The effects of oral nitrendipine and propranolol, alone and in combination, on hypertensive patients with special reference to AV conduction

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1 The effects of oral nitrendipine and oral propranolol, alone and in combination, on AV conduction have been examined in 11 patients with essential hypertension in whom arterial pressure was not adequately controlled despite treatment with thiazide diuretics.

2 The study was performed double-blind. After a drug free period of 1 week, the patients received two 7 day courses of drug therapy after initial control measurements. Five of the eleven patients were randomised to receive nitrendipine 20 mg daily, the other six patients received propranolol (Inderal LA 160 mg daily) for the first week of therapy. During week 2, 10 patients received combined therapy.

3 In the 10 patients who completed the study, oral nitrendipine, given either alone or in combination with oral propranolol, had no significant effect on resting PR, QRS, QT intervals nor on AV conduction as assessed by ambulatory electrocardiography.

4 Propranolol did not affect the resting PR interval but significantly increased PR intervals on the ambulatory ECG recordings during single and combined therapy. However the maximum PR intervals remained within normal limits.

Keywords nitrendipine propranolol PR interval

Introduction

Nitrendipine (Bayer 5009, 3-ethyl 5-methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl) 3,5-pyridine dicarboxylate) is a calcium antagonist drug which has been found to have hypotensive effects in man and experimental animals (Stoepel *et al.*, 1981; Ventura *et al.*, 1983). The drug acts by inhibiting calcium influx in smooth muscle cells thereby causing vasodilatation (Nachshen *et al.*, 1979).

Nitrendipine would appear to have a longer duration of action than nifedipine and clinical trials have shown that it can control blood pressure with once daily administration (Andren *et al.*, 1982; de Divitiis *et al.*, 1984). Nitrendipine has also been used in combination with β -adrenoceptor antagonists in the treatment of hypertension (Oro & Ryman, 1984; de Divitiis *et al.*,

1984) and the combination has been found to be more effective than either agent alone, in keeping with previous experience of combinations of drugs of these groups (Lynch *et al.*, 1980; Harris *et al.*, 1982). However, electrophysiological interactions have been reported between β -adrenoceptor antagonists and certain calcium antagonist drugs, both intravenously (Winniford *et al.*, 1982; Kawai *et al.*, 1981) and orally (Hutchison *et al.*, 1984; Eisenberg *et al.*, 1984; McGourty *et al.*, 1985), particularly with verapamil. It has therefore been recommended that verapamil and perhaps other calcium antagonists should be used cautiously with β -adrenoceptor antagonists especially in patients with underlying abnormalities of the heart's conduction system (Winniford *et al.*, 1982). However such

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adverse effects have not been found with the combination of nifedipine and propranolol in similar patients (Winniford *et al.*, 1982; Kawai *et al.*, 1981). Although previous animal studies have not shown any electrophysiological interactions between nitrendipine and β -adrenoceptor antagonists, a recent clinical study demonstrated an occasional interaction between a high intravenous dose of nitrendipine (2 mg) and oral propranolol on atrio-ventricular (AV) conduction in patients with coronary artery disease (unpublished observations, O'Keefe & Camm, 1984).

The present study was designed to investigate the effects of oral nitrendipine and propranolol, singly and in combination, on AV conduction in patients with mild essential hypertension.

Methods

Patients

The group studied consisted of 11 patients, 44–69 (mean 57.7) years of age; nine were male. Informed written consent was obtained. All had essential hypertension (resting supine blood pressure between 160/100 and 200/115 mm Hg on three successive readings) which persisted despite treatment with a thiazide diuretic. The patient data are summarised in Table 1. Patient 9, who initially entered the trial, was withdrawn because of bronchospasm during propranolol therapy and was not included in any of the subsequent analysis. Patients with diabetes mellitus, known intolerance to β -adrenoceptor or calcium antagonists, child bearing potential,

AV conduction disease, heart failure, obstructive airways disease, concurrent medication other than diuretics and potassium replacements, cardiac pacemaker or cardiac arrhythmias were excluded.

