally effective but with the penalty of a higher incidence of side effects (Jones *et al.*, 1983). The same twice daily dose was selected as the reference nicardipine monotherapy regime for this study because it is already licensed in the United Kingdom as suitable maintenance therapy for those controlled on 20–30 mg three times daily and, if confirmed to be effective, would simplify the patient's dosing regime and so should improve long-term compliance.

Study design

In the absence of a placebo 'treatment' phase it is not possible to quantify the true hypotensive effects for each individual drug or combination, but between treatment comparisons are valid and more sound than comparisons with the placebo run-in phase. The latter may be biased in that they include a time effect and the sitting DBP had to be within a given range. Differences between the three active treatment phases were investigated and were found to be much smaller than the differences between the placebo run-in and the active treatments.

'Peak' efficacy assessments

On the basis of known pharmacodynamic as well as pharmacokinetic data, 2 h post-dose is an appropriate time to assess the 'peak' antihypertensive efficacy of both nicardipine (Graham *et al.*, 1984; Martinez *et al.*, 1985) and propranolol (McAinsh *et al.*, 1978). The 4 week active treatment periods permit the full efficacy and tolerability of both nicardipine and propranolol regimes to be assessed in steady state.

Nicardipine 40 mg twice daily (N40) and propranolol 80 mg twice daily (P80) were both effective monotherapies in this study. Relative to the washout period at the end of 4 weeks on active treatment sitting SBP and DBP at 'peak' drug effect 2 h post-dose were reduced by 34 ± 22/21 ± 13 mmHg and 24 ± 20/15 ± 12 mmHg after N40 and P80 respectively, though the interpretation of this effect needs to be tempered because of the lack of any further placebo period in the randomised phases. Similar results in terms of the achievement of better SBP control on a calcium antagonist rather than on a β-adrenoceptor blocker have been noted before (Nifedipine-Atenolol Study Review Committee, 1988).

In controlling BP 2 h after dosing, propranolol

Table 5 Clinical chemistry parameters – statistically significantly different from end of wash out

Parameter	*End wash out*	*N40*	*P80*	*N20*	*N30*	*N20*	*N30*
				P40		*P80*	
Potassium ($mmol\ l^{-1}$)	4.07 (3.97,4.17)	−0.02 (−0.15,+0.10)	+0.19** (+0.06,+0.31)	+0.11 (−0.02,+0.24)	+0.04 (−0.09,+0.16)	+0.12 (−0.00,+0.25)	+0.18** (+0.06,+0.31)
Creatinine ($\mu mol\ l^{-1}$)	89.5 (83.7,95.3)	+2.0 (−1.5,+5.5)	+6.5** (+2.8,+10.2)	+4.1* (+0.4,+7.7)	+1.5 (−2.1,+5.2)	+3.5* (+0.0,+7.0)	+4.0* (+0.3,+7.7)
Thyroid function							
T4 ($ng\ dl^{-1}$)	8.26 (7.70,8.83)	+0.56* (+0.12,+1.01)	+0.74** (+0.30,+1.17)	+0.77** (+0.33,+1.20)	+0.62** (+0.19,+1.05)	+1.13** (+0.70,+1.57)	+1.24** (+0.81,+1.68)
FT4 ($ng\ dl^{-1}$)	0.180 (0.171,0.188)	−0.002 (−0.010,+0.007)	+0.028** (+0.019,+0.036)	+0.023** (+0.015,+0.031)	+0.022** (+0.014,+0.031)	+0.036** (+0.028,+0.044)	+0.030** (+0.022,+0.039)
T3 ($ng\ ml^{-1}$)	1.47 (1.41,1.53)	+0.04 (−0.03,+0.11)	−0.11** (−0.18,−0.05)	−0.08* (−0.14,−0.01)	−0.07* (−0.14,−0.00)	−0.09** (−0.16,−0.03)	−0.10** (−0.17,−0.04)
rT3 ($ng\ ml^{-1}$)	0.18 (0.17,0.20)	+0.01 (−0.01,+0.02)	+0.09** (+0.07,+0.11)	+0.07** (+0.05,+0.08)	+0.05** (+0.04,+0.07)	+0.10** (+0.08,+0.12)	+0.08** (+0.06,+0.10)
TSH ($nIU\ ml^{-1}$)	3.27 (2.59,3.95)	+0.18 (−0.11,+0.47)	−0.05 (−0.26,+0.17)	−0.00 (−0.22,+0.21)	+0.31* (+0.02,+0.59)	+0.03 (−0.19,+0.25)	+0.29* (+0.01,+0.58)

* $P < 0.05$; ** $P < 0.01$; Figures are mean values with (95% confidence intervals)

alone was least effective, and the combinations N30 P40 and N30 P80 were most effective, both against the other combinations and against the two monotherapies. The improved efficacy of these two combinations was both statistically and clinically significant, but they did not differ from each other.

'Trough' efficacy assessments

The combinations were as effective, and in some cases more effective than nicardipine (40 mg twice daily) or propranolol (80 mg twice daily) monotherapy in controlling 'trough' BP and in this respect there was little to choose between any of them.