Methodology

The study was performed double-blind. Control (pre-treatment) measurements were first made after an initial drug free period of 1 week. Afterwards the patients received two 7 day courses of drug therapy. Five of the 10 patients (patient numbers 1, 4, 6, 8 and 10) were randomised to receive orally nitrendipine 20 mg daily, the other five patients receiving daily oral propranolol (Inderal LA 160 mg daily) for the first week of therapy (patient 9 was withdrawn during the first week). During the second week, the 10 remaining patients received combined therapy with daily oral nitrendipine 20 mg daily and oral propranolol (Inderal LA 160 mg daily). During the two courses of drug treatment, matching tablets were administered. On day 1 (control), day 7 (4 h post-single drug therapy dose) and day 14 (4 h post-combined therapy dose) the following measurements were made:

- (1) Supine blood pressure measurements with a cuff and sphygmomanometer after a 15 min rest, a mean of three readings being obtained (diastolic blood pressure was assessed at the fifth Korotkoff sound).
- (2) Resting 12 lead ECG from which PR, QRS, QT intervals and the heart rate were measured.
- (3) Continuous 24 h ECG recording using a Reynolds Tracker recorder and analysed on

Table 1 Patient data

Patient	Age (years)	Sex	Control BP (mm Hg)	Pre-trial medication
1	58	M	175/105	Navidrex K 1 daily
2	55	M	130/100	Navidrex K 2 daily
3	60	M	160/110	Navidrex K 2 daily Spironolactone 1 daily
4	50	F	175/95	Chlorthiazide 1 daily
5	61	M	190/105	Bendrofluazide 1 daily
6	44	M	190/100	Moduretic 1 daily
7	58	M	165/100	Moduretic 1 daily
8	69	M	200/100	Navidrex K 2 daily
9	60	M	Withdrawn from study	
10	60	F	160/100	Moduretic 1 daily
11	60	M	150/100	Moduretic 1 daily

a Reynold's Pathfinder PA1 and Replay 2 system. PR intervals were measured at hourly intervals from 25 complexes.

A PR interval was considered abnormal if it exceeded 220 ms.

Statistical method

Results obtained were normally distributed and are expressed as mean $\pm$ s.e. mean. Student's paired *t*-test was used to compare the control (pre-treatment) and post-drug results of each variable. A *P* value of less than 0.05 was considered statistically significant.

Results

There was no significant difference between the clinical characteristics, electrocardiographic and blood pressure findings of the two groups of patients before treatment (pre-treatment values, Tables 2 and 3).

Electrocardiographic changes during single drug treatment

The results for nitrendipine therapy alone are summarised in Table 2. There was no significant change in the resting mean PR, QRS, nor QT intervals of the five patients who were treated with nitrendipine alone in comparison with control (pre-treatment) values.

The results during propranolol treatment alone are summarised in Table 3. There was no significant change with treatment in the resting mean PR, QRS, nor QT intervals of five patients who initially received propranolol alone. However the mean PR interval on the ambulatory ECG for this group of five patients prolonged significantly but remained within the normal range.

The mean PR intervals of two of the five individual patients (patients 5 and 11) were significantly prolonged on ambulatory ECG monitoring after propranolol alone. In patient 5, the PR interval lengthened from 150 ± 3 ms during control to 160 ± 0 ms after propranolol (*P* <

Table 2 Blood pressure and ECG changes during nitrendipine and combination therapy

	Blood pressure			Resting ECG			DCG
	SBP	DBP	HR	PR	QRS	QT	PR
	(mm Hg)	(mm Hg)	(beats min ⁻¹)	(ms)	(ms)	(ms)	(ms)
Control (pre-treatment)	180 $\pm$ 8	101 $\pm$ 3	78 $\pm$ 6	168 $\pm$ 9	84 $\pm$ 11	420 $\pm$ 22	168 $\pm$ 8
Nitrendipine	165 $\pm$ 8	91 $\pm$ 3*	79 $\pm$ 2	164 $\pm$ 4	84 $\pm$ 11	412 $\pm$ 23	164 $\pm$ 4
Nitrendipine plus propranolol	160 $\pm$ 8*	92 $\pm$ 6*	60 $\pm$ 3*	164 $\pm$ 4	84 $\pm$ 11	432 $\pm$ 2	172 $\pm$ 7*

Abbreviations: DCG = ambulatory (dynamic) electrocardiographic recording;

**P* < 0.05 compared with control values

Table 3 Blood pressure and ECG changes during propranolol and combination therapy

	Blood pressure			Resting ECG			DCG
	SBP	DBP	HR	PR	QRS	QT	PR
	(mm Hg)	(mm Hg)	(beats min ⁻¹)	(ms)	(ms)	(ms)	(ms)
Control (pre-treatment)	164 $\pm$ 13	103 $\pm$ 3	75 $\pm$ 6	164 $\pm$ 4	76 $\pm$ 4	416 $\pm$ 23	156 $\pm$ 11
Propranolol	169 $\pm$ 7	98 $\pm$ 4	58 $\pm$ 4*	164 $\pm$ 4	76 $\pm$ 4	424 $\pm$ 23	166 $\pm$ 6*
Propranolol plus nitrendipine	149 $\pm$ 7*	85 $\pm$ 4*	58 $\pm$ 4*	164 $\pm$ 4	76 $\pm$ 4	444 $\pm$ 28	167 $\pm$ 5*

DCG = ambulatory (dynamic) electrocardiographic recording;

**P* < 0.05 compared with control values

0.01). The PR interval of patient 11 increased from 142 ± 4 ms during control to 153 ± 3 ms after propranolol ($P < 0.05$). However the maximum PR intervals in these patients were not longer than 200 ms and therefore remained within normal limits.