From the clinical standpoint, the pre-dose ('trough') BP levels we achieved represent only sub-optimal control. Our study design did not permit assessment of the time course of BP control nor of the duration of the shortfall in control. Despite background propranolol therapy given twice daily and persisting β-adrenoceptor blockade, as witnessed by the good pulse rate control throughout, the more prolonged antihypertensive effect of propranolol was insufficient to maintain adequate BP control for 12 h. It seems that administration of the conventional formulation of nicardipine only twice daily would, at best, give only erratic, good BP control. Our results imply that maintenance therapy with nicardipine at least thrice daily is indicated to achieve reliably continuous, adequate 24 h BP control; this finding contrasts with the results in some patients in one previous study (Jones *et al.*, 1983). However, some earlier positive clinical trials of antihypertensive treatment did not utilise such discriminating assessments of continuous 24 h efficacy. Detailed information on 24 h BP response patterns to therapy does improve the prediction of an individual's risk of cardiovascular morbidity, so that 24 h BP control is indeed a desirable therapeutic goal (Brunner *et al.*, 1985; Floras *et al.*, 1981; Devereux *et al.*, 1983; Perloff *et al.*, 1983; Pickering *et al.*, 1985; Sokolow *et al.*, 1966; Waeber *et al.*, 1984). Continuous ambulatory BP monitoring techniques not only provide this information, but they can be adapted to reliably detect important differences in efficacy between treatments, despite, as in our study design, using only very restricted numbers of patients (Conway *et al.*, 1988).

Heart rate

Heart rate following combined treatment with nicardipine and propranolol appeared to be influenced primarily by propranolol, as the rate at the time of 'trough' drug levels was reduced relative to washout and reflex tachycardia was abolished.

Side effects

While the incidence of symptoms was again shown to be higher following nicardipine 40 mg twice daily, the comparison of incidence and frequency of side effects in this study was principally between lower-dose nicardipine combinations. Analysis of the recorded symptoms suggests that in some patients, the higher propranolol dose might have reduced calcium antagonist type side effects, as evidenced by a lower incidence of side effects on N30 P80 than on N30 P40. This, and the abolition of tachycardia on all four combinations, suggests that propranolol reduced the reflex increase in sympathetic activity normally evoked, at least acutely, by nicardipine. It should be noted, however, that in our patients the incidence of β-adrenoceptor blocker type side effects may have been increased at the higher propranolol dose. Nicardipine, by contrast, did not appear to reduce β-adrenoceptor blocker type side effects. The propranolol doses used in this study were relatively low, however, and this may explain the low incidence of β-adrenoceptor blocker side effects. Because of the small numbers of patients in this study, we cannot exclude the possibility that some of these changes might be chance findings rather than treatment-related ones. Further studies would be required to clarify the issue.

Safety

The change in creatinine (Andreasen *et al.*, 1984) and thyroid function parameters (Andreasen *et al.*, 1984; Perret *et al.*, 1984) seen following propranolol, have been previously described. The nicardipine effect on T_4 is contrary to previously reported results from a study in healthy volunteers who were dosed with nicardipine 30 mg (three times daily) and in whom thyroid function was measured on several occasions over a 28 day period (Dow *et al.*, 1986). These effects of the combination of the two drugs have not been reported before.

Comparison with other combinations

The results of the present and other similar calcium antagonist/β-adrenoceptor blocker combination studies need to be seen in the light of yet others, where a calcium antagonist was combined with other than a β-adrenoceptor blocker, e.g., an ACE-inhibitor (Maclean *et al.*,

1988 b), or where propranolol has been combined with, e.g., a thiazide diuretic (Massie *et al.*, 1987; Mitchell *et al.*, 1972). Clearly it is possible to devise many very effective and well-tolerated low dose combination therapies, but their relative merits will only be adequately elucidated by appropriately designed double-blind, randomised, placebo-controlled clinical trials.

Statistical analysis

Finally, this study obviously includes multiple comparisons so that levels of significance should be judged with extra caution. However, usual methods for multiple comparisons are not appropriate because of the treatment structure. We conclude the overall results are valid for the patients we studied because (a) the majority of the reported changes are statistically significant, at least at the 1% level, (b) the trends seen in the sitting pressures are obvious in the erect results, (c) consistent dose responses were obtained, and (d) the results are clinically plausible, e.g., antihypertensive drugs lower blood pressure.

Conclusion

The optimum combination of two drugs should be chosen by looking at the balance between its efficacy and its side effects, remembering, too, from the long-term safety viewpoint, that some unwanted effects, particularly metabolic ones, may only become apparent after many months of therapy, and these are generally dose-related (Ames, 1986). The minimum effective dose of each constituent drug should therefore be administered in any fixed-dose drug combination. Previous experience suggests that calcium antagonist/β-adrenoceptor blocker combinations seem to give adequate BP control even when low doses of each drug are employed (Nifedipine – Atenolol Study Review Committee, 1988; Maclean *et al.*, 1988b). When the β-adrenoceptor blocker is used in full dosage, high doses of a calcium antagonist may significantly increase the side effect burden without further improving BP control (Maclean *et al.*, 1988a).

The results from our study suggest that within the constraints of a twice daily treatment regime the combination of nicardipine 30 mg (twice daily) and propranolol 40 mg (twice daily) should be considered optimum in the short term, and only if side effects are problematic should the propranolol dose be increased to 80 mg (twice daily). The long term efficacy, tolerability and safety of these combinations has not been tested.

It is also possible that our results may not be representative of the results of these treatments in a previously untreated hypertensive population since most (48/60) of our patients had had prior treatment with a calcium antagonist or β-adrenoceptor blocker.

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