Electrocardiographic changes during combined therapy

The results for the two groups of patients are summarised in Tables 2 and 3. During combined treatment with propranolol and nitrendipine, there was no significant change in resting mean PR, QRS nor QT intervals of any of the 10 patients in comparison with their respective controls. However during ambulatory ECG monitoring, five patients had a significant increase in their mean PR intervals after combined therapy in comparison with their respective controls. These included patients 5 and 11, who had received propranolol as the initial therapy, and patients 1, 6 and 8 who had received nitrendipine as the initial therapy.

The prolongation of the PR intervals on ambulatory monitoring were similar during propranolol alone and combined therapy (166 ± 6 ms after propranolol and 167 ± 5 ms after combined including patients 5 and 11 who, like the other patients in their group, had no further prolongation of their mean PR intervals as a result of adding nitrendipine to propranolol therapy).

Blood pressure and heart rate changes

With combined treatment, statistically significant reductions in blood pressure and mean heart rate were achieved in both groups of patients compared with their respective controls (Tables 2 and 3). With nitrendipine alone, there was no change in resting heart rate. Resting heart rate fell with propranolol but did not fall further with the addition of nitrendipine.

Side effects

Patient 9 was withdrawn from the study because of significant bronchospasm which developed during the initial course of treatment with propranolol. Patient 3 had occasional headaches after propranolol and subsequently, mild malaise during combined therapy. Patient 4 noticed mild malaise with combined therapy only, being asymptomatic during treatment with nitrendipine alone.

Discussion

Complications resulting from the combined use of calcium antagonists and β -adrenoceptor antagonists range from conduction disturbance and electro-mechanical dissociation with intravenous verapamil (Krikler & Spurrell, 1972) to peripheral oedema and heart failure with oral nifedipine (Winniford *et al.*, 1982; Kawai *et al.*, 1981). This diversity of side effects reflects the heterogeneity of the calcium antagonist group of drugs. Nitrendipine is a new addition to this group and which, as with the other members, would be expected to be used in combination with β -adrenoceptor antagonists for treatment of both hypertension and angina pectoris. Therefore, potential interactions need to be identified.

Nitrendipine is structurally related to nifedipine, a calcium antagonist without demonstrable electrophysiological effect at clinical doses in man. Despite this, intravenous nitrendipine (2 mg) has been shown to result in occasional, transient AV block (unpublished observations, O'Keefe & Camm, 1984) leading to a current maximum recommended intravenous dose which is half of that given in the above study. Intravenous combinations of verapamil and β -adrenoceptor antagonists are contraindicated because of the severe side effects, yet the two drugs are sometimes combined orally despite reports of occasional problems. This study was undertaken to study the oral combination of nitrendipine and propranolol in terms of effects and side effects.

We are not able, in this clinical trial, to include placebo in the randomisation of treatments. Control values were therefore taken as the pre-treatment values following the drug-free wash out period. Blood pressure was measured with a standard sphygmomanometer rather than a bias-free machine, and therefore a small observer bias in the recordings cannot be excluded. However, the measurement of electrocardiographic variables was carried out under blind conditions, and we consider that our results demonstrate that nitrendipine, like its dihydropyridine related compound nifedipine, appears to be electrophysiologically inert. It affected neither the control intervals (HR, PR, QRS, QT) nor did it aggravate the effects seen with propranolol (Tables 2 and 3). Addition of nitrendipine to the treatment of patients with hypertension not adequately controlled with a β -adrenoceptor antagonist has been shown to be effective (Oro *et al.*, 1984). The results of this study suggest that the combination of nitrendipine and propranolol is safe and effective in patients repre-

sentative of those likely to receive such a combination, i.e. hypertensive patients. However, the number of patients studied is small and this study does not exclude the possibility of an occasional adverse interaction. Expected changes were seen with the use of propranolol but no abnormalities were induced.

AV conduction in this group of patients was normal, the patients having been deliberately chosen for this. β -adrenoceptor antagonists are relatively contra-indicated in patients with AV conduction abnormalities and the inclusion of such patients in this study (which involved long periods of unobserved monitoring) would therefore not have been representative of normal

clinical practice. The use of nitrendipine, either alone or in combination with a β -adrenoceptor antagonist in patients with abnormalities of AV conduction has therefore not been explored here.

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